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Pam Smartt

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The systematic review of the evidence will ultimately be used by the ACC to inform policy decision making in conjunction with other information. The content of the review alone does not constitute clinical advice or policy recommendations.

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Contact Details

Health Services Assessment Collaboration (HSAC)

Health Sciences Centre

University of Canterbury

Private Bag 4800

Christchurch 8140

New Zealand

Tel: +64 3 345 8147 Fax: +64 3 345 8191

Email: hsac@canterbury.ac.nz

Web Site: www.healthsac.net

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Glossary of Selected Terms and Techniques

Afferent	Carrying toward. An afferent nerve carries impulses toward the central nervous system.
Annulus fibrosis	The outer capsule of an intervertebral disc.
Anterolisthesis	The upper vertebral body is positioned abnormally compared to the vertebral body below it. More specifically, the upper vertebral body slips forward on the one below.
Arthrodesis	This is the artificial induction of joint ossification or fusion between two bones via surgery.
Arthroplasty	Surgical reconstruction and replacement of degenerated joints -arthoplasty includes interposition arthroplasty where a spacer is placed between the articular surfaces which are not removed.
Autonomic nervous system (ANS)	Part of the peripheral nervous system that supplies neural connection to glands and smooth muscles of internal organs; made of two divisions (sympathetic and parasympathetic) and sometimes is considered to have a third division called the enteric system
Cauda equina	The cauda equina is the bundle of lumbar and sacral nerves extending from the lower spinal cord (conus terminalis) which usually terminates posterior to the first lumbar vertebra. At each vertebral level a pair of nerves exits via the neural foramina.
Cauda equina syndrome	A triad of symptoms consisting of bilateral lower limb pain or weakness, perineal numbness and altered bladder and bowel function. It is usually caused by large disc protrusions in stenotic (narrowed) spines, commonly at l4/l5 but can also have non-surgical causes. It is important because if not treated urgently can result in permanent impairment with bladder and sexual impairment.
Caudal	Pertaining to the tail, i.e., inferior aspect of spine, vs. cephalad, pertaining to the head.

Caudal, Caudad	Relating to or towards the base of the spine (towards the tail, especially caudad).
Central nervous system	The portion of the nervous system that includes the brain and the spinal cord
Cervical	Relating to the neck, e.g. The first seven vertebrae of the spinal column.
Cervicogenic	Arising from damage to structures in the neck.
Chemonucleolysis	A method for treating back pain caused by lumbar disc herniation. An enzyme, such as chymopapain, is injected into the nucleus pulposus of the herniated disc in order to dissolve it. Chemonucleolysis is a conservative alternative to disc surgery
Corpectomy	Is a surgical procedure that involves removing a major part of, or all of the vertebral body, usually as a way to decompress the spinal cord and nerves. Corpectomy is often performed in association with some form of discectomy.
Decompression	Relief of pressure on one or many compressed nerves (neural impingement) of the spinal column.
Dermatome	An area of skin innervated by sensory fibres from a single spinal nerve.
Discectomy	Removal of all or part of an intervertebral disc, rarely is the whole disc removed. In adulthood the nucleus pulposus is not recognizably separate from the annulus and most discectomies involve removing annular material and end plate. Generally the purpose of discectomy is to relieve sciatica.
Discitis	Inflammation or infection within the disc space.
Discogenic pain	A pain syndrome deriving from an abnormal intervertebral disc.
Discogenic pain	A pain syndrome deriving from an abnormal intervertebral disc.

Dorsal rami	Nerve branches in the back (plural form; singular = dorsal ramus).
Dorsal root entry zone	The site where sensory fibres enter the spinal cord.
Dorsal root ganglion	A collection of nerve cells located close to the spinal cord. There is one dorsal root ganglion for each nerve segment level in the body.
Dura mater	The tough membrane covering the spinal cord.
Dysaesthesia	Abnormal sensation or impairment of sensation, especially that of touch
Epidural	Of or into the epidural space, which lies between the wall of the spinal canal and the dura mater.
Facet joints see also Zygapophyseal joints	The joint that occurs between facets of the interior and superior articular processes of adjacent vertebrae.
Failed back syndrome	Characterised by intractable pain and varying degrees of functional incapacitation occurring after spine surgery.
Fluoroscopy	An imaging technique where X-rays are used to produce live pictures on a screen rather than a snapshot fixed in time.
Foramen	A small opening between two vertebrae through which nerve roots enter or exit the spinal canal, plural foramina.
Ganglion	A cluster of nerve tissue primarily composed of neuron cell bodies. Usually located outside the central nervous system. Plural = ganglia.
Herniated disc	Localized displacement of disc material beyond the normal margins of the intervertebral disc space. The term “herniated disc,” as defined in the ANJR guidelines (Fardon and Milette 2001) refers to localized displacement of nucleus, cartilage, fragmented apophyseal bone, or fragmented annular tissue beyond the intervertebral disc space (disc space, interspace). The herniated material may put pressure on the exiting nerve root causing pain. Herniated discs occur most frequently in the lower lumbar region of the spine.

Hyperalgesia	Abnormally increased response to painful stimuli.
Hypoalgesia	Diminished pain in response to a normally painful stimulus.
Infusion	A method of delivering drug solutions into the body.
Interbody	The part of the spine where the disk is present, between the vertebrae. An interbody fusion can be – i.e. Anterior (alif), posterior (plif) or lateral (llif).
Internal disc disruption see also Discogenic pain	Disorder of the intervertebral disc caused by fissures in the ring of the disc (the annulus fibrosis) that distort the internal architecture of the disc, making it structurally incompetent. Patients with internal disc disruption classically complain of low back pain and may have a radiating component with radicular or nerve root type of pain. Unlike disc herniations, this pain is not the result of disc compression affecting the exiting nerve root.
Intra-articular	Into or within a joint.
Intra-discal electrothermal therapy (IDET)	An intervention during which a catheter is inserted into a spinal disc under fluoroscopic guidance. The catheter is heated to 90 C for 16 - 17 minutes then removed. It is usually performed under light sedation as an outpatient procedure. Now considered to be outmoded.
Intrathecal	Of or into the intrathecal space, which lies between the dura mater and the outside of the spinal cord itself. The space is filled with cerebrospinal fluid and is also known as the thecal sac.
Kyphosis	Is a curving of the spine forward (in distinction from lordosis which is a curving of the spine backwards) that causes a bowing or rounding of the back.
Laminectomy	Surgical procedure to remove the posterior arch portion of the vertebral bone called the lamina. The procedure is usually performed to relieve pressure on the spinal nerves.
Laminoplasty	A surgical procedure for treating spinal stenosis by relieving pressure on the spinal cord or cauda. The procedure involves cutting the lamina on both sides of the affected vertebrae and then "swinging" the freed flap of bone open thus relieving the pressure on the spinal cord. This technique contrasts with vertebral laminectomy in the

	amount of bone and muscle tissue that has to be removed, displaced, or dissected in the procedure
Lordosis	An anterior convex curvature of the spine – the opposite of kyphosis
Lumbar	Relating to the lower back or lower part of the spine. The lumbar spine consists of the five vertebrae between the thoracic region and the sacrum.
Medial branch	Nerves that supply (or "innervate") the zygapophyseal (z-) joints. Each z-joint is innervated by two medial branches, which carry pain signals to the spinal cord. The signals are then conveyed to the brain, where the pain is perceived.
Medial branch of posterior primary ramus	This nerve is a third order division of the spinal nerve root. The spinal nerve root emerges from the spinal foramen, and almost immediately divides into a large anterior primary ramus (Latin = branch) and a posterior ramus. The posterior smaller ramus then divides into medial, lateral and intermediate branches. The medial branch then supplies the facet joint. Two nerve roots, the root of that vertebra and the root of the vertebra above combine to supply any one facet joint.
Meta-analysis	A quantitative secondary research method for combining the results of independent research studies (usually drawn from the published literature) and synthesising their findings and conclusions.
Meta-analysis	A quantitative secondary research method for combining the results of independent research studies (usually drawn from the published literature) and synthesising their findings and conclusions.
Nerve	A bundle of fibres that uses chemical and electrical signals to transmit sensory and motor information from one body part to another.
Nerve block	Interruption of the conduction of impulses in peripheral nerves or nerve trunks by the injection of a local anaesthetic solution or other agent.
Neuroablation	A term describing interventions that aims to relieve pain by destroying the nerves that transit pain signals.
Neuromodulation	A term describing interventions that aims to relieve pain by modifying the way in which nerves transmit pain signals.

Neuron	A neuron or nerve cell is an electrically excitable cell that processes and transmits information by electrical and chemical signalling.
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system, but which outlasts the injury and is associated with nerve and/or central nervous system changes.
Neurotrophins	Neurotrophins are a family of proteins that induce the survival, development, and function of neurons.
Nociceptive pain	Pain in which normal nerves transmit information to the central nervous system about trauma to tissues (nocere = to injure, Latin).
Non- nociceptive pain	Non-nociceptive pain stems from a problem in the central or peripheral nervous system. No pain receptors exist in these two systems; therefore, the pain is caused by nerve dysfunction sending signals.
Nucleus pulposus	The semi-gelatinous tissue in the centre of an intervertebral disc. It is surrounded and contained by the annulus fibrosis, which prevents this material from protruding outside the disc space.
Nurick scale[1]	A six grade system (0-5) based on the 'difficulty in walking'. Classification Scheme: • Grade 0: signs or symptoms of root involvement but without evidence of spinal cord disease • Grade 1: signs of spinal cord disease but no difficulty in walking. • Grade 2: slight difficulty in walking which does not prevent full-time employment. • Grade 3: difficulty in walking which prevented full time employment or the ability to do all housework, but which was not so severe as to require someone else's help to walk. • Grade 4: able to walk only with someone else's help or with the aid of a frame. • Grade 5: chair bound or bedridden.
Paresthesia	A sensation of tingling, pricking, or numbness of a person's skin.
Peripheral	Situated away from the centre, as opposed to centrally located.

[1] Source: Nurick S. The pathogenesis of the spinal cord disorder associated with cervical spondylosis. Brain. 95:87-100 (1972
[2] (K.-T. Kim, Lee, Lee, Bae, & Suk, 2006)

Peripheral nervous system	The portion of the nervous system that includes all the nerves and neurons beyond the brain and spinal cord
Peripheral sensitization	A reduction in the threshold and increase in the responsiveness of the peripheral terminals of nociceptors such that the terminals now can be activated by non-noxious stimuli, and noxious stimuli evoke a greater action input from the peripheral terminal. Typically the inciting event is exposure to inflammatory mediators or sensitizers that act on the nociceptor terminal, changing its functional properties
Posterior primary rami	Nerve branches in the back (singular = posterior primary ramus). These are the first division of the nerve root after emerging from the spinal column, and supply only the bones, joints, muscles and skin of the back.
Posterolateral fusion (PLF)[2]	Bone graft is placed lateral to the facet joints between the transverse processes and / or the sacral ala/ alae. Bone may also be placed within the facet joints.
Posterior lumbar Interbody fusion (PLIF).	Bone graft and/or cage placed within the disc from a posterior approach. It has the advantage of mechanical strength and maintenance of disc height and lordosis. Similar to TLIF, transforaminal lumbar Interbody fusion, done via a more lateral approach through the foramen but with more bony sacrifice of the facet joints and requiring pedicle fixation.
Prolotherapy	A treatment in which an irritant substance (e.g. 20% glucose) is injected into tissues with the aim of stimulating blood flow and promoting healing. Now considered to be outmoded.
Radicular pain	Pain radiating down the arm or leg in a specific pattern secondary to nerve root compression.
Radiculopathy	Pain, numbness or weakness caused by irritation of the spinal nerve roots, often as a result of compression.
Radiofrequency denervation	An intervention during which the tip of an electrode, which has been placed beside a nerve, is heated up in order to coagulate the proteins inside that nerve and thus modify the way it transmits pain.
Radiofrequency neurotomy	A subtype of the above denervation, in which the heating is carried to the point of destroying the nerve (though it may later regenerate).

[2] (K.-T. Kim, Lee, Lee, Bae, & Suk, 2006)

Rhizotomy	Deliberately cutting a nerve root, in order to block the transmission of pain.
Sacral	Relating to the lowest part of the spine. The sacrum is the triangular bone made up of five fused lowest vertebrae and forming the posterior section of the pelvis.
Sagittal alignment	Spine curvature viewed in the vertical plane which passes from front to rear dividing the body into right and left sections.
Sciatica	Irritation of the sciatic nerve (the largest nerve in the body) leading to pain running from the low back down through the leg. Technically known as lumbar radiculopathy. Most commonly caused by a protruding disc that presses on the sciatic nerve.
Somatic pain	Somatic pain is referred to as musculoskeletal pain. It is found in tissue such as skin and muscles as well as in joints, bones and ligaments. Somatic pain is often characterized as a sharp pain localized in a specific area of injury. Swelling, cramping and bleeding may exist with somatic pain. This classification of pain responds to a variety of medications, including opioids and nonsteroidal anti-inflammatory drugs
Spasticity	Uncontrolled contractions (spasms) of the muscles.
Spinal stenosis	A disorder in which the spinal canal narrows, leading to back pain and leg pain that comes and goes with activities such as walking. Although stenosis can occur in all areas of the spine, it most commonly affects the lumbar (lower) region.
Spinal cord stimulation	An intervention that uses electrical stimulation to block nerve pathways in the dorsal part of the spinal cord, thus modifying the way the nerves transmit pain.
Spinal stenosis	A disorder in which the spinal canal narrows, leading to back pain and leg pain that comes and goes with activities such as walking. Although stenosis can occur in all areas of the spine, it most commonly affects the lumbar (lower) region.
Spondylolisthesis	A condition in which a vertebra shifts forward on another. It can occur in the cervical, thoracic (rare) or commonly in lower lumbar. It is the opposite of retrolisthesis. Vertebra may also shift sideways – lateral subluxation. Spondylolisthesis may be further considered as developmental, isthmic, degenerative or pathological.

Spondylolysis	Spondylolysis is a defect in the pars interarticularis which may be developmental or traumatic.
Spondylosis.	Degeneration of the spine and/or degeneration of the zygoapophyseal/facet joints.
Stellate ganglion	A paravertebral sympathetic ganglion in the base of the neck, formed by the fusion of the inferior cervical and first thoracic ganglia
Stenosis	A reduction in capacity of the spinal canal. Can be congenital but stenosis is most acquired following degenerative changes, usually a combination of ligamentous hypertrophy, osteophytes encroachment and / or spondylolisthesis. Plural – stenosis.
Sympathetic nervous system (SNS)	One of the two systems that compose the autonomic nervous system; a sympathetic response dilates pupils, inhibits salivation, relaxes airways, accelerates the heartbeat, inhibits digestion, etc.
Thoracic	Relating to the chest level region of the spine located between the cervical and lumbar vertebrae, e.g. The 12 vertebrae that serve as attachment points for the ribs.
Whiplash injury	Hyperextension injury to the neck, commonly the result of being struck from behind by a vehicle in a traffic accident and often associated with rather low energy collisions.
Zygapophyseal joints/z joints	The joint that occurs between facets of the interior and superior articular processes of adjacent vertebrae. This is the official name for these joints, but the commonly used term is “facet joint”.

Kim, K-T, Lee, S-H, et al. (2006). "Clinical outcomes of 3 fusion methods through the posterior approach in the lumbar spine." Spine 31(12): 1351-7; discussion 1358.

Introduction

The ACC has requested a body of work in seven sections and a proposed methodology which includes evidence-based methods including the reporting of levels of evidence and literature searches carried out to a professional standard.

Additionally the ACCtable 1.7

> *"……..expected that the provider will build wherever possible on systematic reviews, meta-analyses, guidelines and reviews already published rather than reviewing primary sources. For some of the work it is envisaged that the key task is to review other guidelines and draw the evidence findings of others into a single resource. Evidence tables are not required but the level of evidence for the findings should be summarised."*[3]

Causation reviews were required to provide resourceful information in the following areas:

1. **A description**, using standardised nomenclature and classification[4] for the range of changes that occur in the intervertebral disc as people age, to include a descriptive dictionary of Plain X-ray, CT and MRI terms that is likely to meet agreement with ACC's providers.

2. **A descriptive summary** of the known physiology of the ageing disc (to include a short reference to juvenile disc dysfunction).

3. (a) **An evidence based review** of the current knowledge of pain generation in the discs, nerve roots and associated structures of the cervix, thorax and lumbar region (or at least a discussion of their differences), and (b) **an evidence based review** of the current knowledge of pain generation associated with the facet joints and the causes of radicular pain.

4. **An evidence based review** of the current knowledge on how these causes of pain can be modulated which will focus on the effectiveness of use of local steroid and surgery for pain for certain lesions.

5. **A description**, using the terms set out in the descriptive dictionary (see item 1. above), of the likely *causation* and *natural history* of:

   a. Spondylolysis and Spondylolytic Spondylolisthesis (to include a discussion of the effects of these conditions on the unshielded disc space)
   b. Degenerative spondylolisthesis
   c. Synovial cysts/facet joint effusion
   d. Annulus fissure
   e. Spinal stenosis syndromes
   f. Sacralised L5
   g. Disc bar, disc/osteophyte complex and longitudinal ligament.

[3] Supply of resources to ACC; 'Causation reviews; Spinal injuries and diseases'
[4] The following key reference was provided by the ACC which was intended to serve as a focus for this part of the review: Fardon DF, Milette PC: Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine 2001;26(5).

6. **An evidence-based review** of the clinical outcomes of spinal fusion with consequences for adjacent segments (transitional syndrome/upstream disease are some phrases). The focus will be on evidence pertaining to the effectiveness of spinal fusion for the management of spinal lesions on various clinical outcomes.

7. **An evidence-based review** of the effectiveness of spinal fusion and disc replacement treatment with 'return to work' as the outcome.

Using the specific themes and questions provided by the ACC to provide a resource that is in compliance with ACC's legislative mandate[5], the aim of the current report is to provide a summary description of the available evidence pertaining to the standardised nomenclature and classification for describing the range of changes that occurs in the intervertebral discs as people age.

[5] In particular ACC must review each case in the light of the causation or natural history of the condition and decide whether or not it is substantially due to personal injury in which case it may be compensable or to other pathological, non-injury causes including ageing, in which case it may not be compensable. Importantly it is the 'balance of probabilities' in relation to causation that must be considered. The objective is to provide advisors a resource which will assist them to determine whether or not a particular claim is compensable under ACC's legislation.

General methods[6]

This section describes the general methods that apply to the whole report. Methods that are specific to particular sections are described in the section that they apply to. Sections that are particularly long and/or complex have been given their own executive summary.

Outputs

Two different types of outputs were requested:

- Descriptions and/or descriptive summaries (see reports 1,2 and 5)
- Evidence based reviews (see reports 3,4,6 and 7)

Nature of evidence to be included

ACC has requested that only *systematic reviews, clinical guidelines* and other *overviews* be considered in these reviews and briefings. Where systematic reviews, guidelines and overviews did not provide sufficient information to meet ACCs goals the available review evidence was summarised and the limitations noted. Where no systematic reviews, guidelines or overviews were available (e.g. Q5 spinal conditions) selected primary studies formed the evidence source.

Importantly, in order to keep the delivery of the outputs listed above within budget and on-time the *focus will be on the highest quality most recent evidence*.

Wherever possible and appropriate, the research questions were allocated to one of three categories (history, assessment/diagnosis, or treatment). PICO criteria were defined according to the category to which the question belonged. For example, for question number 7 the PICO question was: What is the effectiveness of spinal fusion as compared with disc replacement therapy for patients with low back pain? The PICO criteria for this question are given below, Table 1.

6 For a fuller description of the methods used see the Causation Reviews Protocol.

Table 1 PICO criteria for Question 7 of this review

Patient population	Inclusion: patients with chronic low back pain (lasting longer than 12 weeks) and scheduled for surgery for chronic degenerative disc disease, or for chronic manifestation of disc herniation. No limitation on age, gender or type, location or duration of symptoms. Exclusion: Patients with fractures or tumours.
Intervention	Inclusion: Spinal fusion Exclusion: Other treatment, such as physical therapy, rehabilitation, etc
Comparator	Inclusion: disc replacement Exclusion: Other treatment, such as physical therapy, rehabilitation, etc
Outcomes*	Inclusions: Clinical and/or functional outcomes. Patient centred outcomes will be the primary outcome measures of interest of this question. These will include (but not restricted to): Pain:(including medication use for pain), Overall improvement/satisfaction, Well-being and quality of life: (including daily activity and return-to-work) Secondary outcome measures will include (but not restricted to): Motion segment mobility, General complications Exclusion: not patient-oriented outcomes, such as pure radiological or imaging outcomes.
*The minimal duration of follow-up period of the studies will be 6 months. The short-term follow-up of the outcomes is defined as the period from immediately after the operation to five years and longer. Whereas long term follow-up is defined as longer than five years.	

Searches

A systematic search of the literature for high evidence level studies and overviews (systematic reviews, metaanalyses and clinical guidelines) relating to the conditions of interest was carried out.

The published peer-reviewed medical literature was searched using the following primary sources[7]:

[7] For a full list of literature sources search see the Causation Reviews Protocol.

Table 2 Primary literature sources

Literature source	URL
CINAHL	Via University of Canterbury
EMBASE	http://www.embase.com
GIN	http://www.g-i-n.net
MEDLINE	http://www.ncbi.nlm.nih.gov/pubmed/
Psycinfo	Via University of Canterbury
SIGN	http://www.sign.ac.uk
The Cochrane Library: Systematic Reviews, DARE, HTA, NHS EED	http://www.thecochranelibrary.com
TRIP database	http://www.tripdatabase.co.uk
WHO	http://www.who.int

Search terms (indicative)

The primary searches(s) included the following search terms:

Table 3 Search terms

MeSH (Cochrane Library):	EMTREE	Title/abstract searches:
Intervertebral disk/	Lumbar disk/	Intervertebral NEAR/2 disc*
Intervertebral disk degeneration/	Intervertebral disk/	Intervertebral NEAR/2 disk*
Intervertebral disk displacement/	Lumbar vertebra/	Cervical NEAR/2 disc*
Exp Spinal injuries/	Exp Vertebra/	Cervical NEAR/2 disk*
Exp Spinal Diseases/	Exp Spine Injury/	Cervical NEAR/2 vertebra*
Lumbar vertebrae/	Exp Spine Disease/	Thoracic NEAR/2 disc*
Thoracic vertebrae/	Cervical spine/	Thoracic NEAR/2 disk*
Cervical vertebrae/	Intervertebral disk degeneration/	Thoracic NEAR/2 vertebra*
Differential diagnosis/	Exp Intervertebral disk disease/	Lumbar NEAR/2 disc*
Terminology/nomenclature searches:	Also exp Injury/	Lumbar NEAR/2 disk*
Terminology as topic/	Medical assessment/	Lumbar NEAR/2 vertebra*
Age-related changes searches:	Differential diagnosis/	Trauma*:ti
Aged/	**Terminology/nomenclature searches:**	Terminology/nomenclature searches:
Aging/	Nomenclature/	Terminology
Pain generation:	Disease classification/	Classification
Exp back pain/	**Age-related changes searches:**	Nomenclature
Specific conditions:	Aging/	Lexicon
Exp spondylolysis/ (narrowerterm spondylolisthesis)	**Pain generation:**	Age-related changes searches:
Exp synovial cyst/	Low back pain/	Ageing
Spinal stenosis/	Causation of specific conditions:	Aging
	Exp spondylolisthesis/	Age
	Exp Spondylolysis/	Age-related
	Exp Synovial cyst/	Pain generation:
	Vertebral canal stenosis/	Pain*
	Etiology/	Causation of specific conditions:
	Pathophysiology/	Spondylolysis
	Publication types:	Spondylolisthesis
	Systematic review/	Synovial NEAR/2 cyst*
	Meta analysis/	Spinal NEAR/2 stenosis
	Practice guideline/	Annular NEAR/2 tear*
	Also publication types: review, editorial,	Annulus NEAR/2 tear*
	note, conference review, erratum	Annular NEAR/2 fissure*
		Annulus NEAR/2 fissure*
		Aetiology
		Etiology

MeSH (Cochrane Library):	EMTREE	Title/abstract searches:
		Pathophysiolog*
		Natural NEXT/1 history

Results of the literature search

The initial literature search (March 2011) identified 796 potentially eligible publications, Table 4.

Table 4 Results of the first literature search (March 2011)

Review question	Citations
Q1: Nomenclature and classification	62
Q2: Changes with age	31
Q2: Juvenile disc dysfunction	40
Q3: Pain generation	21
Q3b: causes of radicular pain	13
Q3b: pain generation associated with the facet joints	15
Q4: Treatment of pain and outcomes	128
Q5: Causation and natural history- general	52
Q5a: Causation and natural history - spondylolisthesis	28
Q5a: Causation and natural history - spondylolysis	21
Q5c: : Causation and natural history - synovial cysts/facet joint effusion	10
Q5d: Causation and natural history – annulus fissure	2
Q5e: Causation and natural history – spinal stenosis	27
Q5f: Causation and natural history – sacralised L5	0
Q5g: Causation and natural history – disc bar, disc/osteophyte and LLC	0
Q6: Spinal fusion and adjacent segment disease	21
Q7: spinal fusion vs disc replacement	90
General and unclassified	235
Total	**796**

LLC = longitudinal ligament complex

The material provided by the original search in March 2011, which was limited to overviews systematic reviews, meta-analyses and clinical guidelines failed to provide *did not provide sufficient information to meet ACCs goals* in a number of instances and additional primary studies were sought.

The most serious shortfall in review/overviews was found in material relating to Q5: Spinal conditions, and in September 2001 and May-June 2012 a series of limited sub-searches were carried out to identify primary studies reporting on these conditions, Table 5.

Table 5 Additional searches for primary studies reporting on spinal conditions.

Review question	Citations
Q5 a,b: Causation and natural history – spondylolisthesis, spondylolysis	536
Q5c: : Causation and natural history - synovial cysts/facet joint effusion	335
Q5d: Causation and natural history – annulus fissure	209
Q5e: Causation and natural history – spinal stenosis	106
Q5f: Causation and natural history – sacralised L5	114
Q5g: Causation and natural history – disc bar, disc/osteophyte and LLC	18

Assessing eligibility

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews.

Eligibility was further assessed using criteria supplied by ACC and those identified in the themes and research questions.

Inclusion Criteria

- Study design: systematic reviews, meta-analyses, clinical guidelines and other review/overviews.
- Language: only studies reported in the English language were included.
- Publication dates between 2000 and 2010
- Population: to be determined for each deliverable.
- Types of interventions: as indicated by ACC and determined for each deliverable
- Types of outcome: as indicated by ACC and determined for each deliverable.

Exclusion Criteria

To be determined for each deliverable but citations may be excluded for the following reasons:

- Not a clinical study: including case reports and animal studies,
- Studies not deemed appropriate to the research question or nature of the review
- Wrong patient group: does not include the correct patient group
- Wrong intervention: does not include the correct intervention/s
- Wrong outcomes: does not include the results relating to at least one of the identified outcomes of interest
- Non-comparative studies [if applicable].

Assessment of the quality of the evidence

A number of validated tools were available for the assessment of the quality of systematic reviews and clinical guidelines. Four tools for the assessment of the quality of systematic reviews were considered for the current reviews:

- NHMRC checklist
- Scottish Guidelines group (SIGN) checklist
- NHS Public Health Resource Unit UK (CASP) checklist
- Cochrane endorsed PRISMA checklist

Fewer tools have been developed for the appraisal of clinical guidelines, two of the most well known were considered for the current reviews:

- NHMRC Evidence Statement checklist
- The Appraisal of Guidelines for Research and Evaluation instrument (AGREE)

The SIGN[8] criteria for the assessment of systematic reviews and the AGREE[9] criteria for the assessment of guidelines were considered to be the quality tools that would best serve the aims and objectives of this project (see Causation Reviews Protocol for further details/checklists) . Other reviews/overviews were not assessed for quality and were designated as "expert opinion"

References

Publications identified in the search procedure for the current review together with significant publications identified through pearling references from retrieved articles are cited the bibliography at the end of this report. Other relevant references quoted to support particular statement in the reviewed studies are *referenced in footnotes*.

[8] http://www.sign.ac.uk/pdf/sign50annexc.pdf
[9] http://www.agreetrust.org/

Section 1: Nomenclature and classification

A description, using standardised nomenclature and classification[10] for the range of changes that occur in the intervertebral disc as people age, to include a descriptive dictionary of Plain X-ray, CT and MRI terms that is likely to meet agreement with ACC's providers.

[10] The following key reference was provided by the ACC which was intended to serve as a focus for this part of the review: Fardon DF, Milette PC: Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine 2001;26(5).

Imaging terms and planes

Anatomical planes used in imaging include:

- Sagittal plane: a vertical plane which passes from front to rear dividing the body into right and left sections. The sagittal plane is also called the lateral plane.
- Coronal or frontal plane: divides the body into dorsal and ventral (back and front, or posterior and anterior) portions.
- Transverse plane: divides the body into cranial and caudal (head and tail) portions. The transverse plane is also known as the axial plane, cross-section horizontal plane or transaxial plane. It is an imaginary plane that divides the body into superior and inferior parts. It is perpendicular to the coronal and sagittal planes.

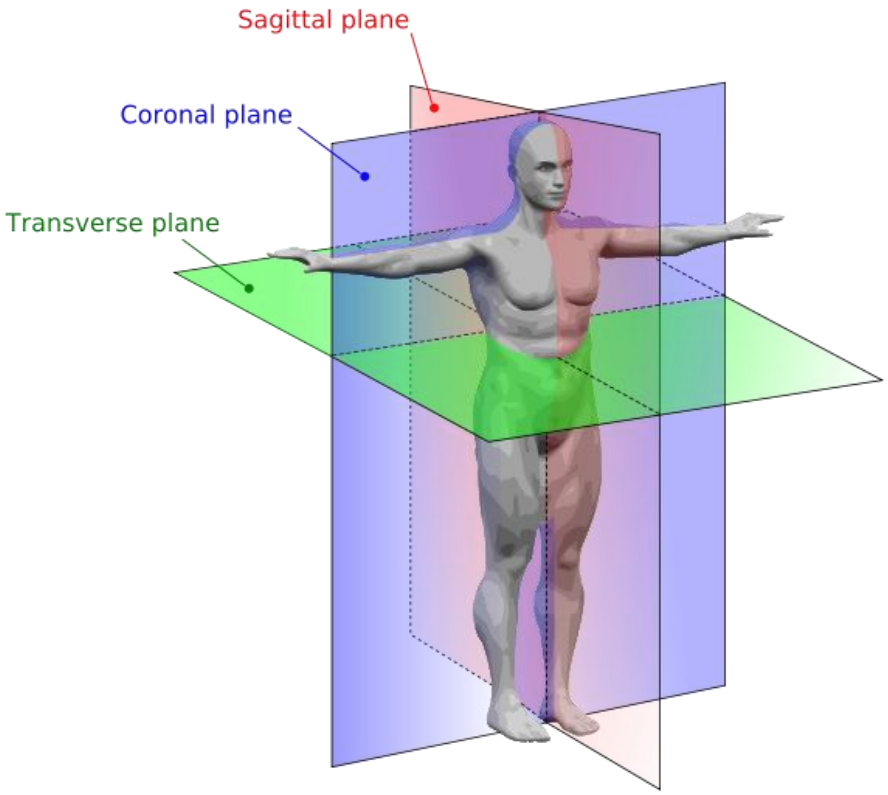

Figure 1.1 The three main planes of the human body.

Main anatomical terms of location include:

- ***Superior***: nearer to head, synonymous with the term *cranial*
- ***Inferior***: nearer to feet, synonymous with the term *caudal*
- ***Anterior***: nearer to front,
- *Posterior*: nearer to back,
- ***Medial***: nearer to median plane

- ***Lateral***: further from medial plane
- *Proximal*: nearer to trunk/centre or point of origin – closer to root of limb/region
- *Distal*: further from trunk/centre or point of origin – away from root of limb/region

Introduction

The ACC has requested a body of work entitled "Causation Reviews: spinal injury and disease" to be reported in seven sections each reviewing one or more specific themes or questions. It is intended that this body of work will provide a resource that is in compliance with ACC's legislative mandate[11].

This first section comprises a description, using standardised nomenclature and classification[12],of the range of changes that occurs in the intervertebral disc with age. The review is required to include a descriptive dictionary of Plain X-ray, CT and MRI terms that is likely to meet agreement with ACC's providers.

The following key reference was provided by the ACC to serve as a focus for this first section of the work:

"Fardon DF, Milette PC: Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine 2001;26(5)."

[11] In particular ACC must review each case in the light of the causation or natural history of the condition and decide whether or not it is substantially due to personal injury in which case it may be compensable or to other pathological, non-injury causes including ageing, in which case it may not be compensable. Importantly it is the 'balance of probabilities' in relation to causation that must be considered. The objective is to provide advisors a resource which will assist them to determine whether or not a particular claim is compensable under ACC's legislation.

Methods[13]

This first report comprises a descriptive analysis and summary of a standardised nomenclature and classification for the reporting of injury and ageing in the intervertebral disc. The descriptive reports in this body of work (sections 1,2 and 5) required slightly different methods and approaches to that of the evidence-based reviews (sections 3,4,6 and 7) and are not intended to be systematic reviews or critical appraisals of the literature.

ACC has requested that only *systematic reviews, clinical guidelines* and other *overviews* be considered in these descriptive reviews and evidence briefings. Where systematic reviews, guidelines and overviews did not provide sufficient information to meet ACCs goals, the available evidence was (a) summarised and the limitations noted, or (more rarely) (b) key primary studies were examined for relevant data/information.

Following a systematic search[14] of the major relevant bibliographic databases (including MEDLINE, EMBASE, CINAHL and PSYCINFO), 62 of an original 789 citations were considered potentially relevant to the current section reporting on nomenclature and classification. Following an examination of the titles and abstracts of these publications, 21 articles contributed to the following descriptive review (see references at the end of the document for details).

The most recent and/or relevant guidelines and systematic reviews reporting on the nomenclature and classification and grading of non-infectious intervertebral disc abnormalities were Fardon & Milette (2001) and Kettler and Wilks (2006) (Fardon & Milette, 2001; Kettler & Wilke, 2006); both are summarised in this report. A further pictorial review of neuroimaging of spinal diseases by Kasdan et al (2008) and relevant works published by Vernon-Roberts, Milette, Pfirrmann and Boos (Boos et al., 2002; P. C. Milette, 2000, 2001; Pfirrmann, Metzdorf, Zanetti, Hodler, & Boos, 2001; Vernon-Roberts, Moore, & Fraser, 2007) also contributed significantly to this section.

[13] A more detailed description of all the methods of the seven reviews can be found in the General Methods section and in the Causation Reviews Protocol.
[14] For a fuller description of the searches and sources used see the Causation Reviews Protocol and the separate scope and methods summary report.

Background

Intervertebral disc (IVD) terminology has been a cause of confusion and controversy. Different observers have used a number of different terms for the same disc abnormality (Murtagh, 2007). Uniformity of classification is essential to compare research results and for effective communication between the professional groups who deal with spinal problems (P. C. Milette, 2000). Many of these groups have expressed a need to standardise the terms and classifications used in the reporting of normal and pathologic conditions of the IVD and, in particular, those terms used in reporting MRI imaging of the lumbar spine (W. Bailey, 2005; W. M. Bailey, 2006); the requirement is for terms and classifications that can be interpreted ***accurately***, ***consistently,*** and with reasonable *precision* (Fardon & Milette, 2001).

The first peer-reviewed proposal of a specific imaging terminology for IVD abnormalities using well defined ***morphological terms*** was published in 1994 (Jensen at al 1994). The focus of this work was on the description of the findings on MRI of the lumbosacral spine in people ***without back pain*** and the determination of the prevalence of abnormal discs. The terms used to classify disc margins were normal[15], bulge, protrusion and extrusion. This terminology for the description of the disc margins was developed to facilitate more precise reporting than the non-specific term "herniation".

Formal criteria to define these terms, however, were not developed and the term "herniation" remained in common use for most disc abnormalities (Murtagh, 2007). In 1995, a multidisciplinary task force from the North American Spine Society (NASS) addressed deficiencies in standardization and practice of the language defining conditions of the lumbar disc. Detailed recommendations for standardization were made[16], however, the work was considered to be deficient in some areas, and superficial in others. It was ***not endorsed by major organizations and was not recognized as authoritative by radiology organizations***. It did however stimulate further work (Fardon, 2002).

In 1999 a joint task force was formed comprising North American Spine Society (NASS), the American Society of Neuroradiology (ASNR), and the American Society of Spine Radiology (ASSR). This task force charged themselves with addressing the remaining needs, and securing endorsement sufficient to result in universal standardization. The task force reported their results in 2001 in an article entitled:

"Nomenclature and Classification of Lumbar Disc Pathology: Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology" *(Fardon & Milette, 2001)*

By 2003 the recommendations had been officially supported, endorsed or web-linked by the following ***American and European*** professional organizations and scientific societies:

- American Academy of Orthopaedic Surgeons (AAOS)
- American Academy of Physical Medicine and Rehabilitation (AAPM&R)
- American College of Radiology (ACR)

[15] Only 36% of subjects studies were reported to have a "normal" disc at all levels.
[16] Fardon DF, Herzog RJ, Mink JH, et al. Nomenclature of lumbar disc disorders. In: Garfin SR, Vaccaro AR, edsOrthopaedic Knowledge Update—Spine. Rosemont, IL: American Academy of Orthopaedic Surgeons, 1997: A3-A14

- American Society of Neuroradiology (ASNR)
- American Society of Spine Radiology (ASSR)
- Joint Section on Disorders of the Spine and Peripheral Nerves of the American
- Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)
- European Society of Neuroradiology (ESNR)
- North American Spine Society (NASS)
- Physiatric Association of Spine, Sports and Occupational Rehabilitation (PASSOR)

The focus of the task force's work was the *lumbar spine*, however it was noted that the principles and most of the definitions of the recommendations could be easily extrapolated to the cervical and dorsal (thoracic) spine.

The task force made every attempt to ensure that in the recommendations the definitions of diagnoses should not (a) define or imply external etiologic events such as *trauma*, (b) imply relationship to *symptoms*, or (c) need for specific *treatment.*

Descriptive dictionary

The following descriptive dictionary of agreed nomenclature for description of the main categories of non-infectious disc abnormalities is taken primarily from the work of Fardon and Milette) (Fardon & Milette, 2001) which defines and describes

- The normal disc
- Annular Tears/Fissures
- Disc Degeneration
- Herniated Disc
- Protruded Discs
- Extruded Discs
- Containment/Continuity
- Volume and Composition of Displaced Material
- Location.

The work of the task force was underpinned by the earlier works of both Fardon and Milette. Where appropriate and/or where clarification was required these earlier works were consulted (Denaro, Papalia, Denaro, Di Martino, & Maffulli, 2009; Fardon, 2002; Fardon & Milette, 2001; P. C. Milette, 2000, 2001). Additional information was also sought through personal communication with David Fardon (Appendix B)

The American Journal of Neuro-Radiology (AJNR) nomenclature guidelines

The AJNR guidelines entitled " Nomenclature and Classification of Lumbar Disc Pathology: Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology" (Fardon & Milette, 2001) have been described as "complex and comprehensive" (W. M. Bailey, 2006). The recommendations present diagnostic categories and subcategories, intended for the classification and the reporting of imaging studies. The diagnostic categories are based on pathology and include normal discs, congenital and development variation, degenerative/traumatic lesions (annular tears, herniation) and degeneration (spondylosis deformans and intervertebral osteochondrosis), inflammation/infection, neoplasia and morphological variants of unknown significance, (Fardon & Milette, 2001). Definitions of these categories are given in Table 1.1

Table 1.1 The AJNR Guidelines category definitions (Fardon & Milette, 2001)

Category	Definition
The normal disc	"....young discs that are morphologically normal, without consideration of the clinical context and not inclusive of degenerative, developmental, or adaptive changes that could, in some contexts (e.g., normal aging, scoliosis, spondylolisthesis) be considered clinically normal."
Congenital and development variants	"....discs that are congenitally abnormal or that have undergone changes in their morphology as an adaptation to abnormal growth of the spine such as from scoliosis or spondylolisthesis."
Degenerative/traumatic lesions	"........a broad category that includes subcategories of Annular Tear; Herniation; and Degeneration. Characterization of this group of discs as Degenerative/Traumatic does not imply that trauma is necessarily a factor or that degenerative changes are necessarily pathologic as opposed to the normal aging process."
Inflammation/ infection	".....infection, infection-like inflammatory discitis, and inflammatory response to spondyloarthropathy. It also includes inflammatory spondylitis of subchondral endplate and bone marrow manifested as Modic Type 1 magnetic resonance imaging (MRI) changes and usually associated with pathologic changes in the disc."
Neoplasia	".....primary or metastatic morphologic changes of disc tissues caused by neoplasia are categorized as Neoplasia, with subcategorization for appropriate specificity."
Morphologic Variant of Unknown Significance	"Instances in which data suggest abnormal morphology of the disc but are not complete enough to warrant a diagnostic categorization."

Note: Each diagnostic category can be subcategorized to various degrees of specificity according to the information available and purpose to be served. The data available for categorization may lead the reporter to characterize the interpretation as "possible," "probable," or "definite."

The following illustrated dictionary covers the agreed terminology relating to two of the categories above, "*the normal disc*" and '*degenerative/traumatic lesions*". The glossary provided by the task force to accompany their work is reproduced at the beginiong of this section.

Nomenclature and definitions of the main categories of noninfectious disk abnormalities

Fardon et al (2001) produced an illustrated narrative of an agreed nomenclature for the description of lumbar disc pathology (Fardon & Milette, 2001), the general sequence of the terms and entities described and defined is given in **Table 1.2**

Table 1.2. Summary of the ANJR nomenclature system adapted from (Parizel, Van Goethem, Ozsarlak, & De Schepper, 2003)

General terminology	Definition	Specification I	Specification II	Definition
Normal	Young discs that are morphologically normal, without consideration of the clinical context..			
Annular tears and fissures	Separations between annular fibers, avulsion of fibers from their vertebral body insertions, or breaks through fibers involving one or many layers of the annular lamellae.	Radial fissures Transverse fissures Concentric fissures		
Bulging	Displacement of over 50% of the periphery of the disc,			
Herniation	Localized displacement (<50% of the periphery of the disc).	Focal (<25%) OR broad based (25-50%).	Protrusion	=no extrusion
			Extrusion	Distance of the edge of the herniated material > disc height OR hernia base.
			Sequestration (= a special form of extrusion)	No continuity with parent disc.

Fardon et al (2001) prefaced their recommendations for a standard nomenclature for lumbar disc pathology with the following statement:

"Because there is confusion in differentiation of changes of pathologic degenerative processes in the disc from those of normal aging, the classification category "Degenerative/Traumatic" includes all such changes, thus does not compel the observer to differentiate the pathologic from the normal consequences of aging. However, this model allows the observer with adequate data to present a more enlightening report by making such a distinction, with appropriate notation of the degree of confidence." (Fardon & Milette, 2001).

The "normal young disc" has been used by the task force as a reference point for the descriptive nomenclature of disc abnormalities, however, the resulting classification has not been otherwise related to the age of the disc; this has been seen by some as a weakness of the AJNR guidelines .

The young normal disc

"Normal" in this context defines young discs that are ***morphologically*** normal, without consideration of the clinical context and not inclusive of degenerative, developmental, or adaptive changes that could, in

some contexts (e.g., normal aging, scoliosis, and spondylolisthesis) be considered clinically normal. Thus categorization of a disc as "normal" means the disc is fully and normally developed and free of any changes of disease, trauma, or aging. Only the morphology, and not the clinical context, is considered.

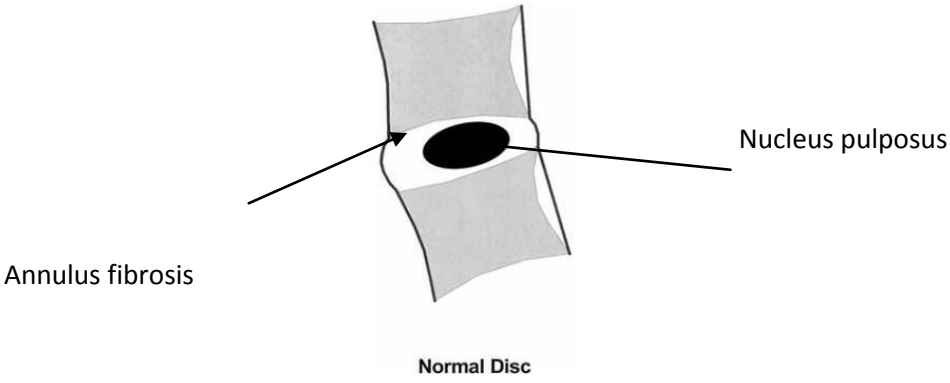

Figure 1.2. Schematic sagittal anatomical section of a "normal" disc. Note: nuclear material is shown in black, and the annulus (internal and external corresponds to the white portion of the intervertebral space. The same convention is used in all the figures in this section (Fardon & Milette, 2001).

In common practice, people with a variety of harmless congenital or developmental variations of discs, minor bulging of annuli, anterior and lateral marginal vertebral body osteophytes, etc. are normal people. By this nomenclature and classification, however, such individual discs are not considered "normal." Therein lays a significant difference of this nomenclature from what many would consider common practice. ***Some people are clinically "normal" even though they have morphologically abnormal discs***. For example, the bilocular appearance of the adult nucleus (see schematic figure below) resulting from the development of a central horizontal band of fibrous tissue is considered a sign of ***normal maturation.***

Figure 1.3. Schematic sagittal anatomical section of an "normal ageing disc" (Milette 1997) or Spondylosis deformans (Fardon et al 2001).

Degenerative/traumatic changes

Degenerative and/or Traumatic changes in the disc are included in a broad category that includes subcategories of Annular Tear; Herniation; and Degeneration (Fardon & Milette, 2001). Degeneration may include any or all (real or apparent) of the following;

- desiccation
- fibrosis
- narrowing of the disc space
- diffuse bulging of the annulus beyond the disc space
- extensive fissuring (i.e., numerous annular tears)
- mucinous degeneration of the annulus,
- defects and sclerosis of the endplates,
- osteophytes at the vertebral apophyses.

A disc demonstrating ***one or more*** of these degenerative changes can be further allocated to one of two subcategories:

- spondylosis deformans , possibly representing changes in the disc associated with a normal aging process
- intervertebral osteochondrosis, possibly the consequences of a more clearly pathologic process

Note: For classification purposes, in the following definitions, the intervertebral disc is considered as a two -dimensional round or oval structure having four 90° quadrants.

Intervertebral disc quadrants

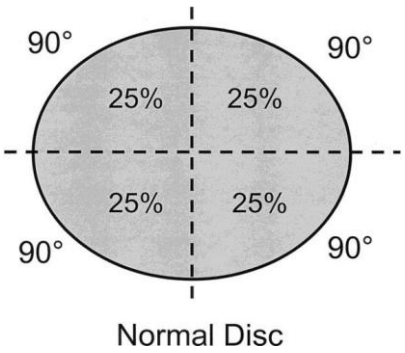

Figure 1.4. Disc quandratnts

The bulging disc

Symmetrical presence (or apparent presence) of disc tissue “circumferentially” (50–100%) beyond the edges of the ring apophyses may be described as a “bulging disc” or “bulging appearance” and is ***not considered a form of herniation,*** nor are diffuse adaptive alterations of disc contour secondary to

adjacent deformity as may be present in severe scoliosis or spondylolisthesis. Furthermore, "bulging" is a ***descriptive term for the shape of the disc contour and not a diagnostic category.***

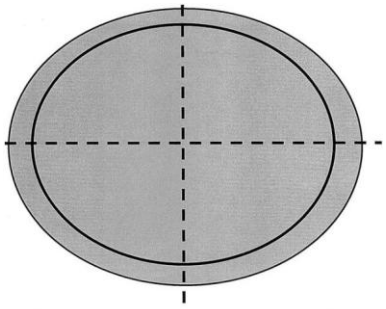

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Figure 1.5. Schematic axial anatomical section of a symmetrical bulging disc: presence or apparent presence of disc tissue circumferentially (50-100%) beyond the edges of the ring apophyses (Fardon & Milette, 2001)

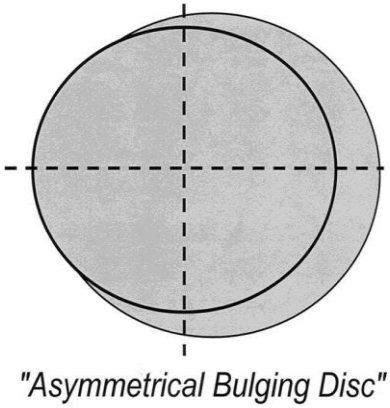


Figure 1.6. A Schematic axial anatomical section of asymmetrical bulging of the disc margin (50-100%) (Fardon & Milette, 2001)

Milette (1997), in a discussion about terminology for the reporting of lumbar disc disorders observed that:

"It is important to realize that the appearance of a diffuse "circumferential" disk bulging on a CT or MR axial section constitutes a visual finding requiring the elaboration of a differential diagnosis (Table 1). A bulging disk is not a pathologic entity, and I agree with Nachemson that this term should not be offered as a diagnosis in radiologic reports."

He went on to describe the ***differential diagnoses*** of a bulging disc on CT or MR axial sections as:

- normal anatomical variant

- illusion caused by a volume-averaging effect
- normal aging disc remodelling related to vertebral body osteoporosis
- pathological disc degeneration (deteriorated collapsed disc)
- posterior disc rupture with subligamentous herniation.

Annular Tears/Fissures

The term "tear" is used to refer to a localized radial, concentric, or horizontal disruption of the annulus without associated displacement of disc material beyond the limits of the intervertebral disc space.

Annular tears (also properly called ***annular fissures)*** are separations between annular fibers, avulsion of fibers from their vertebral body insertions, or breaks through fibers that extend (a) radially, (b) transversely, or (c) concentrically and involving one or many layers of the *annular lamellae (annulus fibrosus).*

Anular Tear

Figure 1.7. Schematic sagittal anatomical section showing a radial annular tear/fissure (Fardon & Milette, 2001).

There is general agreement about the various ***for****ms* of loss of integrity of the annulus, such aa radial, transverse, and concentric separations. It has been recommended that such lesions be termed "fissures" rather than "tears," primarily for fear that the word "tear" could be misconstrued as implying a traumatic aetiology. However, a clear preference has been shown, among authors of various disciplines, for the term "tear," and there is frequent synonymous use in the same articles of the terms "tear" and "fissure".

Given this Fardon et al (Fardon & Milette, 2001) determined that:

"In this instance, it is unwise to recommend contrary to ingrained common usage but wise to reiterate the caveat that the term "annular tear" does not imply traumatic etiology. In the case where a single, traumatic event is clearly the source of loss of integrity of a formally normal annulus, such as with documentation and findings of violent distraction injury, the term "rupture" of the annulus is appropriate, but use of the term "rupture" as synonymous with commonly observed tears or fissures is contraindicated. In conclusion, therefore, "annular tear" and "annular fissure" are both acceptable

terms, can be used properly as synonyms, and do not imply that a significant traumatic event has occurred or that the etiology is known."

Although *some tears* may have ***clinical relevance***, others may be *asymptomatic* and *inconsequential components of the aging process*. Correlation of the characteristics of the tear with responses to discography[17]and other clinically relevant observations may enable the observer to make such distinctions; however, Fardon et al (2001) considered such a distinction *beyond the scope* of their morphologically based definition and classification model.

Overall, the AJNR guidelines (Fardon & Milette, 2001) say little about tears or fissures and does not provide schematic figures to illustrate the different types of tears/fissures. The earlier precursor publications of Milette (Denaro et al., 2009; P. C. Milette, 2000, 2001) are not much more enlightening. Milette (1997) noted that discography was more sensitive than MR imaging for detecting radial annular tears, however, a definite loss of central disk signal intensity, on T2-weighted MR images could be accepted as evidence of the presence of a major tear involving the outer annulus i.e. an annular tear.

The most quoted work on disc tears is that of Vernon-Roberts (Nasca, 2009; Vernon-Roberts et al., 2007). This work has not, to our knowledge, gained universal acceptance and is not included here, however an illustrated summary of this work can be found in Appendix A.

The herniated disc

The herniated disc may be described in relation to

- Morphology – protrusion, extrusion, intravertebral herniation
- Containment
- Continuity
- Relation with PLL complex
- Volume
- Location

The term "herniated disc," as defined in the ANJR guidelines (Fardon & Milette, 2001) refers to *localized displacement of nucleus, cartilage, fragmented apophyseal bone, or fragmented annular tissue beyond the intervertebral disc space* (disc space, interspace). The interspace is defined, craniad and caudad, by the vertebral body endplates.

"The term end plate refers to the entire surface of the vertebral body, and includes both the central cartilaginous plate and the peripheral ring epiphysis. The qualifier normal, in reference to the peripheral margin of the disk, is important and is meant to refer to the initial or original limits of the adult intervertebral space, exclusive of any osteophytes that may have developed. This initial boundary may have been modified by the presence of vertebral body osteophytes. A chronic localized displacement of

[17] Discography has proved to be a controversial procedure. In a guideline and systematic review by Resnick et al (2005) discography was found to be a sensitive but not specific test and not recommended as a standalone test for treatment decisions in patients with low back pain. More recently, Carragee et al (2009) added to the already considerable literature in a study which suggested that discography could accelerate disc degeneration, disc herniation, loss of disc height and signal and the development of reactive endplate changes compared to match-controls. Further discussion of this procedure is outside the remit of this review. (E. J. Carragee et al., 2009; Resnick et al., 2005b)

disk material accompanied by marginal localized vertebral body osteophytes still qualifies as a disk herniation. The bony end plates also delineate the upper and lower boundaries of the normal intervertebral disk, and displacement of disk material inside a vertebral body through a break in the end plate may be properly named an intravertebral disk herniation." (P. C. Milette, 2001)

By convention, a herniation is a "localized" process involving less than 50% (180°) of the disc circumference. The interspace is defined, peripherally, by the edges of the vertebral ring apophyses, exclusive of osteophytic formations.

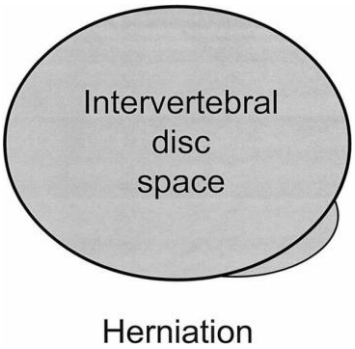


Figure 1.8. Schematic representation of a localized extension of disc material beyond the intervertebral disc space, in a left posterior direction, which qualifies as a disc herniation (Fardon & Milette, 2001).

Localized displacement in the axial (horizontal) plane can be "focal" signifying less than 25% of the disc circumference.

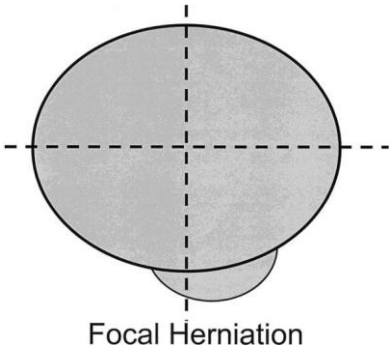


Figure 1.9. Schematic representation of a focal extension of disc material beyond the intervertebral disc space (Fardon & Milette, 2001).

Displacement may also be “broad-based,” by convention involving between 25 and 50% of the disc circumference.

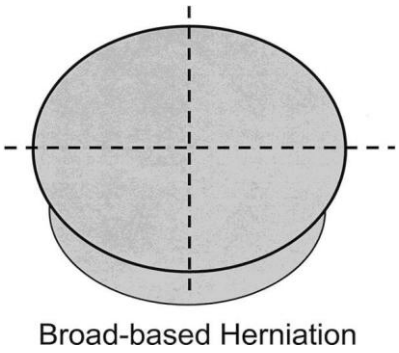


Figure 1.10. Schematic representation of a broad-based extension of disc material beyond the intervertebral disc space (Fardon & Milette, 2001)

Protrusions and extrusions

Herniated discs may take the form of a ***protrusion*** or ***extrusion***, based on the shape of the displaced material.

A disc **protrusion** is present if the greatest distance, in any plane, between the edges of the disc material beyond the disc space, is less than the distance between the ***edges of the base***, in the same plane. The base is defined as the cross-sectional area of disc material at the outer margin of the disc space of origin, where disc material displaced beyond the disc space is continuous with disc material within the disc space. In the cranio-caudal direction, the length of the base cannot exceed, by definition, the height of the intervertebral space.

A B

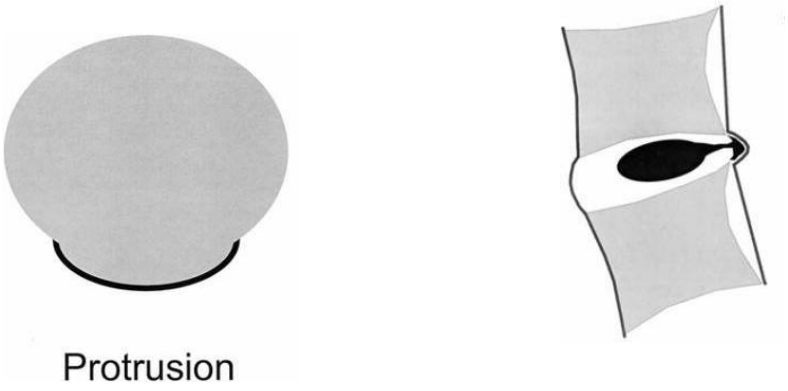


Figure 1.11. Schematic representation of a disc protrusion in axial (A) and sagittal (B) sections (Fardon & Milette, 2001)

A disc **extrusion** is present when, in at least one plane, any one distance between the edges of the disc material beyond the disc space is greater than the distance between the edges of the base, or when no continuity exists between the disc material beyond the disc space and that within the disc space.

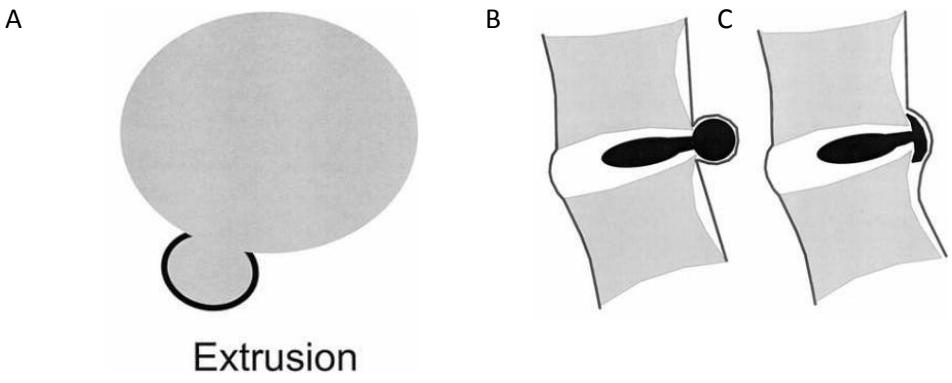


Figure 1.12. Schematic representation of a disc protrusion in axial (A) and sagittal (B and C) sections. In C, although the shape of the displaced material is similar to that of a protrusion, the greatest cranio-caudal diameter of the fragment is greater than the cranio-caudal diameter of its base at the level of the parent disc (Fardon & Milette, 2001).

When a ***relatively large amount*** of disc material is displaced, distinction between protrusion and extrusion will generally only be possible on sagittal magnetic resonance (MR) sections or sagittal computed tomography (CT) reconstructions.

Note: The use of the distinction between "protrusion" and "extrusion" is optional and some observers may prefer to use, in all cases, the more general term "herniation." Further distinctions can often be made regarding containment, continuity, volume, composition, and location of the displaced disc material.

Sequestration

Extrusion may be further specified as **sequestration,** if the displaced disc material has lost completely any continuity with the parent disc.

Figure 1.13. Schematic representation (sagittal section) of subligamentous herniation with downward migration of disc material and sequested fragment (arrow) (Fardon & Milette, 2001).

Migration

The term **migration** may be used to signify displacement of disc material away from the site of extrusion, regardless of whether sequestrated or not.

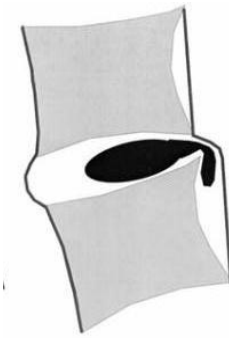


Figure 1.14. Schematic representation (sagittal section) of subligamentous herniation with downward migration of disc material under the posterior longtitudinal liagament. Sagittal section (Fardon & Milette, 2001).

Because posteriorly displaced disc material is often constrained by the posterior longitudinal ligament (PLL) , images may portray a disc displacement as a *protrusion on axial sections and an extrusion on sagittal sections*, in which cases the displacement should be considered an extrusion.

Herniated discs in the cranio-caudal (vertical) direction through a break in the vertebral body endplate are referred to as ***intravertebral herniations***.

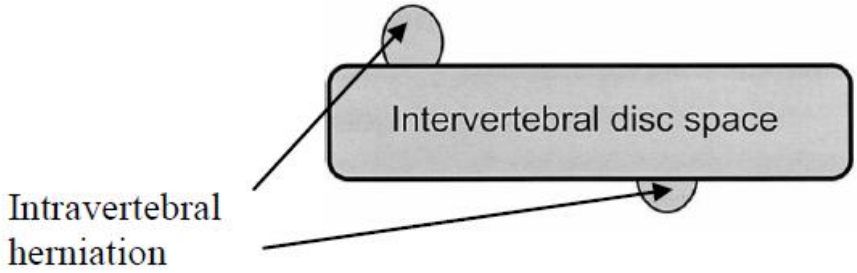


Figure 1.15. Schematic representation of two intravertebral herniations, one with an upward and one with a downward orientation with respect to the disc space (Fardon & Milette, 2001).

Further specification of disc herniations

Disc herniations may be further specifically described as contained, if the displaced portion is covered by outer annulus, or uncontained when any such covering is absent. Displaced disc tissues may also be described by volume, content, location, and relationship to the posterior longitudinal ligament.

Containment

*C*ontainment refers to the integrity of the outer annulus covering the disc herniation. The displaced disc tissues are wholly held within an intact outer annulusnn. A disc with a "contained" herniation would ***not leak*** into the vertebral canal fluid that has been injected into the disc. Although the posterior longitudinal ligament and/or peridural membrane may partially cover extruded disc tissues, such discs are not considered "contained" unless the outer annulus is intact***. The technical limitations of currently available non-invasive imaging modalities (CT and MRI) usually preclude the distinction of a contained from an uncontained disc herniation.***

Continuity

Displaced disc fragments are sometimes characterized as "free." A "free fragment" is synonymous with a "sequestrated fragment" and not the same as "uncontained," as the latter refers only to the integrity of the outer annulus and has no inference as to the continuity of the displaced disc material with the parent disc. A fragment should be considered "free," or "sequestrated," only if there is no remaining continuity of disc material between it and the disc of origin. A "migrated" disc or fragment: refers to displacement of disc material away from the opening in the annulus through which the material has extruded. Some migrated fragments will be sequestrated, but the term migrated refers only to position and not to continuity.

Referring to the posterior longitudinal ligament (PLL), some authors have distinguished displaced disc material as "subligamentous," "extraligamentous," "transligamentous," or "perforated." When the distinction between the outer annulus and the PLL is unclear and a fragment is under such a blended structure (sometimes called "capsule"), it has been called "subcapsular." If the peridural membrane alone surrounds the displaced disc material, the displacement is sometimes called "submembranous."

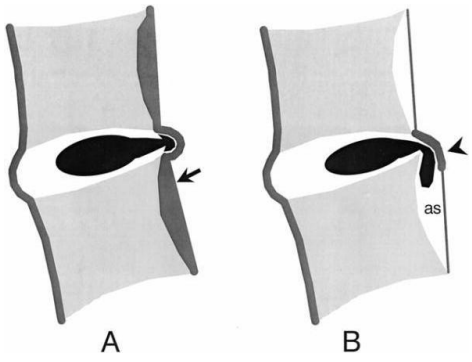


Figure 1.16. Schematic representation of the relationship of typical posterior disc herniations to the posterior longitudinal ligament. A. Midline sagittal section. B. Sagittal para -central section (Fardon & Milette, 2001)

Unless very large, a posterior midline herniation usually remains entrapped underneath the deep layer of the PLL and sometimes a few intact outer annulus fibers joining with the PLL to form a "capsule." The deep layer of the PLL (see arrow in A above) also attaches to the posterior aspect of the vertebral body so that no potential space is present underneath. The PLL may extend laterally at the disc level (see

arrowhead in B above) but, above and below the disc, an anterior epidural space (as in B above), where disc fragments are frequently entrapped, is present between the lateral (peridural) membranes and the posterior aspect of the vertebral bodies.

Such permutations of continuity, containment, and relationships to ligaments and membranes are refinements that may suit certain purposes *but do not supersede the basic definition of disc herniation and the major subcategorizations of extrusion and protrusi*on.

Volume

A scheme to define the ***degree of canal compromise*** produced by disc displacement should be practical, objective, reasonably precise, and clinically relevant. A simple scheme that fulfils the criteria and utilizes measurements taken from an ***axial section at the site of the most severe compromise*** is given below;

- Canal compromise of less than one third of the canal at that section is “mild”;
- Canal compromise between one and two thirds is “moderate”
- Canal compromise over two thirds is “severe.”

The same grading can be applied for foraminal involvement.

Such characterizations of volume describe only the cross- sectional area at one section and do not account for total volume of displaced material, proximity to, compression and distortion of neural structures, or other potentially significant features, which the observer may further detail by ***narrative description.***

Composition of Displaced Material

The composition of displaced material may be characterized by such terms as;

- nuclear
- cartilaginous
- bony
- calcified
- ossified
- collagenous
- scarred
- desiccated
- gaseous
- liquefied

The *clinical significance* related to the observation of volume and composition depends on correlation with clinical data and *cannot be inferred from morphologic data alone*. Permutations of continuity,

containment, and relationships to ligaments and membranes are refinements that may suit certain purposes *but do not supersede the basic definition of disc herniation and the major sub categorizations of extrusion and protrusion*

Location

Anatomic “zones” and “levels” may be defined using the following landmarks: medial edge of the articular facets; medial, lateral, upper, and lower borders of the pedicles; and coronal and sagittal planes at the centre of the disc. On the axial plane, these landmarks determine the boundaries of the “central zone,” the “subarticular zone”, the “foraminal zone”, the “extraforaminal zone”, and the “anterior zone” respectively. On the sagittal (craniocaudal) plane, they determine the boundaries of the “disc level,” the “infra-pedicular level,” the “pedicular level,” and the “supra-pedicular level,” respectively.

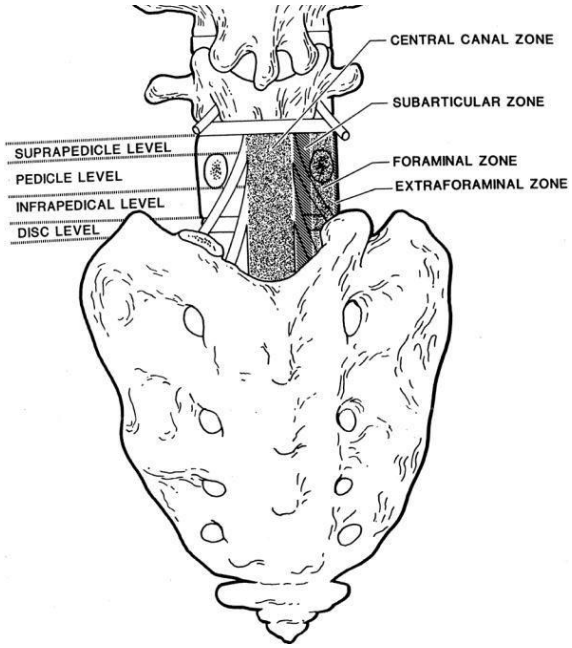


Figure 1.17. Coronal drawing illustrating the main anatomic “zones” and levels relating to the intervertebral disc (Fardon & Milette, 2001)

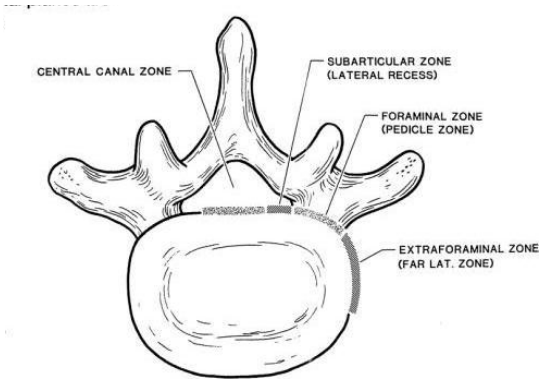


Figure 1.18. Axial image and schematic representation of the anatomic "zones" . The sagittal and parasagittal planes are call zones in the axial image (Fardon & Milette, 2001).

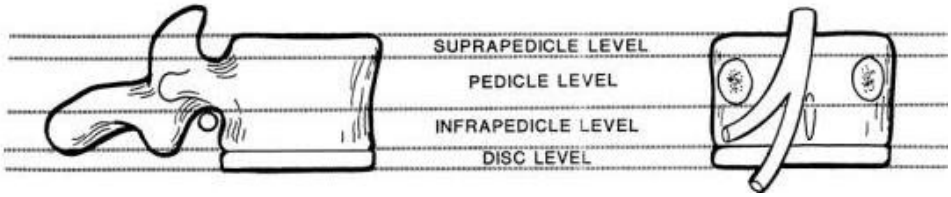


Figure 1.19. Schematic representation of the anatomic "levels" identified on cranio-caudal images (Fardon & Milette, 2001).

Moving from central to right lateral in the axial (horizontal) plane, location may be defined as;

- central
- right central
- right subarticular
- right foraminal
- right extraforaminal.

The term "paracentral" is considered to be less precise than defining "right central" or "left central," but is useful in describing groups of discs that include both, or when speaking informally when the side is not significant.

For reporting of image observations of a specific disc, "right central" or "left central" should supersede use of the term "paracentral."

The term “far lateral” is sometimes used synonymously with “extraforaminal.”

In the sagittal plane, location may be defined as “discal,” “infra-pedicular,” “supra-pedicular,”or “pedicular.” In the coronal plane, “anterior,” in relationship to the disc, means ventral to the midcoronal plane of the centrum.

The ageing process

The task force considered that perceptions of what constitutes the normal aging process of the spine had been greatly influenced by postmortem anatomic studies involving a limited number of specimens, harvested from cadavers from different age groups, with unknown past medical histories, and the presumption of absence of lumbar symptoms.

They suggested that with such methods, pathologic changes were easily confused with the consequences of normal aging. In this context the differentiating features of two degenerative processes involving the intervertebral disc were briefly highlighted spondylosis deformans which affects essentially the annulus fibrosus and adjacent apophyses and intervertebral osteochondrosis which affects mainly the nucleus pulposus and the vertebral body endplates, but also includes extensive fissuring (numerous tears) of the annulus fibrosus, which may be followed by atrophy.

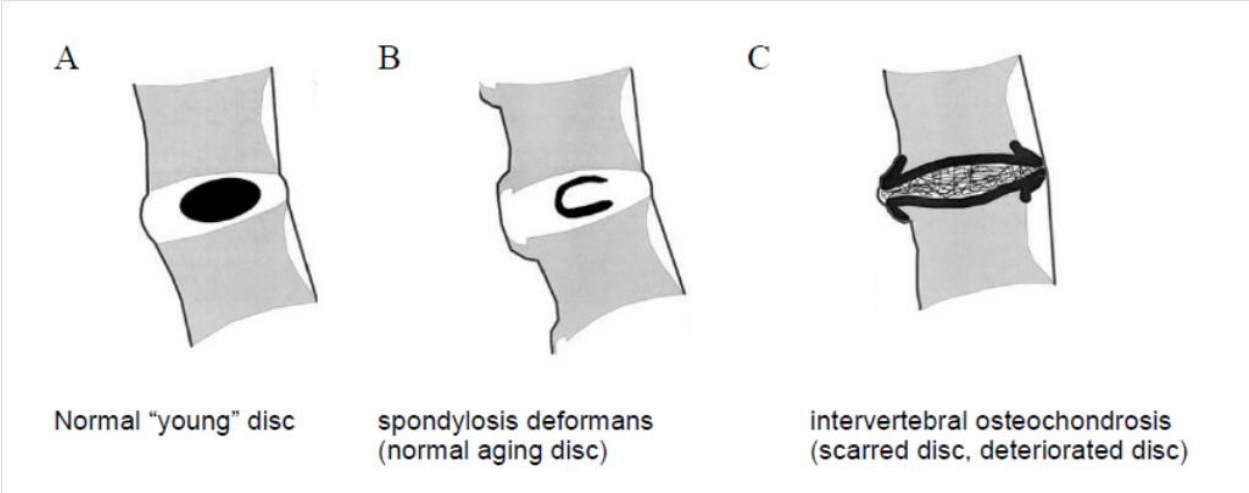


Figure 1.20. Schematic sagittal anatomic sections showing the differentiating characteristics of the normal disc, spondylosis deformans, and intervertebral osteochondrosis. The distinction between these three entities is usually possible on all imaging modalities, including conventional radiographs (Fardon & Milette, 2001).

Scientific studies suggest that spondylosis deformans is the consequence of normal aging, whereas intervertebral osteochondrosis, sometimes also called "deteriorated disc," results from a clearly pathologic, although not necessarily symptomatic, process.

It was also suggested that with normal aging, fibrous tissue replaces nuclear mucoid matrix, but the disc height is preserved and the disc margins remain regular. However, since radial tears of the annulus were found only in a minority of postmortem examinations of individuals over 40 years of age, these could not be considered a usual consequence of aging (Fardon & Milette, 2001). It was considered that slight symmetric bulging of the disc may occur in the elderly remodelling associated with osteoporosis. On conventional radiographs and computed tomography (CT), small amounts of gas can be detected in some elderly individuals at the annular/apophyseal enthesis, probably located in small transverse annular tears, and possibly signifying early manifestations of spondylosis deformans; however, a large

amount of gas in the central disc space was considered to be pathologic and a feature of intervertebral osteochondrosis.

As anterior and lateral marginal vertebral body osteophytes have been found in 100% of skeletons of individuals over 40, they should be considered to be consequences of normal aging. However, posterior osteophytes, which have been found in only a minority of skeletons of individuals over 80, are not inevitable consequences of aging.

Endplate erosions with osteosclerosis and chronic reactive bone marrow changes also appear to be pathologic. Slight to moderate decrease in central disc signal intensity found on T2-weighted MRIs can be a nonpathologic age-related observation but, if the result of a normal process should be relatively uniform among all discs studied in the individual.

Intervertebral osteochondrosis, or deteriorated disc, also sometimes called “chronic discopathy,” shows, on microscopic examination, total structural disorganization and general replacement of normal disc tissue by fibrosis. Radiographically, intervertebral osteochondrosis is characterized by;

- narrowing of the intervertebral space,
- irregular disc contour often associated with bulging,
- multidirectional osteophytes often involving the central spinal canal and foramina,
- endplate erosions with reactive osteosclerosis,
- chronic vertebral body bone marrow changes
- markedly decreased central disc signal intensity on T2 weighted images and at distinct variance, to that seen in unaffected discs of the same individual.

Milette (1997) determined that an assessment of multiple parameters was required to differentiate normal aging disks from truly degenerated or “scarred” disks. He used 11 criteria to distinguish between the normal aging disc and a deteriorated disc/scarred disc, **Table 1.3.**

Table 1.3. Differentiating features of the normal aging disk and the scarred /deteriorated disk (Denaro et al., 2009)

Criteria		Normal ageing disc	Scarred disc
Clinical			
	age	over 40 years	all ages
	symptoms	none	frequent
	history of low back pain	none	frequent
Plain films and CT			
	disk space height	normal	decreased
	posterior disc margin	regular	irregular
	vertebral bodies	normal	osteosclerosis
	osteophytes	anterolateral	all directions
	intradiscal gas	anterolateral	central
	number of affected discs	all	variable
Additional criteria for MR			
	vertebral body marrow	normal for age group	Modic type 2 or type 3 changes
	central disc intensity	slight decrease	marked decrease

In keeping with the relatively neutral position adopted in the AJNR guidelines this scheme was not reproduced in their work.

Radiological reporting

The task force recommended that reports should classify each disc examined into broad diagnostic categories distinguishing interpretations that are made on purely ***morphologic grounds*** from those using *clinical data*. They also advised that the sources of the morphologic data should be described.

They also noted that the ability to distinguish between various forms of herniation and between broad-based protrusion and bulging depended on the *adequacy of available imaging data and the judgment of the interpreter*. Likewise, knowing whether there is a thin thread of continuity between displaced disc material and disc of origin, or whether there is a small lapse in the integrity of the outer fibers of the annulus, may not be possible, except by surgical observation.

Interpretations should be made with ***various degrees of confidence***. Statement of the *degree of confidence* should be considered as an important component of communication. The reporter should characterize the interpretation as;

- "definite" if there is no doubt,
- "probable" if there is some doubt but the likelihood is greater than 50%,
- "possible" if there is reason to consider but the likelihood is less than 50%.

The source and quality of the data were considered to be important qualifiers of the degree of confidence. It may be appropriate to characterize the interpretation with one degree of confidence based on morphologic criteria and another if clinical data are considered (Fardon & Milette, 2001).

Library of MRI images

The following library of MRI T2 weighted images is taken from a pictorial review of spinal diseases by Kasdan et al and published in Seminars in Neurology in 2008 (R. B. Kasdan & J. L. Howard, 2008).

Figure 1.21. T2 sagittal image demonstrating the position of axial slices in a lumbar imaging study. T2-weighted axial images are performed parallel to the disc space. To capture migrated sequestered fragments, contiguous T1 axial images can also be performed from the L2 vertebral body to the sacrum and in the cervical region from the tip of the foramen magnum to T2 (not shown) (R. B. Kasdan & J. L. Howard, 2008)

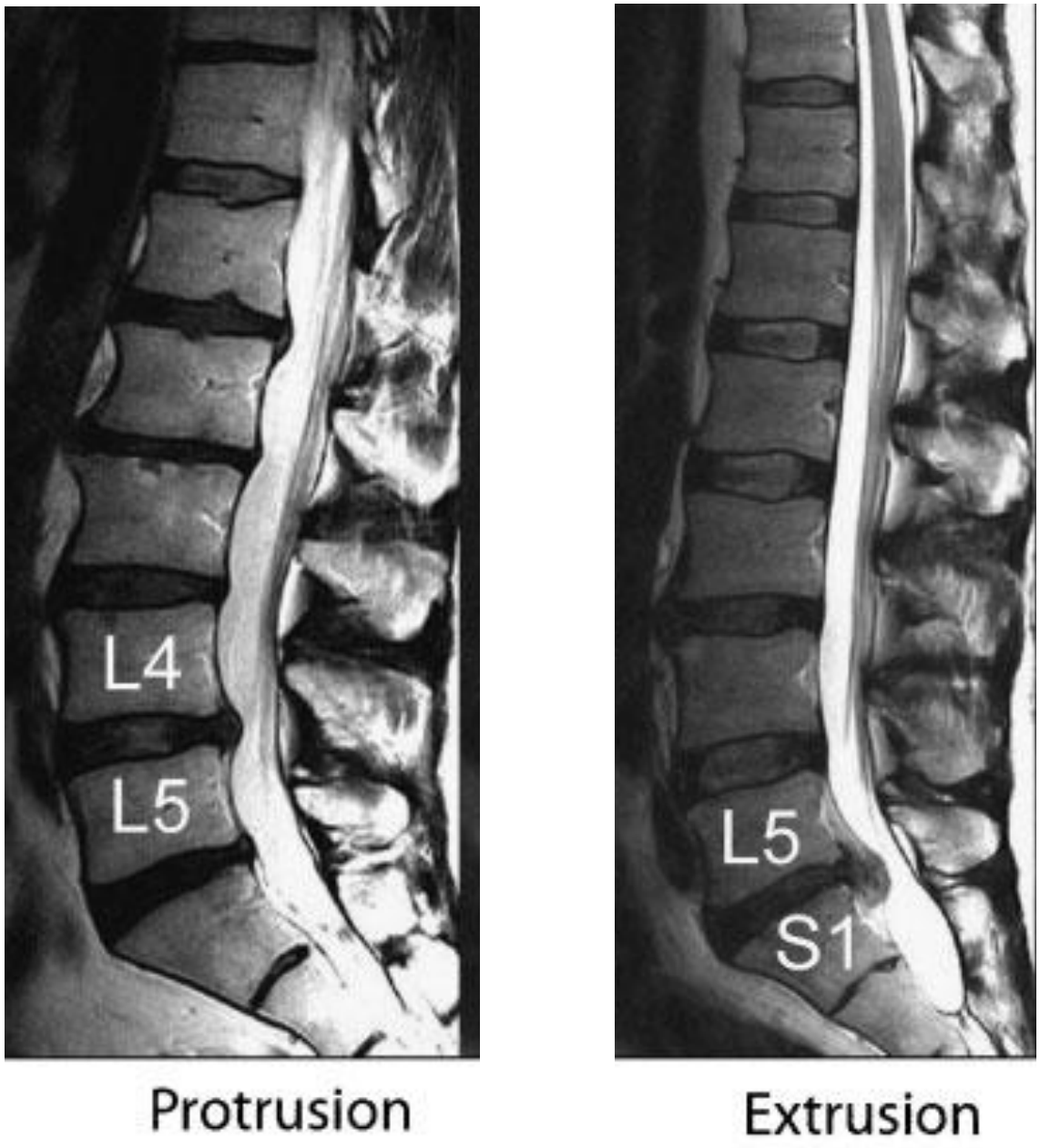


Figure 1.22. T2 sagittal images of a disc protrusion at L4–5, and an extrusion at L5-S1 in two patients (R. B. Kasdan & J. L. Howard, 2008).

Figure 1.23. T2 sagittal images of a disc sequestration (free fragment) at L5 (R. B. Kasdan & J. L. Howard, 2008)

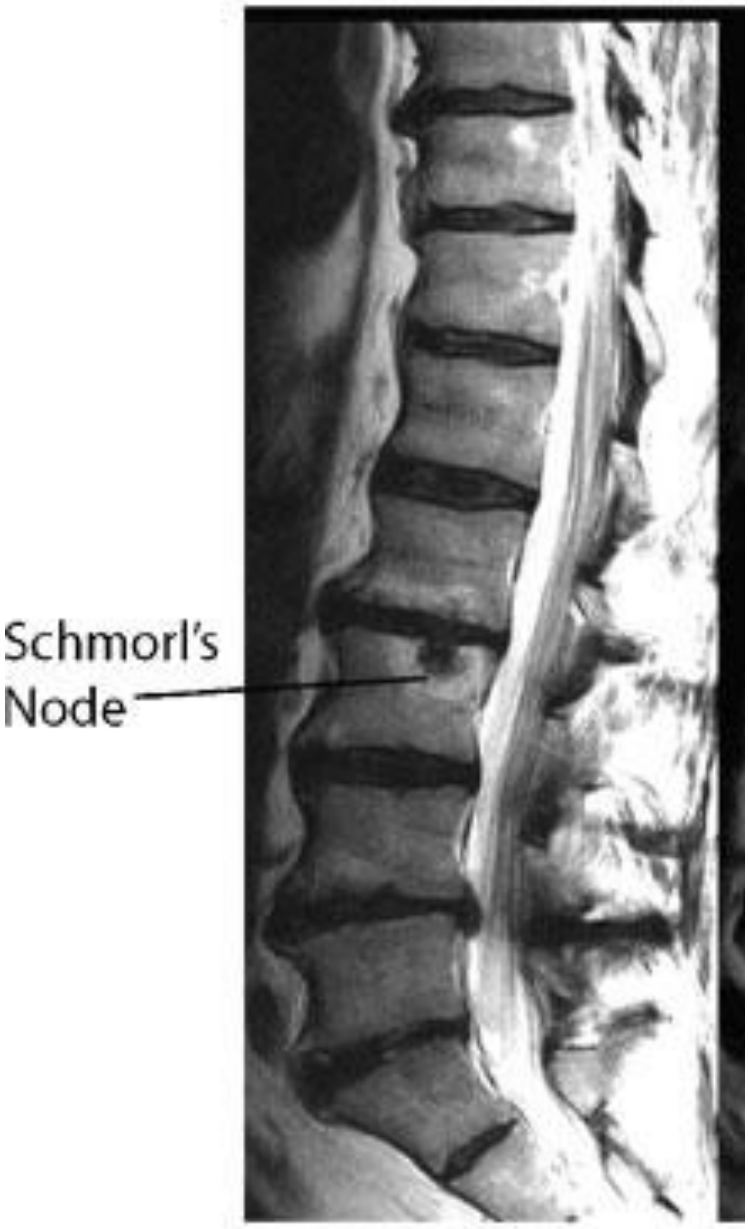


Figure 1.24. **T2 sagittal images of an intravertebral disc herniation (Schmorl's node). The Schmorl's node is adjacent to the inferior end plate of the L3–4 disc and is contiguous with the disc. There is an area of reactive bone change surrounding the Schmorl's node (R. B. Kasdan & J. L. Howard, 2008).**

Other Classification and grading schemes

A number of grading systems have been developed aimed at identifying different stages of disc changes and/or degeneration and relating these to age. All are limited by the lack of an established "gold" standard against which to assess their accuracy and validity and thus rely on their biological credibility, reproducibility and ability to distinguish disc types which conform to accepted features of ageing and degeneration (Thompson 1990), unfortunately the latter is yet to be adequately defined and distinguished from ageing.

Grading systems for lumbar discs

The following short account is based primarily on a systematic review and evaluation of grading systems for cervical or lumbar disc and facet joint degeneration published in 2006 (Kettler & Wilke, 2006). In this review a systematic search of Medline identified 32 publications describing 42 different grading systems; 30 applied to the lumbar spine, 10 to the cervical spine and two to both systems. The design of these grading systems varied considerably as did the method used which included:

- Macroscopic anatomy
- Histology
- Plain radiography
- Magnetic resonance imaging
- Discography

Only four of the 42 systems were recommended (having interobserver reliability tests with either Kappa or Intraclass correlation coefficients >0.60 indicating at least substantial agreement in grading between observers), **Table 1.4.**

Table 1.4. Four grading systems reported in the systematic review of lumbar disc grading systems carried out by Kettler and Wilke (2006).

Reference	Disc type		Method
Thompson et al (1990)	Lumbar	Sagittal section	Macroscopic anatomy
Boos et al (2002)	Lumbar	Sagittal paraffin section	Histology
Lane et al (1993)	Lumbar	Sagittal views	Plane radiology
Pfirrmann et al. (2001)	Lumbar	Sagittal T2 weighted scans	MRI

Thompson first proposed a classification system of the lumbar spine in 1990. A five-category grading scheme for assessing the gross morphology of midsagittal sections of the human lumbar intervertebral disc was developed which reflected the relationship between age and degree of degeneration Table 1 5. & Figure 1.6.

Table 1.5. Thompson et al (1990) macroscopic grading of post mortem lumbar disc degeneration on sagittal sections: description of the morphologic grades.

Grade	Nucleus	Annulus	Endplate	Vertebral Body
I	Bulging gel	Discrete fibrous lamellas	Hyaline, uniformly thick	Margins rounded
II	White fibrous tissue peripherally	Mucinous material between lamella	Thickness irregular	Margins pointed
III	Consolidated fibrous tissue	Extensive mucinous infiltration; loss of annular-nuclear demarcation	Focal defects in cartilage	Early chondrophytes or osteophytes at margins
IV	Horizontal clefts parallel to end-plate	Focal disruptions	Fibrocartilage extending from subchondral bone; irregularity and focal sclerosis in subchondral bone	Osteophytes less than 2 mm
V	Clefts extend through the nucleus and annulus		Diffuse sclerosis	Osteophytes greater than 2mm

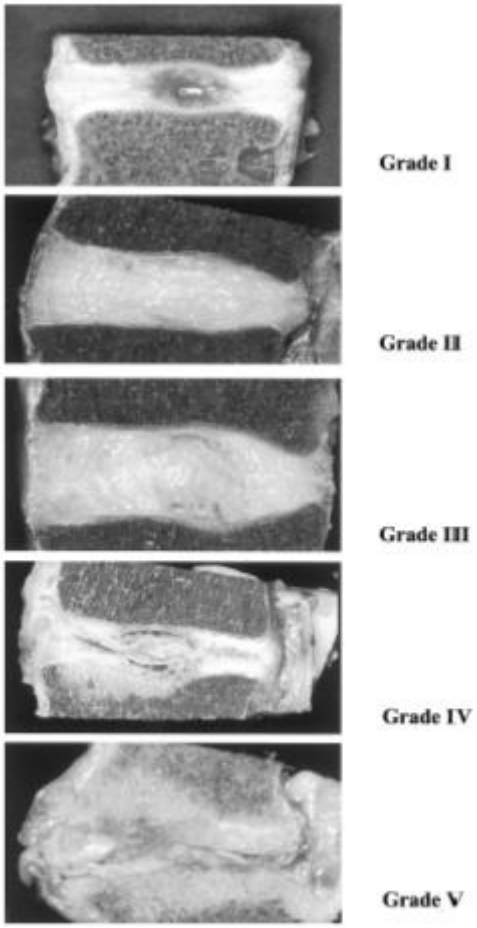


Figure 1.25. Macroscopic grading of age-related disc alterations according to Thompson et al. 1990

In 2002, Boos et al. also classified lumbar disc degeneration using the histology of human cadaver specimens. Boos classified discs into eight groups based solely on age and described the ***general structure of the discs in each age group*** using variables from a macroscopic and histologic aassessment of the discs in each age group, **Table 1.6.**

Table 1.6. Variables and grading of a macroscopic and histological disc assessment (Boos et al., 2002)

Macroscopic and histological features of the disc	Grading
Global disc appearance	
Macroscopic assessment (IVD, endplate, and adjacent bone)	Grade 1 = normal juvenile disc; Grade 2 = normal adult disc; Grade 3 = mild disc degeneration; Grade 4 = moderate disc degeneration; Grade 5 = severe disc degeneration
Intervertebral disc	
Cells (chondrocyte proliferation)	0 = no proliferation; 1 = increased cell density; 2 = connection of two chondrocytes; 3 = small size clones (several chondrocytes, grouped together, 3–7 cells); 4 = moderate size clones (8–15 cells); 5 = huge clones (>15 cells)
Multiple chondrocytes growing in small rounded groups or clusters sharply demarcated by a rim of territorial matrix	
Granular changes	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Eosinophilic-staining amorphous granules within the fibrocartilage matrix	
Mucous degeneration	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Cystic, oval, or irregular areas with an intense deposition of acid mucopolysaccharides (*i.e.,* sulphated glycosaminoglycans) staining dark blue with Alcian blue-PAS	
Edge neovascularity	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Newly formed blood vessels with reparative alteration	
Rim lesions	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Radial tears adjacent to the endplates	
Concentric tears	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Tears after the orientation of collagen fiber bundles in the anulus fibrosus	
Radial tears	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Radiating defects extending from the nucleus pulposus to the outer anulus lamellae parallel or oblique to the endplate (clefts)	
Notochordal cells	0 = absent; 1 = present
Embryonic disc cells	
Cell death	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Altered phenotype	
Scar formation	0 = absent; 1 = present
Amorphous fibrosus tissue without any differentiation	
Tissue defects	0 = absent; 1 = present
Voids within the tissue (*e.g.,* resulting from tissue resorption, probably filled with fluid *in vivo*)	
Endplate	
Cells	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Number of cells (chondrocyte clusters)	
Structural disorganization	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Focal disorganization of the cartilaginous matrix with clumping of chondrocytes	
Clefts	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Tears in the endplate	
Microfracture	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Disruption of the subchondral bone	
Neovascularization	0 = absent; 1 = rarely present; 2 = present in intermediate amounts of 1 to 3; 3 = abundantly present
Vessels penetrating from the bone marrow into the endplate in conjunction with microfractures	
New bone formation	0 = absent; 1 = present
Bone islands within the cartilage	
Bony sclerosis	0 = absent; 1 = present
Formation of new bone	
Physiologic vessels	0 = absent; 1 = present
Obliterated vessels	0 = absent; 1 = present
Scar formation	0 = absent; 1 = present
Amorphous fibrosus tissue without any differentiation	
Tissue defects	0 = absent; 1 = present
Voids within the tissue (*e.g.,* resulting from tissue resorption, probably filled with fluid *in vivo*)	

IVD = intervertebral disc.

Lane et al (1993) developed a three scale grading for the assessment of the presence and severity of radiologic features of lumbar disc degeneration. Three variables were assessed and scored individually; joint space narrowing, osteophyte formation and sub chondral sclerosis. On overall grading was given based on a simple scoring system, **Table 1.7.**

Table 1.7 Three scale grading for the assessment of the presence and severity of radiologic features of lumbar disc degeneration

Score	Joint space narrowing	Osteophytes anteriorand posterior	Sclerosis
0	None	None	None
1	Definite (mild narrowing)	Small	Present
2	Moderate	Moderate	-
3	Severe (complete loss of joint space)	Large	-

The purpose was to develop a method for assessing the presence and severity of radiographic features of lumbar disc degeneration. Joint space narrowing, anterior and posterior osteophyte formation and subchondral sclerosis were assessed individually. Based on these features

An overall grading was given from 0-2;

Grade 0 normal joint (0 for osteophytes and narrowing)

Grade 1 mild (1) narrowing or mild (1) osteophytes

Grade 2 moderate –severe (2-3) narrowing and/or moderate – severe osteophytes (2-2)

Table 1 8. Grading of lumbar disc degeneration on T2-weighted sagittal MRI-scans proposed by Pfirrmann et al 2001.

Grade	Structure	Distinction of nucleus and annulus	Signal intensity (MRI)	Height of intervertebral disc
I	Homogeneous, bright white	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
III	Inhomogeneous, grey	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogeneous, grey to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogeneous, black	lost	hypointense	Collapsed disc space

Pfirrmann et al (2001) (Pfirrmann et al., 2001) further developed Thompson's morphological grading of the lumbar disc using MRI data. They developed a five point grading system and algorithm based on MRI signal intensity, disc structure, distinction between nucleus and annulus, and disc height Table 1.8, and an algorithm for the system, Figure 1.7.

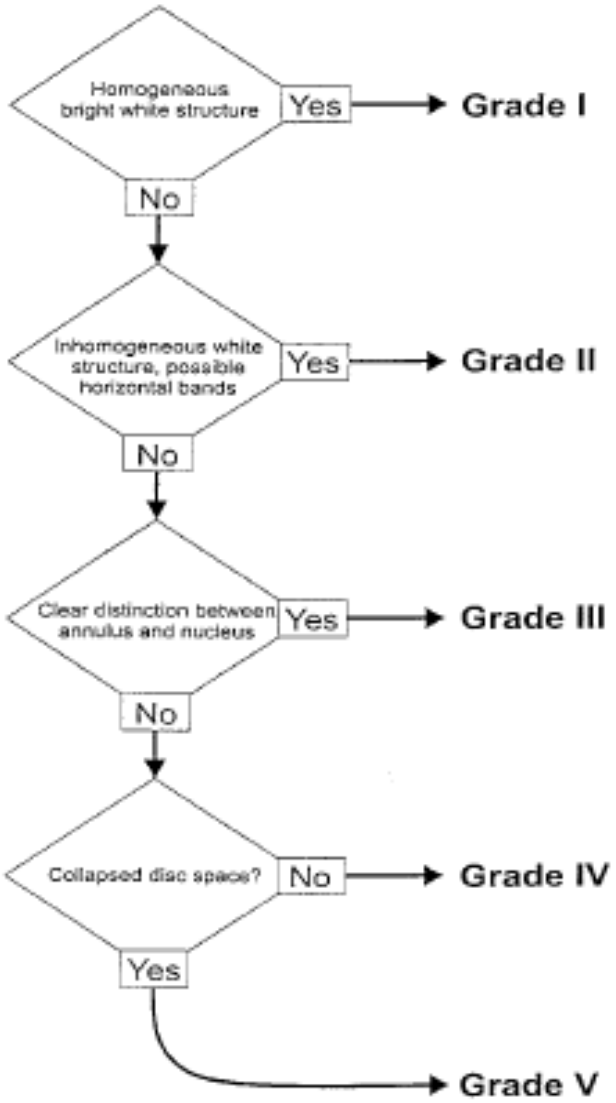


Figure 1.26. Algorithm for the grading Pfirrmann et al 2001 system and for the assessment of the lumbar disc degeneration grade.

In an assessment of the clinical feasibility of the four recommended systems the authors of the review (Kettler & Wilke, 2006) considered that the system with the *highest clinical relevance coupled with a high (but not the highest) clinical feasibility was that developed by Pfirrman et al (2001).* The system by Lane et al (1993) was considered to have the highest clinical feasibility as only lateral radiographs were required and the system could be easily applied. The grading systems of Thompson and Boos were

considered to be more of academic than clinical value since the grading could not be applied on patients.

Kettler et al (2006) highlighted the variability of design in relation to the grading systems reviewed. They noted that some systems started with the normal state others with the degenerated state, and that the scales used for grading varied between two and five with some using linguistic terms e.g. “mild” while other used numerical scales to grade discs. These variations made a direct comparison of the scales difficult and the authors recommended that a set of standards should be defined. They also recommended that all grading systems should be adequately tested for reliability. Since the review by Kettler et al (2006) a number of other grading systems have been published based on MRI data; two are of particular note (Puertas, Yamashita, Oliveira, & Souza, 2009; Watanabe et al., 2007)

Watanabe et al (Duggal, 2009) developed a grading system based on MRI T2 imaging in order to evaluate ***early degeneration*** of the IVD. In axial T2 mapping, degenerative grade of the nucleus pulposus generally increased with age ($p<0.05$) but not the annulus fibrosus However there was huge heterogeneity in the disc grading within and between the different age groups. So for example in four patients between the ages of 23-34 years all ***four stages of disc degeneration could be found,*** **Figure 1.8.**

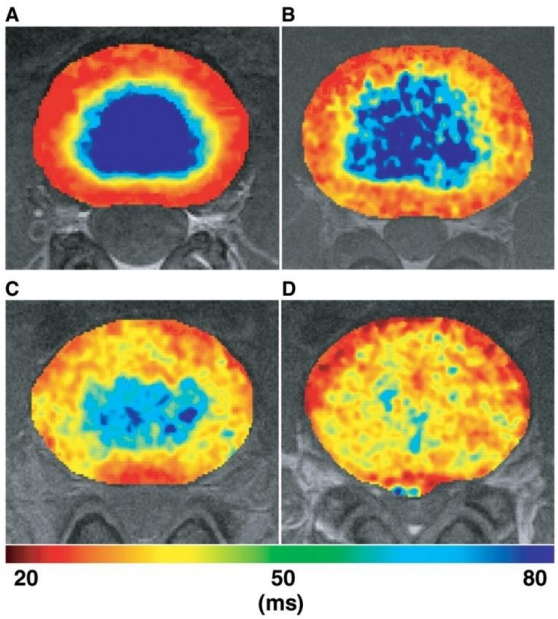
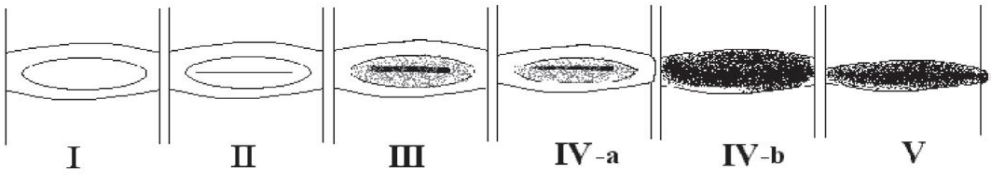


Figure 1.27. Color-coded maps of intervertebral disks obtained with axial T2 mapping. (A) = grade I in 23-year-old woman, B = grade II in 27-year-old man, (C) = grade III in 25-year-old man, and (D) = grade IV in 34-year-old man (Duggal, 2009).

More recently Puertas et al (Mummaneni et al., 2009) produced a five-point classification to categorisDDD using MRI signal intensity. The authors considered that loss of function and repair in the IVD may be regarded as DDD. Loss of homogeneity in T2 signal intensity, and loss of distinction between

nucleus pulposus and annulus fibrosus were generally observed in degenerative intervertebral discs; however, the grading system was *not linked to the age* of the disc, **Table 1.9.**

Table 1.9. Classification of IVD degeneration by MRI: classification model for assisting image analysis (Mummaneni et al., 2009).

Visual model (MRI)  Disc grade						
Structure	Homogeneous	Homogeneous, horizontal line	Heterogeneous, grey	Heterogeneous, grey	Heterogeneous, black	Heterogeneous, black
Nucleus	Light	Light	Dark	Dark	Lost	lost
Signal intensity	Hyperintense	Hyperintense	Intermediate	Intermediate	Hypointense	Hypointense
Disc height	Normal	Normal	Normal	Reduced	Reduced	Collapsed

Grading systems for cervical discs

Cervical disc degeneration is common after middle age and affects more than 80% of people over 60 years without causing symptoms, however in 10-15% of the population disc changes may be symptomatic (Miyazaki, Hong, Yoon, Morishita, & Wang, 2008).

Ten systems for grading cervical disc changes were identified in the review by Kettler et al (2006). Two were based on macroscopic anatomy, four on plain radiography, two on MRI and two on discography. Only one system, published by Kellegran et al (1963) and based on lateral radiographs was recommended. The clinical feasibility of this system was considered to be high, however its clinical relevance was considered to be lower as the discs can only be assessed in terms of reactive changes in the surrounding bone and loss of disc height, **Table 1.10.**

Table 1.10. Kellgren et al (1963) radiographic grading of cervical disc degeneration on lateral view.

Grade	Description
0	Absence of degeneration of the disc
1	Minimal anterior osteophytosis
2	Definite anterior osteophytosis with possible narrowing of the disc space and some sclerosis of vertebral plates
3	Moderate narrowing of the disc space with definite sclerosis of vertebral endplates and osteophytosis
4	Severe narrowing of the disc space with sclerosis of vertebral endplates and multiple large osteophytes.

An additional MRI based grading system for cervical disc degeneration published since the Kettler 2006 review was also identified. A novel grading system was proposed and the reliability

of the system tests (Miyazaki et al., 2008). This system has five reporting grades and has similarities with the grading system proposed by Puerta et al (2009) for lumber disc degeneration, **Table 1.11.**

Table 1.11. Grading system for intervertebral disc degeneration proposed by Miyakaki et al (2008).

Grade	Nucleus signal intensity	Nucleus stucture	Distinction of nucleus and annulus	Disc height
I	Hyperintense	Homogeneous, white	Clear	Normal
II	Hyperintense	Inhomogeneous with horizontal band, white	Clear	Normal
III	Intermediate	Inhomogeneous, gray to black	Unclear	Normal to decreased
IV	Hypointense	Inhomogeneous, gray to black	Lost	Normal to decreased
V	Hypointense	Inhomogeneous, gray to black	Lost	Collapsed

Comment

One of the main criticisms levelled at these grading systems in general is their composite nature and qualitative, gross ordinal scales (Battié, Videman et al. 2009) which may mask or dilute important associations.

Another well reported difficulty is the lack of intra- and inter-rater agreement in the assessment of histologic and other markers of disc degeneration. In the systematic review carried out by Kettler and Wilke (2006) only 4 of 42 grading/classification systems for lumbar disc degenerations had interobserver reliability tests with either Kappa or Intraclass correlation coefficients >0.60 (indicating at least substantial agreement between observers[18]). Boos and Pfirrmman (Pfirrmann, Metzdorf et al. 2001; Boos, Weissbach et al. 2002) both acknowledged this problem when reporting their classification systems and in each case an examination of the reliability of the systems was a primary objective of the study.[19]

[18] Where agreement is rated in terms of kappa statistics as follows: 0 to 0.2 (slight agreement), 0.21 to 0.4(fair agreement), 0.41 to 0.60 (moderate agreement), 0.61 to 0.8 (substantial agreement), and 0.81 or more (excellent agreement). Absolute agreement would be 1.

Appendix A Disc lesions: Clefts, cracks, fissures and tears

The ANJR task force recommendations for the standardisation of nomenclature relating to the description of disc lesions are relatively limited and relates only to annular tears[20]. Many of the accounts of changes in the intervertebral disc with age detail the histological changes which occur prior to gross morphological changes, and in particular, the development of *different types of tear*s/fissures.

The most recent and comprehensive quoted work on the pathology and sequelae of intervertebral tears identified in the search was that of Vernon-Roberts (Nasca, 2009; Vernon-Roberts et al., 2007). As this work and the terminology used, has not, to our knowledge, gained universal acceptance it is included outside the reporting of that work to distinguish it from the AJNR recommended nomenclature.

Vernon-Roberts et al (2007) distinguished the following intervertebral disc tears/lesions

- end-plate separation
- Schmorl's nodes: (intra-vertebral herniation) a portion of the disc is displaced through the end-plate into the centrum of the vertebral body.
- transdiscal tear
- perinuclear tear
- rim lesion 21 (Limbus vertebrae) separation of a segment of rim of vertebral body ring apophysis. Note: it may result from fracture or from developmental abnormalities. Limbus vertebrae are commonly seen in patients who have had Scheuermann's Disease.
- radial tear or fissure: disruption of annular fibers extending from the nucleus outward toward the periphery of the annulus, usually in the vertical (cranio-caudal) plane, with occasional horizontal (transverse) components. Note: Occasionally a radial fissure extends in the transverse plane to include avulsion of the outer layers of annulus from the apophyseal ring..
- concentric tear or fissure of the annulus characterized by separation, or break, of annular fibers, in a plane roughly parallel to the curve of the periphery of the disc, creating fluid-filled spaces between adjacent annular lamellae.

These are illustrated schematically and diagrammatically below.

[20] Perhaps dues to poorer visualisation of other types of tears/histological changes on MRI (Lings et al 2008)
[21] Also know as a "peripheral tear" (Lundon et al 2001).

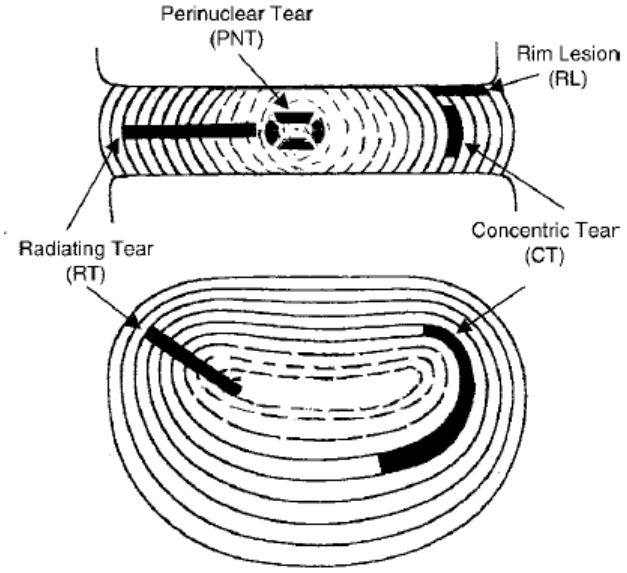


Figure 1.28. Diagram showing perinuclear tear, rim lesion, radiating tear and concentric tear together with their characteristic locations in the disc (Vernon-Roberts et al., 2007).

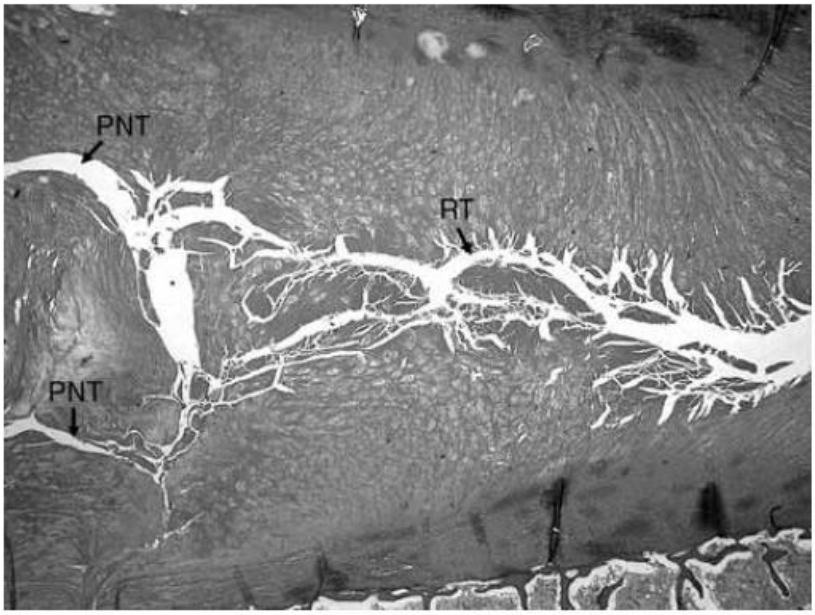


Figure 1.29 Medium power microscopic image of sagittal section of L4-L5 disc from a 54-year old woman, showing the linkage between upper and lower perinuclear tears (PNT) and a radiating tear (Vernon-Roberts et al., 2007)

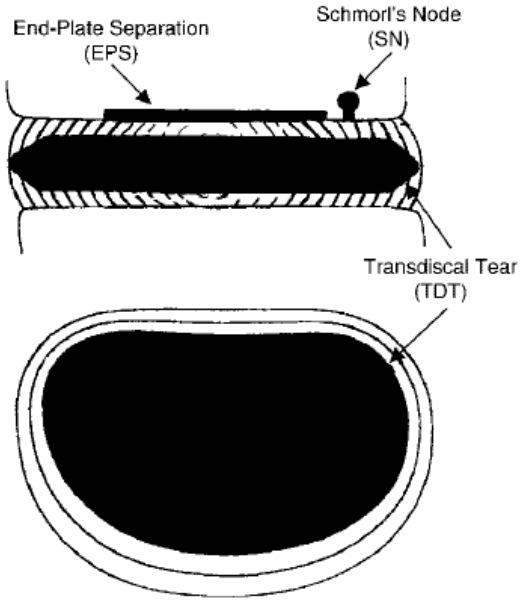


Figure 1.30. Diagram showing end-plate separation, Schmorl's nodes and transdiscal tear together with their characteristic locations in the disc (Vernon-Roberts et al., 2007).

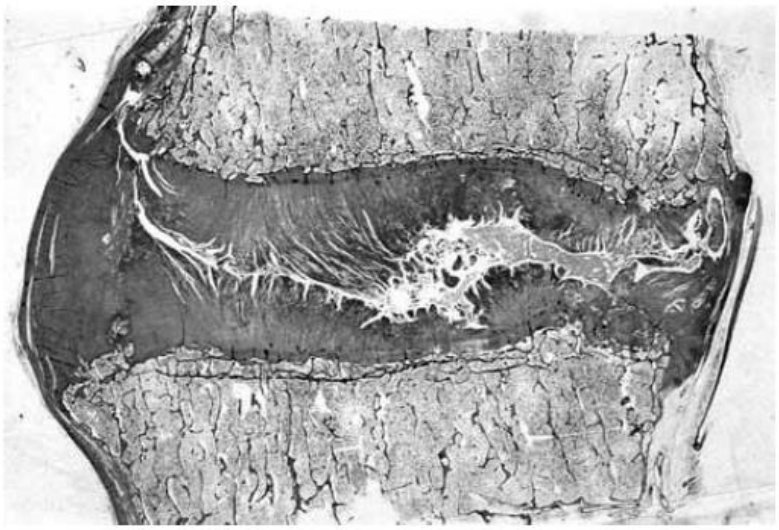
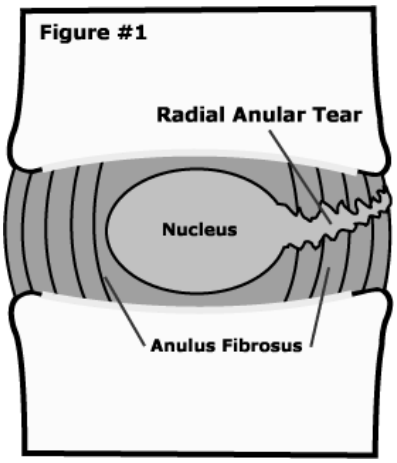
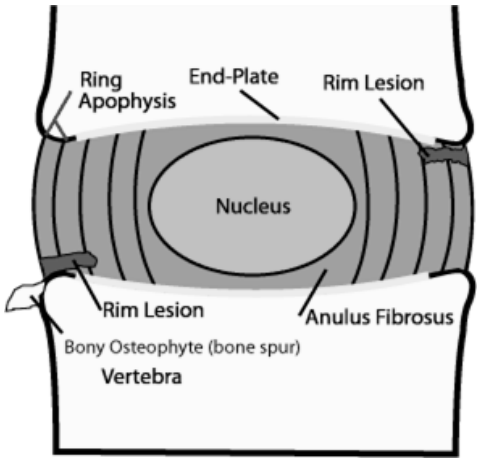


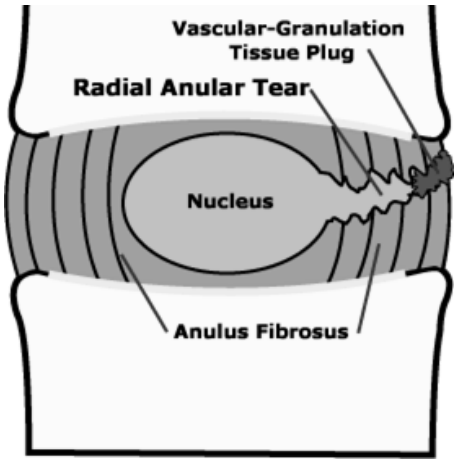
Figure 1.31. Low-power microscopic image of a sagittal section of the L4-L5 disc from a 72 year old man, showing a transdiscal tear with characteristic destructive cavitation of the disc centre containing free fragments and the radiating "bottle brush" pattern of minor clefts (Vernon-Roberts et al., 2007).

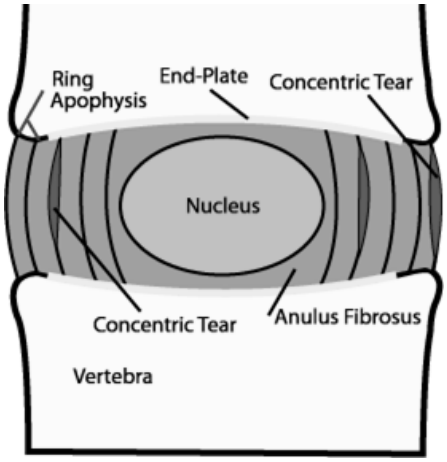
Figure 1.32. Diagrams of tears and lesions

The following diagrams were taken from: http://www.chirogeek.com









Appendix B: Glossary provided by the AJNR to accompany their 2001 guidelines[22]

[This glossary has been taken directly from the publication with the original spellings unaltered.]

Some terms and definitions included in this Glossary are not recommended as preferred terminology but are included to facilitate interpretation of vernacular and, in some cases, improper use. Preferred definitions are listed first. Confusing or inaccurate alternative definitions are placed in brackets and designated as "Non-Standard."

Aging disc: Disc demonstrating the features of normal aging. Spondylosis deformans possibly represents the normal aging process.

Anterior displacement: Displacement of disc tissues beyond the disc space into the anterior zone.

Anterior zone: Peridiscal zone that is anterior to the mid-coronal plane of the vertebral body.

Annulus, annulus (abbreviated form of annulus fibrosus): A multilaminated ligament surrounding the periphery of each disc space, attaching, craniad and caudad, to end-plate cartilage and ring apophyseal bone and blending centrally with nucleus pulposus. Note: Either annulus or annulus is correct spelling. Nomina Anatomica uses both forms whereas Terminologia Anatomica states "annulus fibrosus." 18,21 Fibrosus, has no correct alternative spelling; fibrosis has a different meaning and is incorrect in this context.

Asymmetric bulge: Presence of outer annulus beyond the plane of the disc space, more evident in one section of the periphery of the disc than another, but not sufficiently focal to be characterized as a protrusion. Note: Asymmetric bulge is a morphologic observation of various potential causes and is not a diagnosis. See: bulge.

Balloon disc (colloquial): Diffuse displacement of nucleus through the vertebral end plate, commonly seen in severe osteoporosis.

Base (of displaced disc): The cross sectional area of disc material at the outer margin of the disc space of origin, where disc material displaced beyond the disc space is continuous with disc material within the disc space. In the cranio-caudal direction, the length of the base cannot exceed, by definition, the height of the intervertebral space.

Broad-based protrusion: Herniation of disc material extending beyond the outer edges of the vertebral body apophyses over an area greater than 25% (90 degrees) and less than 50% (180 degrees) of the circumference of the disc. See protrusion. Note: Broad based protrusion refers only to discs in which disc material has displaced in association with localized disruption of the annulus and not to generalized (over 50% or 180 degrees) apparent extension of disc tissues beyond the edges of the apophyses. If the base is less than 25%, it is called "focal protrusion." Apparent extension of disc material, formation of additional connective tissue between osteophytes, or overlapping of non-disrupted tissue beyond the edges of the apophyses of over 50% of the circumference of the disc may be described as bulging. See: bulging disc, focal protrusion.
Bulging disc, bulge (n), bulge (v):

[22] Fardon, D. F. (2001). "Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology." Spine (Phila Pa 1976) 26(5): 461-2.

1. A disc in which the contour of the outer annulus extends, or appears to extend, in the horizontal (axial) plane beyond the edges of the disc space, over greater than 50% (180 degrees) of the circumference of the disc and usually less than 3mm beyond the edges of the vertebral body apophyses.
2. (Non-Standard) [A disc in which the outer margin extends over a broad base beyond the edges of the disc space.]
3. (Non-Standard) [Mild, smooth displacement of disc, whether focal or diffuse.]
4. (Non-Standard) [Any disc displacement at the discal level.] >Note: Bulging is an observation of the contour of the outer disc and is not a specific diagnosis. Bulging has been variously ascribed to redundancy of annulus secondary to loss of disc space height, ligamentous laxity, response to loading or angular motion, remodeling in response to adjacent pathology, unrecognized and atypical herniation, and illusion from volume averaging on CT axial images. Bulging may or may not represent pathologic change, physiologic variant, or normalcy. Bulging is not a form of herniation; discs known to be herniated should be diagnosed as herniation or, when appropriate, as specific types of herniation. See: herniated disc, protruded disc, extruded disc.

Capsule: Combined fibers of annulus and posterior longitudinal ligament. Note: The interface between outer annulus and posterior longitudinal ligament can be indistinguishable, making useful the term "capsule" and the derivative "sub-capsular," which refers to disc tissue beneath the capsule.

Cavitation: Spaces, cysts, clefts, or cavities formed within the nucleus and inner annulus from **disc degeneration.**

Central zone: Zone within the vertebral canal between sagittal planes through the medial edges of each facet. Note: The center of the central zone is a sagittal plane through the center of the vertebral body. The zones to either side of the center plane are right central and left central, which are preferred terms when the side is known, as when reporting imaging results of a specific disc. When the side is unspecified, or grouped with both right and left represented, the term paracentral is appropriate.

Chondrosis: See intervertebral osteochondrosis

Chronic disc herniation: 1. Disc herniation with presence of calcification, ossification, or gas accumulation within the displaced disc material, suggesting that the herniation is not of recent origin. Note: The term implies the presence of calcification, ossification, or gas accumulation and should not be used for herniations of soft disc material, regardless of the duration of displacement. See: degenerated disc, hard disc.

Claw osteophyte: Bony outgrowth arising very close to the disc margin, from the vertebral body apophysis, directed, with a sweeping configuration, toward the corresponding part of the vertebral body opposite the disc.

Collagenized disc or nucleus: A disc in which the glycosaminoglycans of the nucleus have been replaced by fibrous tissue.

Communicating disc, communication (n), communicate (v): Interruption in the periphery of the disc, so that fluid injected into the disc space could flow into the vertebral canal and thus into contact with displaced disc material.
Note: Communication refers to the status of displaced disc tissues with reference to the parent disc. Containment refers to the integrity of the annulus as container of disc tissues. Uncontained, displaced disc tissues could be noncommunicating if the displaced tissue is sealed off by peridural membrane or by healing of the tear in the annulus.

Concentric tear: Tear or fissure of the annulus characterized by separation, or break, of annular fibers, in a plane roughly parallel to the curve of the periphery of the disc, creating fluid-filled spaces between adjacent annular lamellae. See: radial tears, transverse tears.

Contained herniation, containment (n), contain (v): 1. Displaced disc tissue that is wholly within an outer perimeter of uninterrupted outer annulus or capsule.
2. (Non-standard) [A disc with its contents mostly, but not wholly, within annulus or capsule.]
3. (Non-Standard) [A disc with displaced elements contained within any investiture of the vertebral canal.] Note: The preferred meaning encompasses disc tissues that are enclosed by distended portions of the outer annulus or composite of fibers of the annulus and posterior longitudinal ligament. A disc whose substance is less than wholly contained by annulus is uncontained, as is a disc outside of annular fibers but under a distinct posterior longitudinal ligament or peridural membrane. Designation of a disc as contained, or uncontained, should define the integrity of the annulus enclosing the disc, though such distinction may not be possible with currently available imaging modalities.

Continuity: 1. Connection of displaced disc tissue by a bridge of disc tissue, however thin, to tissue within the disc of origin.
2. (Non-Standard) [Connection of displaced disc tissue by a substantial bridge of disc tissue to disc within the disc of origin].
3. (Non-Standard) [Connection of displaced disc tissue by any tissue to disc tissue within the disc or origin.] Note: Tenuous attachments, beyond recognition by most imaging methods, may have significance to the surgeon or endoscopist. Bridges of peridural membrane, or scar, do not represent continuity. See sequestration.

Crock disc: See internal disc disruption syndrome.
Degenerated disc, degeneration (n), degenerate (v):
1. Changes in a disc characterized by desiccation, fibrosis and cleft formation in the nucleus, fissuring and mucinous degeneration of the annulus, defects and sclerosis of end-plates, and/or osteophytes at the vertebral apophyses.
2. Imaging manifestations commonly associated with such changes.
3. (Non-Standard) [Changes in a disc related to aging.] Note: Either of the first two definitions may be correct, depending upon context. Clinical features must be considered to determine whether degenerative changes are pathologic and what may or may not have contributed to their development. The term degenerated disc, in itself, does not infer knowledge of cause, relationship to aging, presence of symptoms, or need for treatment. See intervertebral osteochondrosis, spondylosis, spondylosis deformans.

Degenerative disc disease: 1. A clinical syndrome characterized by manifestations of disc degeneration and symptoms thought to be related to those changes.
2. (Non-Standard) [Abnormal disc degeneration.]
3. (Non-Standard) [Imaging manifestations of degeneration greater than expected, considering the age of the patient]. Note: Causal connections between degenerative changes and symptoms are often difficult clinical distinctions. The term carries implications of illness that may not be appropriate if the only manifestations are from imaging. The preferred term for description of imaging manifestations alone, or imaging manifestations of uncertain relationship to symptoms, is degenerated disc rather than degenerative disc disease.

Delamination: Separation of annular fibers along planes parallel to the periphery of the disc, thought to represent separation of laminated layers of the outer annulus fibrosus.

Desiccated disc: Disc with reduced water content, usually primarily of nuclear tissues. 2. Imaging manifestations of reduced water content of the disc; or apparent reduced water content, as from alterations in the concentration of hydrophilic glycosaminoglycans.

Deteriorated disc: See intervertebral osteochondrosis.

Disc (disk): Complex structure composed of nucleus, annulus, cartilaginous end-plates, and vertebral body ring apophyseal attachments of annulus. Note: Most English language publications use the spelling disc more often than disk.12 Nomina Anatomica designates the structures as "Disci intervertebrales" and Terminologia Anatomica as "discus intervertebralis/Intervertebral disc."18,21

Disc of origin: Disc from which a displaced fragment originated. Syn: parent disc. Note: Since displaced fragments often contain tissues other than nucleus, disc of origin is preferred to nucleus of origin. "Parent disc" is synonymous, but more colloquial.

Discography (added later): lumbar provocative discography is an invasive diagnostic procedure for evaluation for intervertebral disc pathology. Needles are inserted through the back into the disc near the suspect area, guided by fluoroscope imaging. Fluid is then injected to pressurise the disc and any pain responses are recorded.

Disc space: 1. Space limited, craniad and caudad, by the end-plates of the vertebrae and peripherally by the edges of the vertebral body ring apophyses exclusive of osteophytes. Syn: intervertebral disc space.

Disc space height: The distance between the planes of the end-plates of the vertebrae craniad and caudad to the disc.

Discal level: Level of the vertebral canal between axial planes through the bony end-plates of the vertebrae craniad and caudad to the disc.

Discogenic vertebral sclerosis: Increased bone density and calcification adjacent to the end-plates of the vertebrae craniad and caudad to a degenerated disc, usually a manifestation of intervertebral osteochondrosis.

Displaced disc: A disc in which disc material is beyond the outer edges of the vertebral body ring apophyses (exclusive of osteophytes) of the craniad and caudad vertebrae, or, as in the case of intravertebral herniation, penetrated through the vertebral body end-plate. Note: Displaced disc is a general term that does not imply knowledge of the underlying pathology, cause, relationship to symptoms, or need for treatment. The term includes, but is not limited to, disc herniation and disc migration. See: herniated disc, migrated disc.

Epidural membrane: See peridural membrane.

Extra-foraminal zone: The zone beyond the sagittal plane of the lateral edges of the pedicles, having no well-defined lateral border. Syn: far lateral zone, far-out zone.

Extra-ligamentous: Posterior or lateral to the posterior longitudinal ligament. Note: Extra-ligamentous disc refers to displaced disc tissue that is located lateral, or posterior to the posterior longitudinal ligament. If the disc has extruded through the posterior longitudinal ligament it is sometimes called "trans-ligamentous" or "perforated," and if through the peridural membrane, it is sometimes refined to as "trans-membranous."

Extruded disc, extrusion (n), extrude (v): A herniated disc in which, in at least one plane, any one distance between the edges of the disc material beyond the disc space is greater than the distance between the edges of the base in the same plane, or when no continuity exists between the disc material beyond the disc space and that within the disc space.
Note: The preferred definition is consistent with the common language image of extrusion as an expulsion of material from a container through and beyond an aperture. Displacement beyond the outer annulus of disc material with any distance between its edges greater than the distance between the edges of the base distinguishes extrusion from protrusion. Distinguishing extrusion from protrusion by imaging is best done by measuring the edges of the displaced material and remaining continuity with the disc of origin, whereas relationship of the displaced disc material to the aperture through which it has passed is more readily observed surgically. Characteristics of protrusion and extrusion may co-exist, in which case the disc should be subcategorized as extruded. Extruded discs in which all continuity with the disc of origin is lost may be further characterized as sequestrated. Disc material displaced away from the site of extrusion may be characterized as migrated. See: herniated disc, migrated disc, protruded disc.

Fissure of annulus: Separations between annular fibers, avulsion of fibers from their vertebral body insertions, or breaks through fibers that extend radially, transversely, or concentrically, involving one or more layers of the annular lamellae. Syn: tear of annulus, torn annulus. Note: The terms fissure and tear are commonly used synonymously. Neither term implies any knowledge of etiology, relationship to symptoms, or need for treatment. Tear or fissure are both used to represent separations of annular fibers from causes other than sudden violent injury to a previously normal annulus, which can be appropriately termed "rupture of the annulus," which, in turn, contrasts to the colloquial, non-standard, use of the term "ruptured disc," referring to herniation.

Focal protrusion: Protrusion of disc material so that the base of the displaced material is less than 25% (90 degrees) of the circumference of the disc. Note: Focal protrusion refers only to herniated discs that are not extruded and do not have a base greater than 25% of the disc circumference. Herniated discs with a base greater than 25% are "broad-based protrusions."

Foraminal zone: The zone between planes passing through the medial and lateral edges of the pedicles. Note: The foraminal zone is sometimes called the "pedicle zone," which can be confusing because pedicle zone might also refer to measurements in the sagittal plane between the upper and lower surface of a given pedicle, which is properly called the "pedicle level." The foraminal zone is also sometimes called "lateral zone," which can be confusing because lateral zone can also mean extra-foraminal zone or an area including both the foraminal and extra-foraminal zones.

Free fragment: 1. A fragment of disc that has separated from the disc of origin and has no continuous bridge of disc tissue with disc tissue within the disc of origin. Syn: sequestrated disc . 2. (Non-Standard) [A fragment that is not contained within the outer perimeter of the annulus.] 3. (Non-Standard) [A fragment that is not contained within annulus, posterior longitudinal ligament, or peridural membrane.] Note: Sequestrated disc and free fragment are virtually synonymous. When referring to the condition of the disc, categorization as extruded with sub-categorization as sequestrated is preferred, whereas free fragment or sequestrum is appropriate when referring specifically to the fragment.

Hard disc: Disc displacement in which the displaced portion has undergone calcification or ossification and may be intimately associated with apophyseal osteophytes. Note: The term hard disc is most often used in reference to the cervical spine to distinguish chronic hypertrophic and reactive changes in the periphery of the disc from acute extrusion of soft, predominantly nuclear tissue. See: chronic disc herniation.

Herniated disc, herniation (n), herniate (v): 1. Localized displacement of disc material beyond the normal margins of the intervertebral disc space.
2. (Non-Standard) [Any displacement of disc tissue beyond the disc space]. Note: Localized means, by way of convention, less than 50% (180 degrees) of the circumference of the disc. Disc material may include nucleus, cartilage, fragmented apophyseal bone, or fragmented annular tissue. The normal margins of the intervertebral disc space are defined, craniad and caudad, by the vertebral body end-plates and peripherally by the edges of the vertebral body ring apophyses, exclusive of osteophytic formations. Herniated disc generally refers to displacement of disc tissues through a disruption in the annulus, the exception being intravertebral herniations (Schmorl's nodes) in which the displacement is through vertebral end-plate. Herniated discs in the horizontal (axial) plane may be further subcategorized as protruded or extruded. Herniated disc is sometimes referred to as "herniated nucleus pulposus," but the term herniated disc is preferred because displaced disc tissues often include cartilage, bone fragments, or annular tissues. The term "ruptured disc" is used synonymously with herniated disc, but is more colloquial and can be easily confused with violent, traumatic rupture of the annulus or end-plate. The term "prolapse" has also been used as a general term for disc displacement, but its use has been inconsistent. The term herniated disc does not infer knowledge of cause, relation to injury or activity, concordance with symptoms, or need for treatment.

Herniated nucleus pulposus (HNP): See herniated disc.

High intensity zone (HIZ): Area of high signal intensity on T2-weighted magnetic resonance images of the disc, usually referring to the outer annulus. Note: High intensity zones within the posterior annular substance may reflect fissure or tear of the annulus, but do not imply knowledge of etiology, concordance with symptoms, or need for treatment.

Infra-pedicular level: The level between the axial planes of the inferior edge of the pedicle craniad to the disc in question and the inferior end-plate of the vertebral body above. Syn: superior vertebral notch.

Internal disc disruption: Disorganization of structures within the disc space.
Internal disc disruption syndrome: Internal disc disruption associated with symptoms, which are thought, on clinical grounds, to be caused by the disruption. Syn: Crock disc.

Interspace: See disc space.

Intervertebral chondrosis: See intervertebral osteochondrosis

Intervertebral disc: See disc.

Intervertebral disc space: See disc space.

Intervertebral osteochondrosis: Degenerative process of the spine involving the vertebral body end-plates, the nucleus pulposus, and the annulus fibrosus, which is characterized by disc space narrowing, vacuum phenomenon, and vertebral body reactive changes. Syn: deteriorated disc, chronic discopathy, osteochondrosis.

Intra-annular displacement: Displacement of central, predominantly nuclear, tissue to a more peripheral site within the disc space, usually into a fissure in the annulus. Syn: (Non-Standard) [intra-annular herniation], [intra-discal herniation]. Note: Intra-annular displacement is distinguished from

disc herniation, in that herniation of disc refers to displacement of disc tissues beyond the disc space. Intra-annular displacement is a form of internal disruption. When referring to intra-annular displacement, it is best not to use the term "herniation" in order to avoid confusion with disc herniation.

Intra-annular herniation (Non-Standard): See intra-annular displacement.

Intra-discal herniation (Non-Standard): See intra-annular displacement.

Intra-dural herniation: A disc from which displaced tissue has penetrated, or become enclosed by, the dura so that it lies within the thecal sac.

Intra-vertebral herniation: A disc in which a portion of the disc is displaced through the end-plate into the centrum of the vertebral body. Syn: Schmorl's node.

Lateral membrane: See peridural membrane.

Lateral recess: See sub-articular zone.

Lateral zone: See foraminal zone.

Limbus fracture: Traumatic separation of a segment of bone from the edge of the vertebral ring apophysis at the site of annular attachment. Note: Limbus fractures of various types may be accompanied by disc herniation, usually by either focal or broad-based protrusion. They may occur into the anterior zone or posteriorly into the zones where they may compress neural tissues.

Limbus vertebrae: Separation of a segment of rim of vertebral body ring apophysis. Note: Limbus vertebrae may result from fracture or from developmental abnormalities. Limbus vertebrae is commonly seen in patients who have had Scheuermann's Disease. The lesions may be called "rim lesions." The term is derived from the Latin nominative limbus and genitive modifier vertebrae, thus is singular.

Marginal osteophyte: Osteophyte that protrudes from and beyond the outer perimeter of the vertebral end-plate apophysis.

Marrow changes (of vertebral body): See vertebral body marrow changes (Modic classification).

Migrated disc, migration (n), migrate (v): 1. Herniated disc in which a portion of extruded disc material is displaced away from the tear in the outer annulus through which it has extruded. 2. (Non-Standard) [A herniated disc with a free fragment or sequestrum beyond the disc level.] Note: Migration refers to the position of the displaced disc material, rather than to its continuity with disc tissue within the disc of origin; therefore, it is not synonymous with sequestration.

Modic Type 1, 2, 3: See vertebral body marrow changes.

Non-marginal osteophyte: Osteophyte that occurs at sites other than the vertebral end-plate apophysis. See: marginal osteophyte.

Normal disc: 1. A fully and normally developed disc with no changes attributable to trauma, disease, degeneration, or aging. The bilocular appearance of the adult nucleus is considered a sign of normal maturation.

2. (Non-Standard) [A disc that may contain one or more morphologic variants which would be considered normal given the clinical circumstances of the patient.]. Note: Many congenital and developmental variations may be normal in that they are not associated with symptoms; certain adaptive changes in the disc may be normal considering adjacent pathology, and certain degenerative phenomena may be normal given the patient's age; however, classification and reporting for medical purposes is best served if such discs are not considered normal. What is clinically normal for a given patient is a clinical judgment independent of the need to describe any variation in the disc itself.

Nucleus of origin: The central, nuclear portion of the disc of reference, usually used to reference the disc from which tissue has been displaced. Syn: parent nucleus, disc of origin.

Osteochondrosis: See intervertebral osteochondrosis.

Osteophytes: Focal hypertrophy of bone surface and/or ossification of soft tissue attachments to the bone.

Paracentral: In the right or left central zone of the vertebral canal. See central zone. Note: The terms right central or left central are preferable when speaking of a single site when the side can be specified, as when reporting the findings of imaging procedures. Paracentral is appropriate if the side is not significant or when speaking of mixed sites.

Parent disc: See disc of origin.

Parent nucleus: See nucleus of origin, disc of origin.

Pedicular level: The level between axial planes through the upper and lower edges of the pedicle. Note: The pedicular level may be further designated with reference to the disc in question as "pedicular level above" or "pedicular level below." Distinction should be made between designation of the pedicular level in the sagittal plane and the "foraminal zone" which is defined by the planes of the medial and lateral walls of the pedicles in the axial plane. Syn: peduncular level.

Perforated: (Non-Standard) See trans-ligamentous.

Peridural membrane: A delicate, translucent membrane that attaches to the under surface of the deep layer of the posterior longitudinal ligament, and extends laterally and posteriorly, encircling the bony spinal canal outside the dura. The veins of Batson's plexus lie on the dorsal surface of the peridural membrane and pierce it ventrally. Syn: lateral membrane, epidural membrane.

Prolapsed disc, prolapse (n), prolapse (v): (Non-Standard) 1. A herniated disc in which disc tissue has protruded or extruded at the level of the disc and below into the supra-pedicular level.
2. (Non-Standard) [Any herniated disc.] Note: The term prolapse is not used widely outside of medicine. Medically, it usually means to fall out and down, as with prolapse of the rectum or uterus. Analogy to the disc would apply most closely to disc tissue that has displaced beyond the disc space into the supra-pedicular zone. It has been used often, non-specifically, as synonymous with herniation. Prolapse is not a recommended term for description of disc displacement.

Protruded disc, protrusion (n), protrude (v): 1. A herniated disc in which the greatest distance, in any plane, between the edges of the disc material beyond the disc space is less than the distance between the edges of the base in the same plane.
2. (Non-Standard) [A disc in which disc tissue beyond the disc space is contained within intact annulus].

3. (Non-Standard) [Any, or unspecified type of, disc herniation.] Note: The test of protrusion is that there must be a localized (less than 50% or 180 degrees of the circumference of the disc) displacement of disc tissue so that the distance between the edges of the displaced portion must not be greater than the distance between the corresponding edges of the base. A disc that has broken through the outer annulus at the apex, but maintains a broad continuity at the base, is protruded and uncontained. While sometimes used as a general term in the way herniation is defined here, the use of the term protrusion is best reserved for sub-categorization of herniations meeting the above criteria. See: extruded disc.

Radial fissure or tear: Disruption of annular fibers extending from the nucleus outward toward the periphery of the annulus, usually in the vertical (cranio-caudal) plane, with occasional horizontal (transverse) components. Note: Occasionally a radial fissure extends in the transverse plane to include avulsion of the outer layers of annulus from the apophyseal ring. See: concentric tears, radial tears.

Rim lesion: See limbus vertebrae.

Ruptured annulus: Disruption of the fibers of the annulus by sudden violent injury. Note: Separation of fibers of the annulus from degeneration, repeated minor trauma, other non-violent etiology, or when injury is simply a defining event in a degenerative process should be termed fissure or tear of the annulus. Rupture is appropriate when there is other evidence of sudden violent injury to a previously normal annulus. Ruptured annulus is not synonymous with ruptured disc, which is a colloquial equivalent of disc herniation.

Ruptured disc, rupture: (Non-Standard) 1. A herniated disc. 2. (Non-Standard) [A disc in which the annulus has lost its integrity.] See herniated disc, ruptured annulus. Note: Ruptured disc is used colloquially to encompass the same nonspecific meaning as the preferred term herniated disc. The common, non-medical meaning of rupture, to break apart or burst, and the medical use of rupture in the sense of complete tears of ligament or tendon are analogous to the annulus disrupted by violent injury, which may be appropriately characterized as "ruptured annulus," which is not synonymous with "ruptured disc."

Scarred disc: See collagenized disc.

Schmorl's node: See intravertebral herniation.
Sequestrated disc, sequestration (n), sequestrate (v); (var: sequestered disc): An extruded disc in which a portion of the disc tissue is displaced beyond the outer annulus and maintains no connection by disc tissue with the disc of origin. Note: An extruded disc may be subcategorized as "sequestrated" if no disc tissue bridges the displaced portion and the tissues of the disc of origin. If there is a fragment of disc tissue that is not continuous with parent nucleus, but still contained, even in part, by annular tissues, the disc may be characterized as protruded or extruded, but not as sequestrated. If even a tenuous connection by disc tissue remains between a displaced fragment and disc of origin, the disc is not sequestrated. If a displaced fragment has no connection with the disc of origin, but is contained within peridural membrane or under a portion of posterior longitudinal ligament that is not intimately bound with the annulus of origin, the disc is considered sequestrated. If the fragment is attached to the disc of origin by scar, or other non-discal tissue, or is merely in apposition to the disc of origin and not connected by disc tissue, it is considered sequestrated. Sequestrated and sequestered are used interchangeably.

Sequestrum: Disc tissue that has become displaced from the disc space of origin and lacks any continuity with disc material within the disc space of origin. Syn: disc fragment. See: sequestrated disc.

Note: Sequestrum refers to the isolated fragment itself, whereas sequestrated disc defines the condition of the disc.

Spondylitis: Inflammatory disease of the spine, other than degenerative disease. Note: Spondylitis usually refers to non-infectious inflammatory spondyloarthropathies.

Spondylosis: 1. Spondylosis deformans, for which spondylosis is a shortened form.
2. (Non-Standard) Any degenerative changes of the spine that include osteophytic enlargement of apophyseal bone. Note: Spondylosis deformans has specific characteristics that distinguish it from intervertebral osteochondrosis. Both processes include vertebral body osteophytes. The term "spondylosis" is often used in general as synonymous with "degeneration" which would include both processes, but such usage is confusing, so it is best that "degeneration" be the general term and "spondylosis deformans" a specifically defined sub-classification of degeneration. See: degeneration, intervertebral osteochondrosis, spondylosis deformans.

Spondylosis deformans: Degenerative process of the spine involving essentially the annulus fibrosus and characterized by anterior and lateral marginal osteophytes arising from the vertebral body apophyses, while the intervertebral disc height is normal or only slightly decreased. See: degeneration, spondylosis.

Sub-annular herniation: (Non-Standard) Disc herniation in which a displaced portion is contained by annulus. Syn: contained herniation. Note: Sub-annular describes a herniated disc that is contained by annulus and is not synonymous with the non-herniated "intra-annular displacement." See intra-annular displacement.

Sub-articular zone: The zone, within the vertebral canal, sagittally between the plane of the medial edges of the pedicles and the plane of the medial edges of the facets, and coronally between the planes of the posterior surfaces of the vertebral bodies and the under anterior surfaces of the superior facets. Syn: lateral recess, posterolateral zone. Note: The subarticular zone cannot be precisely delineated because the structures that define the planes of the zone are irregular. The lateral recess refers more appropriately to the space beneath the facet at the pedicular level than as synonymous with the entire subarticular zone.

Sub-capsular: Beneath the composite of annulus and posterior longitudinal ligament. See sub-ligamentous.

Sub-ligamentous: Beneath the posterior longitudinal ligament. Note: Though the distinction between outer annulus and posterior longitudinal ligament may not always be identifiable, sub-ligamentous has meaning distinct from sub-annular, when the distinction can be made. When the distinction cannot be made, sub-capsular is appropriate. Sub-ligamentous contrasts to extra-ligamentous, trans-ligamentous, or perforated. See extra-ligamentous,, trans-ligamentous.
Sub-membranous: Enclosed within peridural membrane. Note: With reference to displaced disc material, characterization of a herniation as sub-membranous usually infers that the displaced portion is extruded beyond annulus and posterior longitudinal ligament so that only the peridural membrane invests it. The peridural membrane may also enclose injectate, hematoma, or abscess. See: trans-membranous.

Supra-pedicular level: The level within the vertebral canal between axial planes of the superior end-plate of the vertebra caudad to the disc space in question and the superior margin of the pedicle of that vertebra. Syn: inferior vertebral notch.

Syndesmophytes: Thin and vertically oriented bony outgrowths extending from one vertebral body to the next and representing ossification within the outer portion of the annulus fibrosus.

Tear of annulus, torn annulus: See fissure of annulus and rupture of annulus.

Traction osteophytes: Bony outgrowth arising from the vertebral body apophysis, 2-3 mm above or below the edge of the intervertebral disc, projecting in a horizontal direction.

Trans-ligamentous: Displacement, usually extrusion, of disc material through the posterior longitudinal ligament. Syn: perforated. See also extra-ligamentous, trans-membranous.

Trans-membranous: Displacement, usually of extruded disc material, through the peridural membrane.

Transverse tear: Tear or fissure of the annulus, running in the axial plane (horizontally), usually limited to rupture of the outer annular attachments to the ring apophysis. Note: Transverse tears are usually small and are located at the junction of the annulus and ring apophysis. They may fill with gas and, thereby, become detectable on conventional radiographs or CT. They may be early manifestations of spondylosis deformans. More extensive radial tears may have a transverse component. See: concentric tears, radial tears.

Uncontained: 1. Displaced disc material that is not contained by uninterrupted outer annulus. 2. (Non-Standard) [A disc in which a substantial portion of the displaced portion of the disc is outside of disc tissues.]
3. (Non-Standard) [A disc in which a displaced portion is wholly outside of disc tissues].
4. (Non-Standard) [A disc in which a displaced fragment is not contained within disc tissues, ligament, or membrane]. See discussion under contained disc.

Undisplaced disc: A disc in which all disc material is within the intervertebral disc space.

Vacuum disc: A disc with imaging characteristics suggestive of gas in the center of the disc space, usually a manifestation of disc degeneration.

Vertebral body marrow changes (Modic's classification): Reactive vertebral body modifications associated with disc inflammation and degenerative disc disease, as seen on MR images.
Type 1 refers to decreased signal intensity on T1-weighted spin-echo images and increased signal intensity on T2-weighted images, indicating bone marrow edema associated with acute or sub-acute inflammatory changes.
Types 2 and 3 indicate chronic changes.
Type 2 refers to increased signal intensity on T1-weighted images and isointense or increased signal intensity on T2-weighted images, indicating replacement of normal bone marrow by fat.
Type 3 refers to decreased signal intensity on both T1 and T2-weighted images, indicating reactive osteosclerosis.

Vertebral notch (inferior): Incisura of the upper surface of the pedicle corresponding to the lower part of the foramen (supra-pedicular level).

Vertebral notch (superior): Incisura of the under surface of the pedicle corresponding to the upper part of the foramen (infra-pedicular level).

Appendix C: Comment on the 2001 AJNR Nomenclature Guidelines

Personal communication with David Fardon

"I don't know how to resolve the issue of injury vs degeneration in the pathogenesis of disc herniation. There are many articles that detail the degenerative process. Most believe, and there are studies to back up, the idea that it would take extraordinary violence to rupture a normal disc. Those who favor the idea that disc herniation and annular defects are all degenerative cite those two groups of studies as evidence that disc herniation is not due to injury. Those who favor the idea that injury can play a role say that a disc weakened by degeneration can be disrupted by injury that is not necessarily violent. My own efforts have been directed to defining terms and recommending standard usage that do not force the issue of degeneration vs. injury. The work you cite, which Pierre Milette and I spear-headed is almost ten years old and we are taking a serious look at modifying it. Major issues involving how language may affect concepts are annulus tear vs. annulus fissure and broad-based protrusion vs. bulge. At this point I am not sure where the revision, if there is one, will take us. As of this writing, I am convinced that there is not a better guideline to the nomenclature of lumbar disc pathology. I will keep your project in mind and send you appropriate references if I run across them."

David Fardon: email of 01/10/2010

Reference

Fardon, D. F. and P. C. Milette (2001). "Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology." Spine (Phila Pa 1976) 26(5): E93-E113.

Section 2: Physiology of the aging disc

A descriptive summary of the known physiology of the ageing disc (to include a short reference to juvenile disc dysfunction).

Executive Summary

This second report comprises a **descriptive summary** [23]of the known biology of the ageing disc. An overview of the scope and methods of this body of work is provided in a separate document entitled "Causation Reviews: spinal injury and disease. Scope and Methods". A more detailed description of the methods used for all seven reports/sections can be found in the Causation Reviews Protocol and in the General Methods section of the review. Methods specific to a particular report/section are summarised briefly at the start of the relevant section.

Background

Back pain and sciatica both have a high prevalence in the general population. For many patients a precise diagnosis is not possible and a failing or "degenerate" intervertebral disc is often cited as the most likely cause.

Intervertebral discs change as a natural consequence of ageing and although painful back conditions can arise from these changes, many aged discs are asymptomatic. In much of the scientific and medical literature "changes in the intervertebral disc with age" is used interchangeably with "degeneration of the intervertebral disc" and may or may not imply changes in the ability of the disc to function properly, or that changes in the disc with age are responsible for pain or other clinical symptoms. Thus in the literature , the relation between "disc aging" and "disc degeneration" is a vexed one and concern has been expressed in relation to the use of the word "degeneration" in the context of spinal injury and any assumption of causality.

In the following evidence based account of changes in the intervertebral disc with age, use of the term "degeneration" has been minimised. Where it is used, it relates to the following;

"The process of disc degeneration is an aberrant, cell-mediated response to progressive structural failure. A degenerate disc is one with structural failure combined with accelerated or advanced signs of aging. Early degenerative changes should refer to accelerated age-related changes in a structurally intact disc." (M. A. Adams & P. J. Roughley, 2006)

And at a more detailed level to;

"real or apparent desiccation, fibrosis, narrowing of the disc space, diffuse bulging of the annulus beyond the disc space, extensive fissuring (i.e., numerous annular tears), and mucinous degeneration of the annulus, defects and sclerosis of the endplates, and osteophytes at the vertebral apophyses." (Fardon & Milette, 2001)

Neither statement implies that disc degeneration is synonymous with pain or other symptoms.

[23] This is not intended to be a systematic review or critical appraisal of the literature.

Morphology and histology of the "normal young disc"

Detailed knowledge of the temporal changes in the micro and macroscopic structure of the "*normal young disc*" and its functioning is a necessary prequel to the interpretation and assessment of disc imaging and the assessment of disc abnormalities.

Normal intervertebral discs are made up of a mixture of white fibrous tissue which gives the disc flexibility and toughness, and cartilaginous tissue which gives the disc elasticity. Three areas of the disc are usually distinguished; a central gelatinous mass known as the *nucleus pulposus,* a fibrous outer ring enveloping this known as the *annulus fibrosus* and vertebral endplates which comprise a cartilaginous layer covering the upper and lower surfaces of the adjacent vertebrae. These different regions of the disc have different compositions and structures which govern their mechanical functioning.

The central nucleus pulposus contains collagen and elastin fibres embedded in a highly hydrated aggrecan-containing gel. Interspersed at a low density are chondrocyte like cells. The annulus fibrosus is made up of a series of 15–25 concentric rings, or lamellae, with the collagen fibres lying parallel within each lamella. Elastin fibres lie between the lamellae. The cells of the annulus tend to be fibroblast-like, elongated and thin and aligned parallel to the collagen fibres.

Collagen is the main macromolecular component of the disc. Collagen concentration is highest in the outer annulus and lowest in the nucleus of the lumbar disc. The other major disc macromolecule is aggrecan. This is a major structural and functional component of the disc. Aggrecan plays an important part in binding water and in regulating the movement of molecules through the extracellular matrix of the disc.

The physiology of the "normal young disc"

The normal adult disc consists predominantly of an extracellular matrix which governs the discs mechanical functioning. The matrix is composed of a complex hydrated network of proteoglycan macromolecules synthesized by a small population of disc cells[24]. These disc cells also produce a complex array of proteinases[25] which are able to degrade all matrix components. In the normal disc a steady state is maintained between the rates of synthesis and degradation of matrix components by proteinases the most potent of which are metalloproteinase[26].

Disc hydration

The mechanical behaviour of the disc is highly non-linear and is dependent on (a) the mechanical loading history of the disc and (b) disc hydration. Mechanical loading at the physiologic level stimulates proteoglycan synthesis and the tissue *inhibitors* of the destructive metalloproteinase; higher or lower loadings stimulate catabolic cell metabolism, reduction of proteoglycan and an *increase* in destructive matrix metalloproteinase.

The normal hydration state of the disc varies with the disc region. Proteoglycan and water content increases on progressing from the outer annulus fibrosus to the inner nucleus pulposus. Large

[24] Disc cells comprise elongated fibroblast-like cells and more rounded chondrocyte-like cells.
[25] A group of enzymes that breakdown proteins.
[26] These are enzymes whose catalytic mechanism involves a metal. Most metalloproteinases are zinc-dependent, but some use cobalt.

proteoglycan aggregates (aggrecan) in the central nucleus pulposus are entrapped in a collagen fibre network. The hydration properties of the aggrecan molecule causes the tissue to swell until an equilibrium is reached in which the swelling potential is balanced by tensile mechanical forces in the collagen fibre network. Compressive loading of the spine forces some water from the disc, effectively increasing the aggrecan concentration and resisting further disc compression. On removal of the compressive load, disc height is restored as water is drawn back into the tissue to re-establish the original equilibrium.

The annulus fibrosus has lower water content than the nucleus. Its high collagen content is organized in dense concentric lamellae forming a fibrous network that *maintains the disc shape* by containing the nucleus pulposus which would otherwise extrude because of the high pressure acting on it. Any parameter that decreases proteoglycan concentration in the nucleus pulposus or weakens the collagen network of the annulus fibrosus is likely to be detrimental to disc function.

Disc metabolism and matrix turnover

Factors regulating nutrient supply to the disc are not well understood, however, failure in the supply of nutrients to the disc cells has been implicated in the initiation and/or progression of disc degeneration. The main nutrients required to maintain the disc cells (and the extracellular matrix), are oxygen and glucose. In the normal young adult disc, blood vessels feeding the disc are *sparse* and, together with some nerves, restricted to the outer layers of the annulus fibrosus. Capillaries providing nutrients and removing waste may be 6-8 mm away from the cells in the centre of the disc and here the movement of nutrients and waste is achieved by diffusion or bulk flow through the extracellular matrix.

Lack of blood supply to the tissue, as result for example of atherosclerosis of the vertebral arteries or partial calcification of the endplates, is believed to be a *potential rate-limiting* step in the transport process. Under conditions in which supply becomes limited, nutrient levels may fall to a level at which cell viability can no longer be sustained and the cells in the centre of the disc may be the first to die; it is noteworthy that the first signs of disc degeneration are often observed in images of the central prat of the disc.

The cells of the disc secrete proteinases[27] that are capable of degrading the extracellular matrix. These enzymes are involved in both the normal turnover and the degradation of the extracellular matrix. Damaged collagen molecules become entrapped in the fibril structure and, due in part to the slow collagen turnover, accumulate. This eventually leads to a weakening of the biomechanical properties of the disc.

Disc healing

Injured discs are reported to have increased levels of catabolic cytokines, increased matrix metalloprotein activity, scar formation (especially in the vicinity of annular tears), renewed matrix turnover and a more variable range of collagen fibre diameters. It has been suggested that *gross injuries* to the disc do not fully heal and that annular tears are not remoddled. However, Many studies of aged

[27] Matrix metalloproteinases (MMPs)

and/or degenerate disc report substantial numbers of granular cells[28] particlarly in tears and fissures which are thought to be part of a healing and repair process.

The ageing intervertebral disc

Reported details of the ageing process depend upon the method of evaluation (MRI vs. histology slides vs. cadaver disc sections), the number and location of the samples/slices taken of each disc, and the population sampled. These different approaches give different perspectives on the ageing of the disc, highlight different features and processes and have led to a plethora of studies describing age-related changes in particular disc populations; not all of these studies concur and most of the studies report on changes in the lumbar discs.

No comprehensive overview of the current state of knowledge of the aging of the intervertebral discs of the spine was identified and no systematic reviews of the aging of the discs of the lumbar spine were found; one recent systematic review of the causes of degeneration of the cervical spine was identified. However, there was general agreement in the literature that aging of the intervertebral disc is universal and that degeneration of the disc as a result of aging was *not necessarily accompanied by clinical symptoms*.

The descriptive account that follows draws on a number of different sources and describes the features of disc aging from a number of different perspectives.

Age related morphological changes in the lumbar disc

Adults

In its 2001 recommendations[29] the combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology considered that perceptions of what constitutes the normal aging process of the spine had been greatly influenced by post-mortem anatomic studies in which pathologic changes were easily confused with the consequences of normal aging. The task force suggested that with *normal aging*, fibrous tissue replaced the nuclear mucoid matrix, but that *disc height was preserved* and the *disc margins remained regular*. Since *radial tears* of the annulus were found only in a minority of post-mortem examinations of individuals over 40 years of age, the task force suggested that these could *not be considered a usual consequence of aging*. They also considered that slight symmetric bulging of the disc could occur in the elderly remodelling of the disc associated with osteoporosis. Large amounts of gas in the central disc space was considered to be pathologic and a feature of intervertebral osteochondrosis rather than a feature of normal aging. Anterior and lateral marginal vertebral body osteophytes were considered to be consequences of normal aging, however, *posterior* osteophytes, were not considered to be inevitable consequences of aging. Endplate erosions with osteosclerosis and chronic reactive bone marrow changes were also considered to be pathologic.

[28] The process of granulation includes neoangiogenesis (formation of new blood vessels) and collagen formation. Granular tissue is also called "scar tissue"

[29] Nomenclature and Classification of Lumbar Disc Pathology: Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology.

Later studies (2002-2007) described a gross sequence of age changes in the intervertebral disc in which;

- the boundary between the nucleus pulposus and the annulus fibrosus becomes less distinct
- the nucleus pulposus becomes more fibrotic and less gel-like
- the disc morphology changes becoming progressively more disorganised
- the lamellae of the annulus fibrosus become irregular with bifurcation and interdigitation
- the collagen and elastin networks become more disorganised
- there is frequent cleft and fissure or tear formation particularly in the nucleus pulposus which is the first part of the disc to show morphological changes with age[30].
- neovascularisation and neo-innervation are increasingly found with degenerative changes
- cell proliferation occurs leading to cluster formation, and particularly in the nucleus pulposus, large amount of granular (repair) tissue may be found filling the tears/fissures .

Juvenile disc disorder/ juvenile degenerate disc disease

There is a population of juveniles that present with chronic low back pain and have degenerative disc disease identified on MRI. There is very little peer reviewed literature about the condition and only one clinical study was identified.

In one information source twenty percent of teenagers were reported to have lumbar discs that show early signs of deterioration which is called "Juvenile" Degenerative Disc Disease when its sufferers are under twenty-one. Disc deterioration was reported to accelerate rapidly with time - especially in boys. The condition as described appears to be very much like degenerative disc disease in the adult population, but with degeneration starting at a *much earlier age,* and usually involving most of the discs of the lumbar spine (as opposed to only one or two discs typically involved in adult degenerative disc disease).

Age related morphological changes in thoracic and cervical intervertebral discs

The cervical spine does not carry the same burden as the lumbar spine and is designed for higher mobility in exchange for less stability. Nevertheless, neck pain is reported to be almost as back pain common in the general population.

The volume of relevant work identified which detailed changes in the cervical and thoracic vertebrae with age was smaller than that found for the lumbar vertebrae, however, a recent systematic review of the causes of cervical spinal degeneration was identified. This review linked disintegration and degrading processes with processes of adaptive remodelling and healing involving cell proliferation. The authors of the review suggested that these changes constituted a “degenerative cascade” which comprised a dysfunctional phase of degenerative changes without biomechanical impact, a hypermobility phase of segment instability due to progressing degeneration and a reestablishment phase characterised by adaptive remodelling to counteract hypermobility. Degenerative changes were listed and included the presence of the following features;

[30] Some studies report that the first changes leading to degeneration are found in the endplate.

- reduced disc height
- osteophytes
- sclerosis of the vertebral endplates
- annular tears
- disc intensity alterations
- disc bulging
- disc herniation (prolapse)

The authors noted that these changes were very similar to those reported for lumbar discs. They also noted that the changes were not specific to humans being found in other species and very common in human prehistoric human materials.

In another study of age-related changes of the thoracic and cervical discs in asymptomatic Japanese subjects approximately half of the subjects exhibited positive MRI findings indicating degeneration at one or more intervertebral levels of the thoracic spine. The positive rates of each MRI finding increased with age. Degenerative MRI findings in the thoracic spine were rarer than those in the cervical spine

The physiology of the aging disc

The maintenance of a healthy fully functional disc requires careful regulation of the extracellular matrix. However, little is known about matrix turnover (matrix synthesis and degradation) in the ageing human intervertebral disc.

A recent study using quantitative MRI measured the concentrations of key matrix turnover molecules and correlated them with aging and grade of degeneration. Three matrix turnover phases were identified and illustrated by collagen II changes:

- *Growth phase (0-15 years):* characterised by active synthesis and denaturation of matrix collagen II molecules.
- *Maturation and ageing phase (15-40 years):* characterised by a progressive reduction in synthetic activity and denaturation of collagen II molecules.
- *Degeneration and fibrotic phase (over 40 years):* characterised by a lack of synthesis of type II procollagen but an increase in collagen II denaturation.

The pattern of type I collagen and aggrecan changes were reported to be similar to that of collagen II. Matrix synthesis was reported to decrease steadily throughout life but sometimes increase again in old and severely disrupted discs.

Age-related classifications and grading systems for lumbar discs

In order to assist a clinical assessment of the intervertebral disc, many studies describing the ageing of the disc also classify and grade the changes according to age-related features and/or the perceived severity of disc changes.

In 2006 Kettler and Wilke carried out a systematic review and evaluation of classification and grading systems for intervertebral discs. Forty-two different grading systems for the discs of the lumbar and cervical spinal regions were identified. Only two were recommended, both proposed classification/grading systems for the lumbar spine;

- Thompson et al (1990) reporting on age related features of the macroscopic anatomy of the lumbar spine
- Boos et al (2002) reporting on age related features of the histology of the lumbar spine.

Thompson (1990) proposed a five-category grading scheme for assessing the gross morphology of mid-sagittal sections of the human lumbar intervertebral disc which reflected the *relationship between age and degree of degeneration.* The disc grades were regressed against age, however, grades were not assigned to discrete age groups and the variation in grade at each age point was fairly large and increased with age.

In 2002, Boos et al classified lumbar disc degeneration based on the histology of human cadaver specimens. Discs were classified into eight groups based solely on age. The *general structure of the discs in each age group* was described using variables from a macroscopic and histologic assessment of the discs in each age group. Ten grades were recognised describing changes in the disc from the foetus to old age (>70 years). General changes and changes in the nucleus pulposus and endplates were described for each grade; however, changes in the annulus fibrosus did not appear in any of the age group descriptions.

Overall, this grading system charted what appeared to be an increasing production of granular tissue, particularly in the areas of tears and fissures, which contrary to other reports, suggests disc tissue repair and/or remodelling. Two major phases of structural change were also apparent. The first phase appeared at ages 3-16 years (Grades 3-4) when the blood vessels supplying the young disc with nutrients become obliterated, the original cells of the nucleus pulposus (notochord cells or chordocytes) disappear and tears/fissures in the nucleus pulposus become abundant. The second appeared at ages 50-<70 years (Grade 8) when the disc appeared to be trying to repair disc faults – with major cell proliferation and granular cells filling clefts and tears and neovascularisation at the edge of the disc.

Since the review by Kettler et al (2006) a number of other grading systems have been published. Only one of these systems related the grade to the age of the disc. In 2007 Watanabe et al developed a grading system based on MRI T2 imaging. In a small sample of healthy volunteers the authors evaluated *early degeneration* of the intervertebral disc. In axial T2 mapping, degenerative grade of the nucleus pulposus generally increased with age ($p<0.05$) but not the degenerative grade of annulus fibrosus. Among all early grade (I and II) intervertebral disks, no herniation was observed. Among grade III intervertebral disks, one third exhibited disk herniation (protrusion in all cases). Among grade IV intervertebral disks, three quarters exhibited disk herniation; two showed protrusion, three showed extrusion, and two showed sequestration. There was huge heterogeneity in the disc grading within and between the different age groups, for example, in four patients between the ages of 23-34 years all *four stages of disc degeneration could be found.*

Age-related classifications and grading systems for cervical discs

No publications were identified that reported on the grading of cervical discs in relation to the age of the disc.

Methods[31]

This second report comprises a **descriptive summary** [32]of the known physiology of the ageing disc.

In the following evidence based account the use of the term "degeneration" has been minimised. Where it is used, it relates to the following;

> *"The process of disc degeneration is an aberrant, cell-mediated response to progressive structural failure. A degenerate disc is one with structural failure combined with accelerated or advanced signs of aging. Early degenerative changes should refer to accelerated age-related changes in a structurally intact disc." (M. A. Adams & P. J. Roughley, 2006)*

And at a more detailed level to;

> *"real or apparent desiccation, fibrosis, narrowing of the disc space, diffuse bulging of the annulus beyond the disc space, extensive fissuring (i.e., numerous annular tears), and mucinous degeneration of the annulus, defects and sclerosis of the endplates, and osteophytes at the vertebral apophyses." (Fardon & Milette, 2001)*

Neither statement implies that disc degeneration is synonymous with pain or other symptoms (Boos et al., 2002).

[31] A more detailed description of all the methods of the seven reviews can be found in the General Methods section and in the Causation Reviews Protocol.

[32] This is an evidence based summary and not intended to be a systematic review or critical appraisal of the literature. ACC has requested that only *systematic reviews*, *clinical guidelines* and other *overviews* be considered in these descriptive reviews and evidence briefings. Where systematic reviews, guidelines and overviews did not provide sufficient information to meet ACCs goals, the available evidence has been (a) summarised and the limitations noted, or (more rarely) (b) key primary studies examined for relevant data/information.

Background

The human spine has 23 intervertebral discs (IVDs) separating the vertebrae. Together these discs account for 20-30% of the length of the spine and increase in size progressively from the cervical to lumbar regions (Roughley, 2004), **Figure 2.1.**

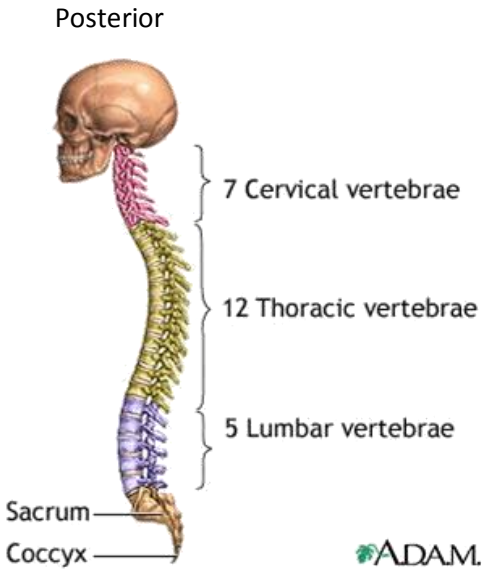


Figure 2.1. Changes in the intervertebral disc and curves of the skeletal spine. http://www.nlm.nih.gov/medlineplus/ency/imagepages/1116.htm

The human IVD has a number of unique characteristics. Firstly, it is the largest avascular structure and one of the most sparsely cellular tissues in the *adult* human body. Secondly, in most individuals the disc undergoes extensive changes throughout the human lifespan and undergoes these changes *earlier* than other tissues in the body and far earlier than other musculoskeletal tissues. Thirdly, the adult IVD appears to be unable to repair extensive damage. Fourthly, there are important differences between the development of the human disc and those of the usual laboratory animals and few animals show degenerative changes resembling those in the human (M. A. Adams & P. J. Roughley, 2006; Meyer, 2010). This has reduced to some extent the relevance of animals models in the study of degeneration and aging of the human IVD and increased (a least in the early days), reliance upon cadaver studies to distinguish between normal aging of the IVD and pathological changes.

Thus the ***reference state*** of the IVD (i.e. the normal disc) is a *moving target* which ***changes with age***, and through the early onset ageing, is to some extent out of step with the rest of the musculoskeletal system.

The central part played by the IVD in the support and mobility of the spine and lack of good animal models of disc degeneration has led increasingly to reliance upon imaging studies to investigate both

normal aging and pathological changes in the IVD. Commonly used imaging techniques include conventional radiography (X-ray imaging), computed tomography (CT) and magnetic resonance imaging (MRI), **Table 2.1.**

Table 2.1. Imaging techniques used in the study of the human IVD. (Lings, Winkel Holm, & Leboeuf-Yde, 2008)

Imaging techniques	Characteristics of the method	Visualisation of
X-ray imaging	Poor visualisation of disc soft tissue	disc space narrowing, disc calcification, gas accumulation
Computed tomography	Better visualisation of soft tissue changes Superior is demonstrating changes in osseous structures	facet joint changes
Magnetic resonance imaging	Better visualisation of soft tissue changes such as	disc bulging disc protrusion disc herniation annular tears nuclear fissures and clefts scarring and calcification of the endplates

However, because of its better ability to visualise soft tissue changes and particularly to demonstrate (using T2 weighted imaging) early changes in the disc due to dehydration, MRI has become the imaging of choice in the study of the IVD (Lings et al., 2008). Thus most of the recent IVD imaging studies rely heavily on the interpretation of MRI images.

The “normal young” intervertebral disc

Intervertebral discs, particularly those in the lumbar spine, undergo extensive morphological changes with age. These changes have been described as a “degenerative cascade” which leads to structural defects and loss of normal function in the spine. The extent of change and the speed with which it occurs is known to vary considerably between individuals; young individuals may have discs that are more characteristic of an elderly person and vice versa. This makes it difficult to distinguish between age-related changes, premature degenerative changes and pathological processes (M. Haefeli et al., 2006). One approach is to compare a given disc with what may be expected for a disc of that age, i.e. a “normal” disc for that age group. Detailed knowledge of the temporal changes in the micro and macroscopic structure of the “normal young disc” and its functioning is a necessary prequel to the interpretation and assessment of client disc imaging.

The Combined Task Force (Fardon & Milette, 2001) defined “normal” intervertebral discs as;

“.....young discs that are morphologically normal, without consideration of the clinical context and not inclusive of degenerative, developmental, or adaptive changes that could, in some contexts (e.g., normal aging, scoliosis, spondylolisthesis) be considered clinically normal.”

This definition allows (a) for an approach in which imaging features of a given disc (e.g. in a patient presenting with back pain) is assessed against what may be considered to be a normal disc for the individuals age, b) makes no assumption about causality and (c) does not infer clinical symptoms.

Morphology and histology of the normal young disc

Intervertebral discs are made up of a mixture of white fibrous tissue giving the disc flexibility and toughness and cartilaginous tissue which gives the disc elasticity. This fibrocartilagenous structure allows the disc to resist spinal compression by spreading the load evenly on the vertebral bodies while allowing limited movement. Thus the disc, together with its adjacent vertebral bodies, forms the basic functional unit of the spine which is generally referred to as the “spinal motion segment”[33]; any two vertebrae (except the fused sacral and coccygeal vertebrae) can represent a motion segment of a particular spinal region **Figure 2.2.**

[33] Together with the associated ligaments this is also known as the “functional spinal unit”.

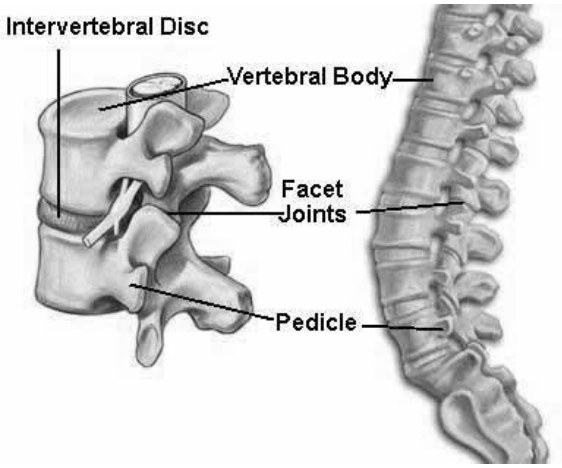


Figure 2.2. The spinal motion segment showing the three joints of the unit, two posterior facet/ postzygapophogeal joints and the intervertebral disc.

While differences exist, there is a *common basic structure* for IVDs from all sites/levels in the spine. Each IVD comprises:

- A central gelatinous mass known as the nucleus pulposus (NP)
- A fibrous outer ring enveloping the NP known as the annulus fibrosus (AF)
- Vertebral endplates (EP) comprising a cartilaginous layer covering the upper (superior) and lower (inferior) surfaces of the adjacent vertebrae

Gross structure of the normal disc

The gross structure of a normal disc is shown in **Figure 2.3.**

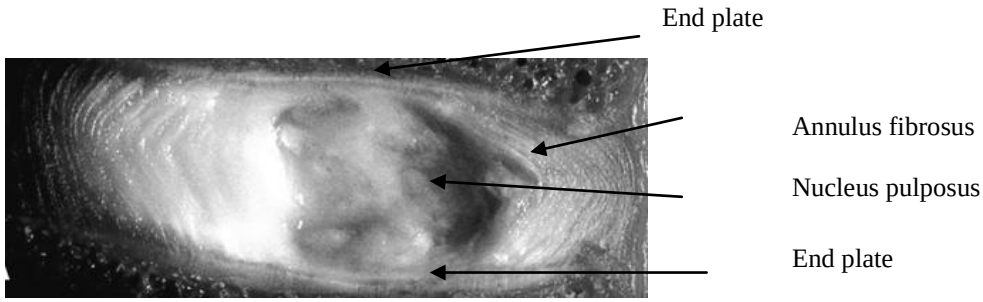


Figure 2.3. Cadaveric lumbar disc from a young male (35 years) sectioned in the mid-sagittal plane (M. A. Adams & P. J. Roughley, 2006)

The *nucleus pulposus* (NP) comprises an oval shaped, highly hydrated gelatinous area contained within a ring of collagen fibres formed from the inner lamellae of the AF.

The *annulus fibrosus* comprises large number (up to 25) lamellae or layers composed of oblique collagen fibres which lie in alternating directions in the different lamellae **Figure 2.4.**

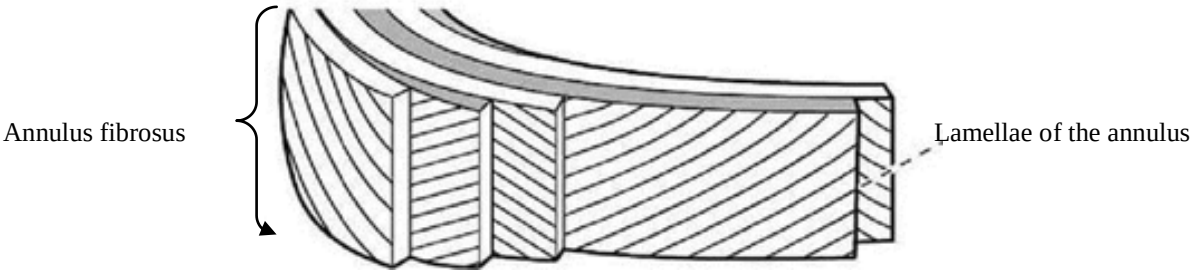


Figure 2.4. Lamellae structure of the annulus fibrosus (M. A. Adams & P. J. Roughley, 2006)

The inner layers of the annulus have high water content, while the outermost layers acts as a tensile skin which retains the hydrostatic nucleus.

The *vertebral endplate* is a thin and incomplete layer of cartilage 0.1-1.6mm thick covering the area of the vertebral body that is encircled by the ring apophysis.

Cellular organisation and microstructure of the normal disc

The normal IVD in adulthood consists predominantly (≈ 99% by volume) of extracellular matrix (ECM) interspersed with a *small number* (≈1% by volume) of disc cells. The disc cells appear to comprise at least two phenotypically distinct populations, elongated fibroblast-like cells more rounded chondrocyte-like cells (S. Roberts, Evans, Trivedi, & Menage, 2006). The IVD has no dedicated phagocyte cells. The *composition and organisation* of the extracellular matrix of the IVD governs its *mechanical functioning.*

The different regions of a disc have different cellular composition and structure, **Figure 2.5.**

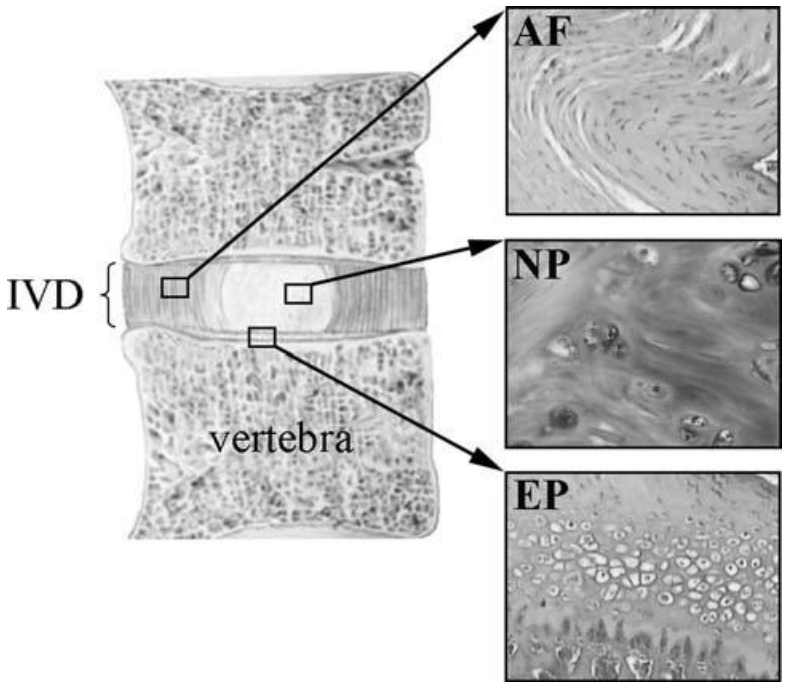


Figure 2.5. The histology of the intervertebral disc showing the cellular structure of the annulus fibrosus (AF), nucleus pulposus (NP) and the cartilaginous endplate (EP). The annulus fibrosus (AF) is a fibrocartilage organized with the fibroblast-like cells in dense concentric lamellae. The nucleus pulposus (NP) is a less structured gelatinous substance with chondrocyte-like cells. The IVD lies between cartilaginous endplates (EP) (Mwale, Iatridis, & Antoniou, 2008).

In the adult[34] NP chondrocytic cells are enmeshed in an aqueous matrix consisting of proteoglycans (macromolecules such as aggregan), collagen fibres and other non-collagenous proteins and elastins (Dang & Liu, 2010; Lundon & Bolton, 2001). The chondrocytes secrete the NP proteoglycans and type II collagen (Beattie, 2008).

The AF tissue bears resemblance to both ligaments and large arteries. The lamellae of the *inner* AF consist mostly of fibrochondrocytes and type II collagen , while the lamellae of the *outer* AF are composed predominantly of type I collagen and are populated by fibroblasts that secrete the type I collagen (Beattie, 2008; Dang & Liu, 2010).

The human endplate functions as a growth plate for the vertebral bodies and has the structure of an epiphyseal growth plate. Initially the EP is thick and occupies a *substantial fraction* of the disc and is penetrated by cartilage canals and small blood vessels. At maturity the EP consists of a thin (<1 mm)

[34] The notochord gives rise to the nucleus pulpous. The immature NP contains large chordocytes and small chordoblasts inherited from its precursor the notochord. The surrounding AF is derived from the mesoderm and in the embryonic disc there is a distinct demarcation between the fluid-like NP rich in notochord cells and proteoglycan, and the fibrous AF which is rich in fibroblast-like cells and collagen. Following birth the notochord cells of the NP decline in abundance and are replaced by chondrocyte-like cells of mesoderm origin, by the age of 10 years there are no notochord cells in the NP and the chondrocyte-like cells alter the composition of the NP which becomes firmer due to collagen fibre accumulation (Roughley 2004)

avascular layer of hyaline cartilage that is partially calcified at the vertebral body-endplate junction (Meyer, 2010). It is strongly attached to the disc via the annulus fibrosus and only weakly attached to the vertebral body. The thinnest region of the endplate is the central portion that covers the nucleus pulposus.

Physiology of the normal disc

There is a relatively poor understanding of the physiology of the normal disc, and in particular, the relationships between function, or malfunction, and structure at both the cellular and molecular levels. The requisite information is difficult to acquire largely due to experimental difficulties of various sorts.

The intervertebral disc is closely coupled structurally, physiologically, and biomechanically, to the vertebral body and surrounding ligaments and musculature. The value of many measurements on excised discs *in vitro* is therefore severely compromised because these relationships are inevitably disrupted. *In vivo* approaches are also limited. Because these measurements generally involve extensive interventions, they have generally been confined to animals, but as previously noted, there is great variability in disc structure between species and few animals show degenerative changes resembling those in the human.(M. A. Adams & P. J. Roughley, 2006; Meyer, 2010)

Disc composition

In the normal young disc the disc matrix the hydrated network of proteoglycan macromolecules is synthesized by a *small population of disc cells*. The latter also produce a complex array of proteases[35] which are able to degrade all matrix components. The macromolecular composition of the disc varies in the different regions of the disc and a steady state is maintained between the rates of synthesis and degradation of matrix components.

Collagen is the main macromolecular component of the disc. Collagen content is highest in the outer annulus and lowest in the nucleus of the lumbar disc. The other major disc macromolecule is *aggreca*n which is a large aggregating proteoglycan consisting of a protein core to which are attached many side-chains (such as hyaluronan). Aggrecan is a major structural component of the disc and plays an important part in binding water, and also in regulating the movement of molecules through the matrix (Meyer, 2010). Other smaller interstitial proteoglycans are thought to play a role in the regulation of ECM assembly and repair after injury (Beattie, 2008).

Disc hydration

The composition and organization of the extracellular matrix of the IVD governs the disc's *mechanical function*. The main constituents of the ECM (collagen and proteoglycans) control the mechanics and water content of the discs. The latter is regulated through osmotic pressure exerted by the proteoglycans and the resistance to swelling provided by the fibrilic collagens[36].

The mechanical behaviour of the disc is highly non-linear and is dependent on both *loading history* as well as hydration. Mechanical loading at the physiologic level stimulates proteoglycan synthesis and

[35] A group of enzymes that breakdown proteins.

[36] Thus the IVD may be considered as a biphasic tissue comprising a porous and permeable, fibre-reinforced solid phase and a fluid phase of water mixed with ions. In general, proteoglycans of the solid phase provide much of the compressive stiffness while collagen helps to immobilize proteoglycans within the tissue and provides tensile and shear properties (Mwale et al., 2008).

tissue inhibitors of metalloprotienases-1. *Higher or lower* loadings stimulates *catabolic cell metabolism, reduction of proteoglycan and increase in destructive metalloprotienases-3* (Kishen & Diwan, 2010).

The normal hydration state of the disc varies with region. The proteoglycan and water content increases on progressing from the outer AF to the inner NP. It also varies with spinal level; the proteoglycan content of the NP is highest in the cervical discs and lowest in the lumbar discs (Roughley, 2004).

The large proteoglycan aggregates of the NP (aggrecan) are entrapped in a collagen fibre network. The hydration properties of the aggrecan molecule causes the tissue to swell until an equilibrium is reached in which the swelling potential is balanced by tensile forces in the collagen network **Figure 2.6a**. Compressive loading of the spine forces some water from the disc effectively increasing the aggrecan concentration and its swelling potential and resisting further compression **Figure 2.6b.** On removal of the compressive load, disc height is restored as water is drawn back into the tissue to restore the original equilibrium conditions (M. A. Adams & P. J. Roughley, 2006).

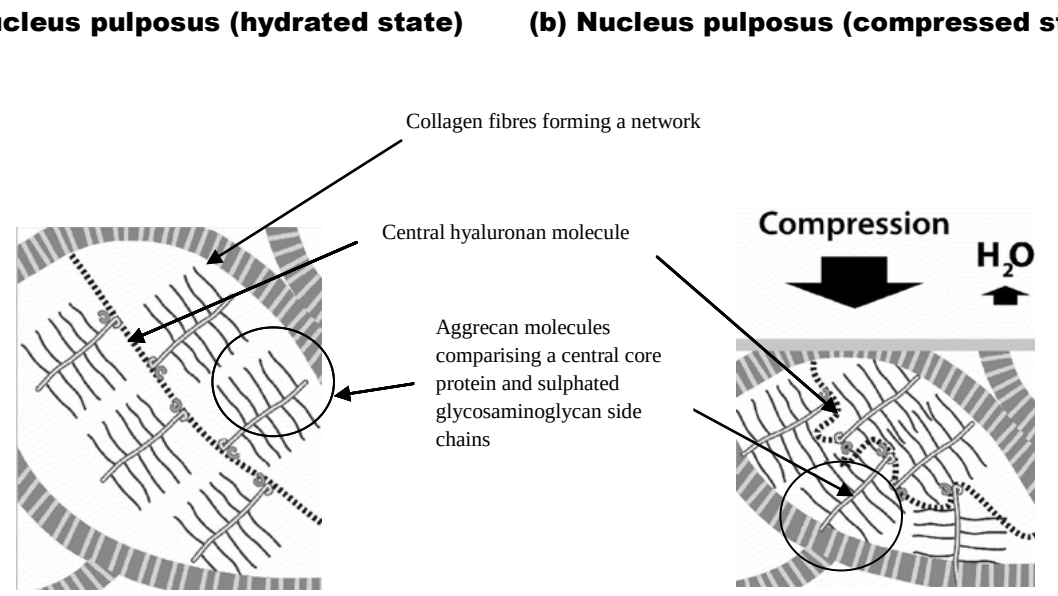


Figure 2.6. The role of aggrecan and collagen in the ability of disc to resist compression, a) hydrated state b) compressed state (M. A. Adams & P. J. Roughley, 2006).

Any parameter that decreases proteoglycan concentration or weakens the collagen network will be detrimental to disc function (M. A. Adams & P. J. Roughley, 2006).

The annulus fibrosus has a lower water content than the nucleus (Cheung & Al Ghazi, 2008). It is composed predominantly of type I collagen organized in dense concentric lamellae forming a fibrous

network that *maintain the disc shape*, **Figure 2.7.** Its function is to contain the NP which would otherwise extrude because of the high pressure acting on it (Cheung & Al Ghazi, 2008).

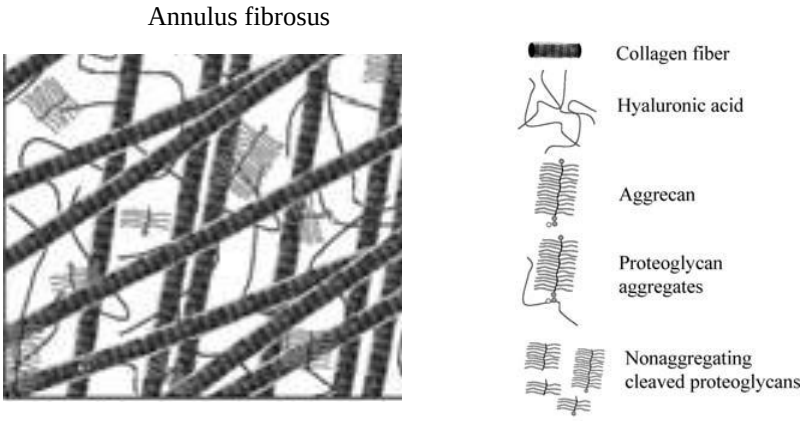


Figure 2.7. Schematic representation of the extracellular matrix of the annulus fibrosus (Mwale et al., 2008).

Disc metabolism

Factors regulating nutrient supply to the disc are not well understood, however, failure in the supply of nutrients to the disc cells has been implicated in the *initiation and/or progression of disc degeneration*[37] (Boos et al., 2002). The main nutrients required to maintain the disc cells and the extracellular matrix are oxygen and glucose. Disc cells obtain energy primarily by glycolysis of glucose and die within 2-3 days under low glucose conditions. Disc cells can operate under low oxygen; however their ability to make and repair the disc matrix is compromised if levels fall too low. Lactic acid (which accumulates as a breakdown product) has to be removed from the matrix or the drop in pH (which results from lactic acid accumulation), will adversely affect matrix synthesis and maintenance and kill the disc cells.

In the normal young adult disc, blood vessels feeding the disc are sparse and, together with some nerves, restricted to the outer layers of the annulus.

Capillaries providing nutrients and removing waste may be 6-8 mm away from the cells in the centre of the disc and the movement of nutrients and waste is achieved by diffusion or bulk flow through the dense extracellular matrix.

Information on the movement of solutes and water in the disc is limited. Lack of blood supply to the tissue (as result for example of atherosclerosis of the vertebral arteries), or partial calcification of the endplates are believed to be potential rate-limiting steps in the transport process. Under conditions in which supply becomes limited, nutrient supply may fall to a level in which cell viability can no longer be sustained and the cells in the centre of the disc may be the first to die; it is noteworthy that the first signs of disc degeneration are often observed in images of the disc centre.

Matrix turnover

The cells of the disc secrete proteinases that are capable of degrading the extracellular matrix. Matrix metalloproteinases (MMPs) are able to degrade all of the major components of the IVD. They are involved in both the normal turnover and the degradation of the extracellular matrix. MMP-1, -8, and -13 (collagenases) can cleave the triple helical part of the collagens types I, II, and III. The damaged collagen molecules are then entrapped in the fibril structure and accumulate, due in part to the slow collagen turnover. This eventually leads to a weakening of the biomechanical properties of the disc.

Similarly, the mature human disc contains a high proportion of the non-aggregating proteoglycans derived by proteolytic degradation and retained in the disc. In the adult disc most of the proteoglycans are non-aggregated and undergo extensive proteolytic processing. However, the cleaved fragments are not lost, but are entrapped into the matrix and can still temporarily contribute to resisting compressive forces (Mwale et al., 2008).

Aggrecan is degraded by proteases (aggrecanases) which are members of the ADAM[38] family of proteins. The proteases MMP-1 and ADAMTS-4 are expressed in few cells of normal discs. Protease MMP-2 is present in *early phases of disc degradation* and MMP-1, -3, -9, and -13, as well as ADAMTS-4, have been

[37] This one of a number of factors that has been reported as central to degeneration, others are fatigue failure (repeated subliminal insults to the disc) of the NP and accumulation of degraded ECM products are two others – essential the cause of degenerative changes is not known. (A. G. Hadjipavlou, M. N. Tzermiadianos, N. Bogduk, & M. R. Zindrick, 2008)

[38] A Disintegrin And Metalloprotease

observed in *degenerated IVDs*, and MP-1, -3, and -13 and ADAMTS-4 expression appear to *increase with the severity of disc degeneration*.

Disc healing

Injured discs are reported (M. A. Adams & P. J. Roughley, 2006) to have the following characteristics

- increased levels of catabolic cytokines,
- increased matrix metalloprotein activity
- scar formation, especially in the vicinity of annular tears
- renewed matrix turnover
- a more variable range of collagen fibril diameters

Adams et al (2004) suggested that gross injuries to a disc never fully heal and that annular tears are not remodelled (presumably because the sparse cell population is unable to break down the large collagen fibre bundles of the annulus and replace them with new). Collagen turnover time in articular cartilage is approximately 100 years and could be even longer in the disc. Proteoglycan turnover is faster, possibly 20 years, and some regeneration of nucleus pulposus is possible in young animals. Injuries that affect the inner annulus or endplate decompress the nucleus, and healing processes are then overtaken by severe degenerative changes. Many studies of aged and/or degenerate disc report substantial numbers of granular cells[39] particlarly in tears and fissures which are thought to be part of a healing and repair process.

[39] The process of granulation includes neoangiogenesis (formation of new blood vessels) and collagen formation. Granular tissue is also called "scar tissue"

The aging of the intervertebral disc

As individuals age their spines undergo *characteristic changes* which are part of the *normal aging or maturation process*. The aging of the intervertebral disc has been widely studied. This is due in no small part because the ageing process is viewed as an important *confounder* in the relationship between imaging findings and symptoms (i.e. there is a strong association between aging and the prevalence of imaging abnormalities) (Jarvik & Deyo, 2000).

Different disciplines use different tools and *see different things* (A. G. Hadjipavlou et al., 2008). There is general agreement that aging of the intervertebral disc is *universal* and that degeneration of the disc as a result of aging is *not necessarily accompanied by clinical symptoms* (Beattie, 2008). However, reported details of the ageing process depends upon the method of evaluation (MRI vs. histology slides vs. cadaver disc sections), the number and location of the samples/slices taken of each disc, and the population sampled. These different approaches give different perspectives on the ageing process and highlight different features and processes. This has led to a plethora of studies describing age-related changes in particular disc populations and the classification and grading of these changes; not all of these studies concur.

The evidence base

No comprehensive overview of the current state of knowledge of the aging spinal disc or systematic reviews of the aging lumbar spine was identified. One recent systematic critical literature review of the causes of *cervical* spinal degeneration was found (Lings et al., 2008). However, over the past 10 years there have been a number of narrative reviews and overviews describing the aging of the intervertebral disc from different perspectives. These reviews have reported variously on;

- macroscopic and microscopic/histological changes (M. A. Adams & P. J. Roughley, 2006; Beattie, 2008; M. Haefeli et al., 2006; S. Roberts et al., 2006; Sukthankar, Nerlich, & Paesold, 2008),
- cell biology changes (Kishen & Diwan, 2010; Roughley, 2004),
- structure and functional changes (A. G. Hadjipavlou et al., 2008; Lundon & Bolton, 2001; Meyer, 2010; Mwale et al., 2008),
- natural history (Benoist, 2003),
- epidemiology and genetics (Cheung & Al Ghazi, 2008; Nunes, Conforti-Froes, Negrelli, & Souza, 2007)
- biomechanical changes (Ferguson & Steffen, 2003).

Cadaver, genetic, radiographic, MRI and epidemiological data have been reported in these reviews; in some instances the data have been used to produce classification of age-related changes and grade those changes [insert page references for classification and grading schemes)

These narrative reviews have been supplemented post publication by additional studies (Matsumoto et al., 2010; Okada et al., 2009; Vernon-Roberts et al., 2007; Videman, Gibbons, & Battié, 2008). In addition, because “age-related alterations” and “degeneration” have to some extent been used

interchangeably in the literature a number of reviews of disc degeneration are relevant (M. A. Adams & P. J. Roughley, 2006; Roughley, 2004; Vernon-Roberts et al., 2007; Videman et al., 2008).

Since no comprehensive overview of the current state of knowledge of the aging intervertebral disc was identified, the descriptive account that follows draws on a number of different sources and describes the features of disc aging from a number of different perspectives. It should also be noted that there have been several shifts in expert opinion over time regarding causation in relation to changes in the intervertebral disc; these have been reflected in changing terminology and underlying models. Two of the most notable underlying models are summarised below:

- Traditional wear and tear injury or repetitive loading model which implies that overloading from a single excessive force or repetitive loading results in structural damage (accelerated degeneration/age related changes or herniation),
- A more recent genetic40 model (derived from exposure discordant studies of twins) suggests that heredity rather than age and external insults/influences may play a major role in disc degeneration and that there is a genetic susceptibility to a that accelerates progressive age related degenerative process(Battie et al., 2009; Battié, Videman, & Parent, 2004). Thus individuals with specific gene polymorphisms may develop disc degeneration at an earlier age than those without (Hangai et al., 2008)41.

Differing underlying models may in part explain the lack of concurrence between studies describing age-related changes and the classification and grading of these changes.

Age related changes in the lumbar disc

The normal ageing of the disc: the Combined Task Force[42]

The Task Force considered that *perceptions* of what constitutes the *normal aging process* of the spine had been greatly influenced by post-mortem anatomic studies involving a limited number of specimens, harvested from cadavers from different age groups, with *unknown past medical histories*, and the *presumption of absence of lumbar symptoms*. They suggested that with such methods, *pathologic changes were easily confused with the consequences of normal aging*.

In this context the differentiating features of two degenerative processes involving the intervertebral disc were briefly highlighted;

- spondylosis deformans which affects essentially the annulus fibrosus and adjacent apophyses , Figure 2.8b
- intervertebral osteochondrosis which affects mainly the nucleus pulposus and the vertebral body endplates, but also includes extensive fissuring (numerous tears) of the annulus fibrosus, which may be followed by atrophy, Figure 2.8c.

[40] A large number of genes have been identified that are linked to disc degeneration, and number of specific gene forms (polymorphisms) have been associated with disc degeneration.
[41] Original studies include Kawaguchi Y, Kanamori M, Ishihara H, Ohmori K, Matsui H, Kimura T. The association of lumbar disc disease with vitamin-D receptor gene polymorphism. J Bone Joint Surg Am 2002;84-A: 2022–8. Seki S, Kawaguchi Y, Chiba K, et al. A functional SNP in CILP, encoding cartilage intermediate layer protein, is associated with susceptibility to lumbar disc disease. Nat Genet 2005;37:607–12.
[42] The Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology

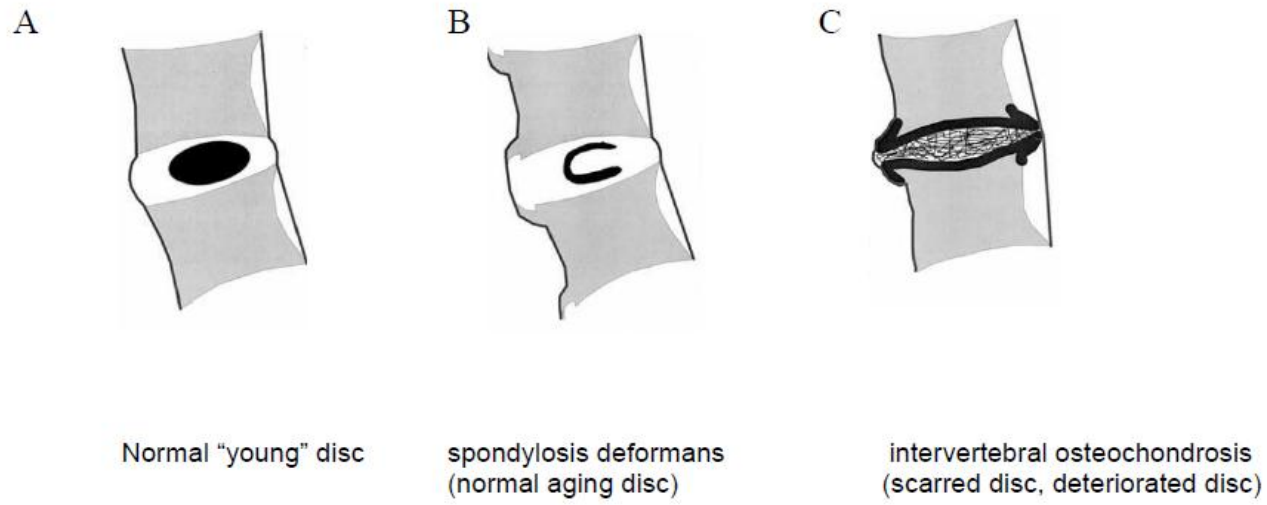


Figure 2.8. Schematic sagittal anatomic sections showing the differentiating characteristics of the normal disc, spondylosis deformans, and intervertebral osteochondrosis. The distinction between these three entities is usually possible on all imaging modalities, including conventional radiographs (Fardon & Milette, 2001; P. Milette, 1997)

Scientific studies suggest that spondylosis deformans is the consequence of normal aging, whereas intervertebral osteochondrosis, sometimes also called "deteriorated disc," results from a clearly pathologic, although not necessarily symptomatic, process. A number of other observations relating to the ageing of the IVD were made;

- The task force suggested that with normal aging, fibrous tissue replaced the nuclear mucoid matrix, but that disc height was preserved and the disc margins remained regular. Since radial tears of the annulus were found only in a minority of post-mortem examinations of individuals over 40 years of age, the task force suggested that these could not be considered a usual consequence of aging (Fardon & Milette, 2001).
- It was considered that slight symmetric bulging of the disc could occur in the elderly remodelling of the disc associated with osteoporosis.
- On conventional radiographs and computed tomography (CT), small amounts of gas which can be detected in some elderly individuals at the annular/apophyseal enthesis, were thought to probably be located in small transverse annular tears, and possibly signify early manifestations of spondylosis deformans; however, a large amount of gas in the central disc space was considered to be pathologic and a feature of intervertebral osteochondrosis.
- As anterior and lateral marginal vertebral body osteophytes have been found in 100% of skeletons of individuals over 40, they should be considered to be consequences of normal aging. However, posterior osteophytes, which have been found in only a minority of skeletons of individuals over 80, were not considered to be inevitable consequences of aging.
- Endplate erosions with osteosclerosis and chronic reactive bone marrow changes were also considered to be pathologic. Slight to moderate decrease in central disc signal intensity found

on T2-weighted MRIs could be a non-pathologic age-related observation but, if the result of a normal process should be relatively uniform among all discs studied in the individual.

The task force thus distinguished clearly between normal ageing and what they termed the "deteriorated disc" or intervertebral osteochondrosis (also sometimes called "chronic discopathy,") and drew attention to the differential characteristics of the latter noting that on microscopic examination, intervertebral osteochondrosis was characterised by total structural disorganization and general replacement of normal disc tissue by fibrosis. Radiographically, intervertebral osteochondrosis was characterized by;

- narrowing of the intervertebral space,
- irregular disc contour often associated with bulging,
- multidirectional osteophytes often involving the central spinal canal and foramina,
- endplate erosions with reactive osteosclerosis,
- chronic vertebral body bone marrow changes
- markedly decreased central disc signal intensity on T2 weighted images and at distinct variance, to that seen in unaffected discs of the same individual.

In one of the studies that underpinned the task forces work, Milette (1997) determined that an assessment of *multiple parameters* was required to differentiate normal aging disks from truly degenerated or "scarred" disks. He used 11 criteria to distinguish between the normal aging disc and a deteriorated disc/scarred disc, **Table 2.2.**

Table 2.2 Differentiating features of the normal aging disk and the scarred /deteriorated disk (Denaro et al., 2009)

Assessment	Criterion	Normal ageing disc	Scarred disc
Clinical			
	age	over 40 years	all ages
	symptoms	none	frequent
	history of low back pain	none	frequent
Plain films and CT			
	disk space height	normal	decreased
	posterior disc margin	regular	irregular
	vertebral bodies	normal	osteosclerosis
	osteophytes	anterolateral	all directions
	intradiscal gas	anterolateral	central
	number of affected discs	all	variable
Additional criteria for MR			
	vertebral body marrow	normal for age group	Modic type 2 or type 3 changes
	central disc intensity	slight decrease	marked decrease

In keeping with the relatively neutral position adopted in the Task Force's guidelines, this scheme was *not reproduced* in their work. Moreover, Modic changes[43], which are reported by radiologists and indicate changes in the MRI texture of the bone adjacent to the disc and indicate acuteness or otherwise of the changes, are also not detailed.

The morphology and histology of the ageing (lumbar) disc

The morphology and histology of the aging disc has been well described in later studies (Boos et al., 2002; J. Urban & Roberts, 2003; Vernon-Roberts et al., 2007) and the gross sequence of change is now well known and are summarised below and reported in more detail in the subsequent text;

- the boundary between the nucleus pulposus and the annulus fibrosus becomes less distinct
- the nucleus pulposus becomes more fibrotic and less gel-like
- the disc morphology changes becoming progressively more disorganised
- the lamellae of the annulus fibrosus become irregular with bifurcation and interdigitation
- the collagen and elastin networks become more disorganised
- there is frequent cleft and fissure formation particularly in the nucleus pulposus which is the first part of the disc to show morphological changes with age44.
- neovascularisation and neo-innervation are increasingly found with degenerative changes
- cell proliferation occurs leading to cluster formation, particularly in the nucleus pulposus, large amount of granular (repair) tissue may be found filling the tears/fissures .

Macroscopic changes to the disc were first detailed in cadaver specimens. Gross structural changes to the disc were graded to reflect degenerative stages; these did not necessarily correlate with age, **Figure 2.9.**

[43] Reactive vertebral body modifications associated with disc inflammation and degenerative disc disease, as seen on MR images. Type 1 refers to decreased signal intensity on T1 –weighted spin-echo images and increased signal intensity on T2-weighted images, indicating bone marrow oedema associated with acute or sub-acute inflammatory changes. Types 2 and 3 indicate chronic changes. Type 2 refers to increased signal intensity on T1 -weighted images and isointense or increased signal intensity on T2-weighted images, indicating replacement of normal bone marrow by fat. Type 3 refers to decreased signal intensity on both T1 and T2 -weighted images, indicating reactive osteosclerosis.
[44] Some studies report that the first changes leading to degeneration are found in the endplate**.**

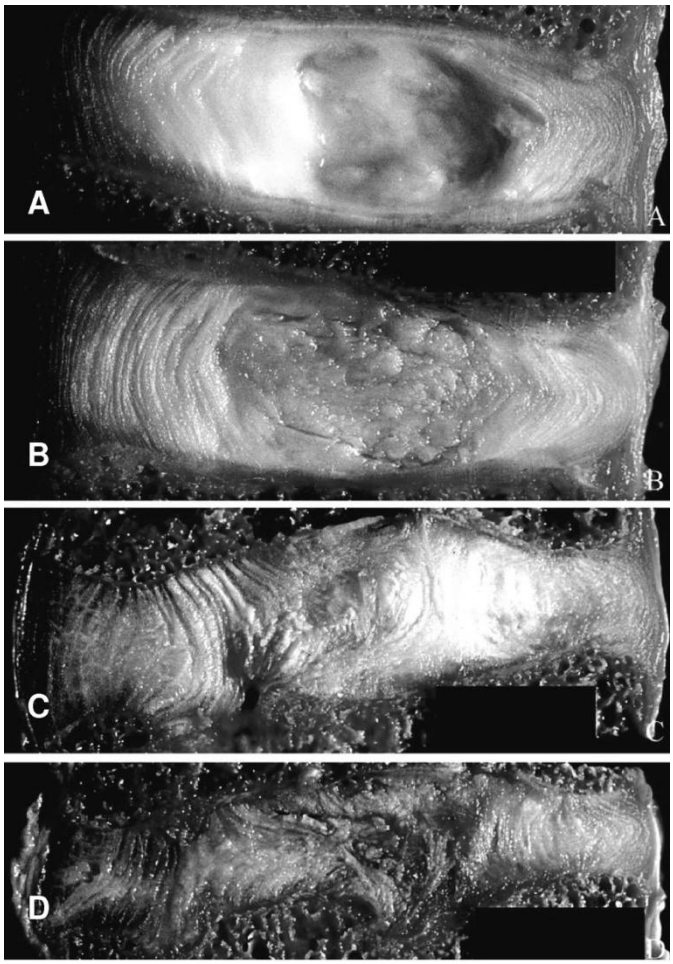
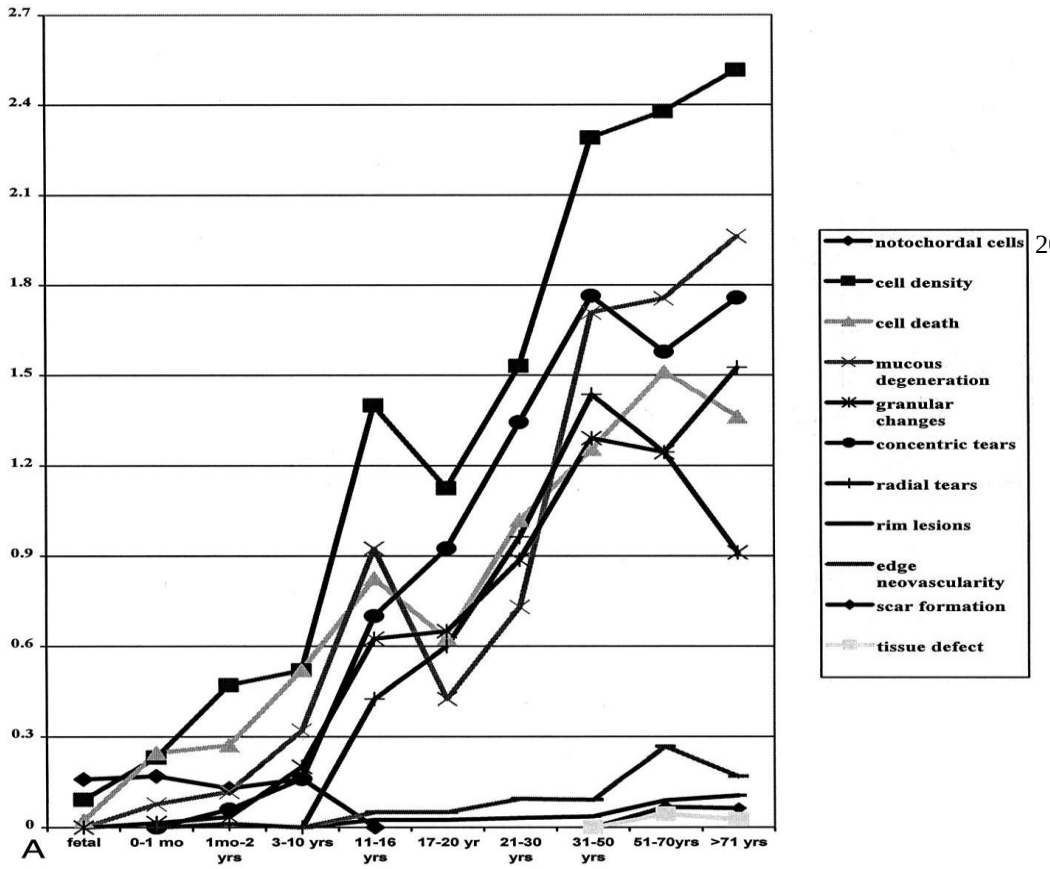


Figure 2.9. Cadaveric lumbar intervertebral discs sectioned in the mid-sagittal plane (anterior on left). (A) Young disc (male, 35 years old). (B) Mature disc (male, 47 years old). (C) Disrupted young disc (male, 31 years old). Note the endplate damage and inward collapse of the inner annulus. (D) Severely disrupted young disc (male, 31 years old). Note the collapse of disc height. Discs (A–D) correspond to the 4-point scales typically used to grade "disc degeneration" from macroscopic features. (M. A. Adams & P. J. Roughley, 2006)

In an effort to improve the rather poor resolution provided by previous macroscopic approached to disc changes Boos et al (2002) analysed the histological features of age-related changes to the lumbar intervertebral disc and end plate in spines harvested during routine autopsy from individuals without any known spinal problems aged 0-88 years. Histological variables (i.e. mucous degeneration, rim lesions, radial and concentric tears scar formation etc.) were correlated with age and macroscopic degeneration to provide a classification and grading of age-related histological disc alterations, **Figure 2.10.**



2002).

Figure 2.10: Temporal variation in histological variables for the intervertebral disc (Boos, N., Weissbach, S. et al. 2002)

The temporal course of histological change in lumbar intervertebral discs with age included an increase in cell density and in tears and lesions in the annulus fibrosus and the nucleus pulposus. Important changes in the end plate were also described which included a decrease in endplate vascularity between the ages of 0-10 years. The obliteration of blood vessels was accompanied by an increase in cartilage disorganisation, cracks and cell density in the endplate which reaches a first maximum between the ages of 11-16 years. Changes in the endplate largely preceded changes in the nucleus pulposus which started in the second decade of life. Clefts and tears develop in the central area of the disc and there is a substantial increase in cell death. From the age of 17 years there is a steady increase in the in structural abnormalities within the disc and in cell density, granularity, mucoid degeneration and decaying cells. Between the ages of 50-70 years tissue alterations become most severe, tears become filled with granular material and in the endplate micro fractures and bone sclerosis may be seen; in some cases scar formation and advanced tissue destruction occur. In the elderly (over 70 years) large tissue defects may be observed and frequently the distinction between the anatomical regions of the disc is lost. In general, histological changes in the disc and the endplate were mirrored macroscopically.

These changes with age are summarised in the next section in relation to the grading of age-related changes (**Table 2.4**). The full description of the changes with age as reported by Boos et al (2002) is given in **Appendix A.**

Boos et al (2002) developed a histological degeneration classification which was reported to correlated well with both age (P<0.0001) and macroscopic grade of degeneration[45] (P<0.001). However, the authors demonstrated that discs of a very young person could exhibit very advanced histological alterations while those of some elderly persons exhibited only minor histological changes. They also noted that that *severe disc abnormalities revealed by MRI remain asymptomatic in the majority of individuals.*

Overall, this work demonstrated (a) an early occurrence of nuclear clefts (i.e. in the second decade of life), (b) heterogeneity in the alterations within the disc (c) relevant spatial differences (e.g. more alterations were usually present in the posterolateral aspects of the disc) and importantly (d) the importance of nutritional supply to the disc for the maintenance of a health disc, (e) the continuous destructive and reparative changes in the tissues with age; the early onset (second decade of life) of disc tissue breakdown following the decrease in vascularisation of the endplate; and the considerable variation in the degree of histological change with some young individuals showing advanced tissue alterations and some elderly individuals exhibiting only minor histological change.

The hallmarks for degenerative changes in the *IVD* suggested by this work were;

- chondrocyte proliferation (increasing cell clusters due to reactive proliferation)
- mucous degeneration (accumulation of mucous substances)
- cell death
- tear and cleft formation
- granular changes: increasing accumulation of granular tissue

The hallmarks for degenerative changes in the *endplate* suggested by this work were;

- cell proliferation
- cartilage disorganization
- presence of cracks in the cartilage (fissure formation)
- presence of micro fractures
- formation of new bone
- bony sclerosis

(Lundon & Bolton, 2001; Sukthankar et al., 2008)

More recently Vernon-Roberts et al (2007) used freshly removed intact lumbar spines used to develop an *age-related three-dimensional survey of tears or fissures in the L4-L5 discs* (Vernon-Roberts et al., 2007).

Transdiscal tears, radiating tears concentric tears, perinuclear tears and rim were recorded using a "crack-map" system. The total "crack-map" score was highly correlated with age (P<0.00006) suggesting

[45] All the intervertebral discs were evaluated macroscopically and the degree of disc degeneration was ranked from Grade 1 (normal juvenile disc) to Grade 5 (severe degeneration) using Thompson's grading scheme.

a linear increase in the extent of the disk involved with tears with age. The results were partitioned into 3 age groups; 10-30 years, 31-50 years and 51-80 years, **Figure 2.11.**

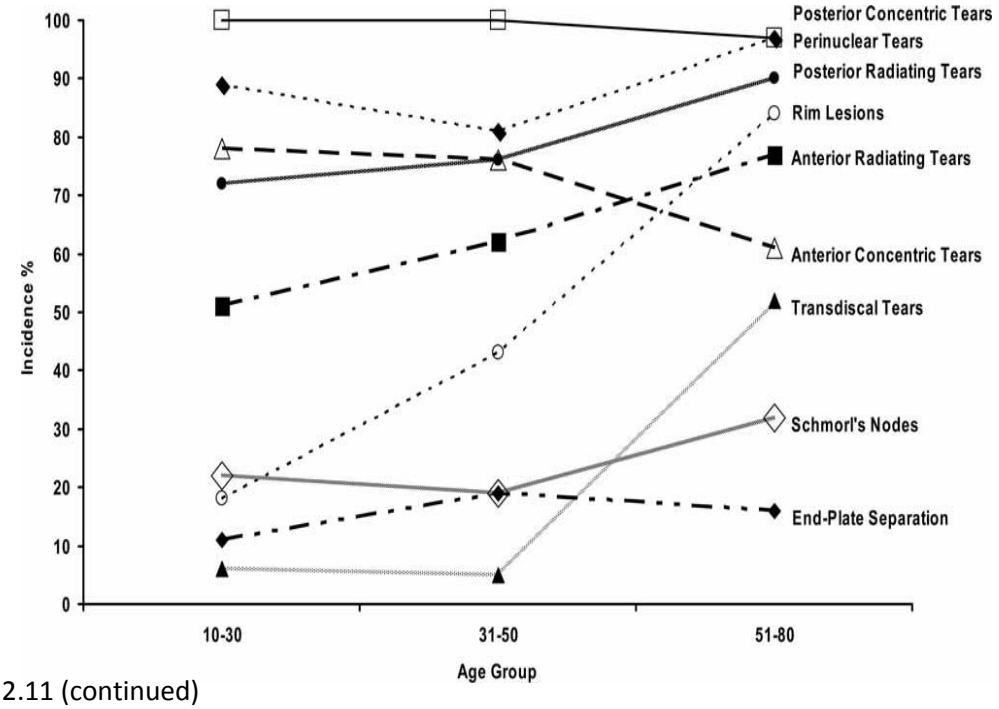


Figure 2.11 (continued)

Feature		10-30 years	31-50 years	51-80 years
Radiating tears	Post	68%	Increasing	~90%
	Ant	47%		>75%
Concentric tears	Post	100%	100%	100%
	Ant	75%	75%	75%
Perinuclear tears		~90%	~82%	~98%
Transdiscal tears		Rare	Rare	50%
Rim lesions		~18%	~45%	>80%
Endplate separations		10%	19%	17%
Schmorl's nodes		~20%	~17%	~30%

Figure 2.11. Graph and data table showing percentage incidence of each type of tear in the L4 –L5 disc in 3 age groups and the frequency of different type of disc tears or fissures with age as determined from the examination of freshly removed lumbar discs (Vernon-Roberts et al., 2007).A high incidence of tears was demonstrated in the 10-30 year old age group. Concentric tears at the junction of the outer (thicker) and inner (thinner) bands of the posterior annulus were the first to appear followed by perinuclear tears at the upper and lower borders of the

nucleus pulposus and posterior rim tears. These tears were frequently observed to appear in the posterior disc first. (Vernon-Roberts et al., 2007)

Rim lesions and transdiscal tears showed a low incidence (20%) in the 10-30 year old age group but were present in over 90% of 51-80 year-old discs. Trandiscal tears were rarely recorded outside this group. Neovascularisation of tears was not apparent before the age of 50 years. After 50 years neovascularisation was observed in approximately 40 % of transdiscal tears and 14 % of posterior radial tears; anterior radial tears did not appear to show revascularisation at any age. Despite revascularisation there was no evidence of successful repair by scar tissue formation within transdiscal or radiating tears. Nerves appeared to accompany the in-growing blood vessels. Schmorl's nodes were present in nearly 20% of discs before the age of 30 years.

The nucleus pulposus showed the earliest signs of deterioration with perinuclear tears commonly present during adolescence. Extension of the axial arms of these perinuclear tears formed anterior and posterior radial tears in many cases (i.e. radiating tears start from within the nucleus pulposus before extending radially).

Posterior concentric tears were the first tears to appear in the annulus and rarely absent after the age of 30 years. Substantial differences between the anterior and posterior annulus were reported consistent with a dominant compressive role for the outer anterior annulus and a major tensile role for the inner posterior annulus

Juvenile disc disorder/ juvenile degenerate disc disease

There is a population of juveniles that present with chronic low back pain and have degenerative disc disease identified on MRI. There is very little peer reviewed published literature about the condition and the brief account below was informed by one case series (W. Jacobs et al., 2004) and a number of websites reporting on juvenile disc disease.

It is reported that twenty percent of teenagers have lumbar discs that show early signs of deterioration. [46]. This is called "Juvenile" Degenerative Disc Disease when its sufferers are under twenty-one. Disc deterioration accelerates rapidly with time - especially for boys. The condition appears to be very much like degenerative disc disease in the adult population, but the degeneration starts at a *much earlier age,* and usually involves most of the discs of the lumbar spine (as opposed to only one or two discs typically involved in degenerative disc disease).

It is not clear from the sparse literature if juvenile degenerative disc disease is the same as juvenile discogenic disorder, a condition where the endplates of the disc spaces are not strong enough to withstand the pressures generated within the disc spaces leading to disc herniation into the vertebral bodies and back pain at an early age. There also appears to be some confusion also with Scheuermann's disease or kyphosis (adolescent kyphosis) and juvenile disc /juvenile discogenic disorder) to describe the condition of adolescent degenerative disc disease.

[46] http://www.spine-health.com/conditions/spinal-deformities/juvenile-disc-disorder;
http://www.losethebackpain.com/resources/lumbar-degenerative-disc-disease-in-teenagers.html;
http://www.spine-health.com/conditions/spinal-deformities/scheuermanns-disease-thoracic-and-lumbar-spine

Age related changes in thoracic and cervical intervertebral discs

With neck pain reported to be almost as common in the general population as back pain, it is perhaps surprising that there is not a greater volume of relevant work detailing changes in the cervical and thoracic vertebrae with age. This is perhaps due to the uncertainty regarding the relationship between spinal degenerative changes and symptoms (Lings et al., 2008).

The cervical spine does not carry the same burden as the lumbar spine and is designed for higher mobility in exchange for less stability.

In a recent systematic review of the causes of cervical spinal degeneration Lings et al (Lings et al., 2008) noted that;

> *"Disintegrating or degrading processes seem closely interlinked with processes of adaptive remodelling and healing involving cell proliferation"*

Moreover, changes were conceived as three subsequent sets of events in a "degenerative cascade" comprising;

- a dysfunctional phase characterised as incipient degenerative changes without biomechanical impact
- an instability or hypermobility phase of segment instability due to progressing degeneration
- a reestablishment phase characterised by adaptive remodelling to counteract hypermobility.

Lings et al (Lings et al., 2008) reported the following as cervical spinal "degenerative" changes;

- reduced disc height
- osteophytes
- sclerosis of the vertebral endplates
- annular tears
- disc intensity alterations
- disc bulging
- disc herniation (prolapse)

These changes are very similar to those reported above for the lumbar discs and Lings et al (2008) also noted that these changes were not specific to humans being found in other species and very common in human prehistoric human materials.

The evidence reviewed comprised 62 studies (18/62 of good quality). The degenerative changes listed above increased with age, however, the severity and specifics of the changes differed between individuals. In relation to changes in the cervical disc with age the authors concluded that:

".....so called "degenerative changes" in the cervical spine should be considered a biological phenomenon that begins in teenagers and progresses with a clear age association. In old age, everybody will have them. Further, the speed with which it develops is probably strongly genetically determined." (Lings et al., 2008)

The following year Okada et al (Okada et al., 2009) published the results of a *longitudinal* MRI imaging study of the ageing of the cervical spine in healthy Japanese volunteers.[47] 497 asymptomatic healthy subjects were followed for an average of 11.7 years (±0.8 years).

At the start of the study (1993-1996) the incidence of degenerative changes on MRI was 17% and 12% in male and female teenagers respectively rising to 86% and 89% in male and female subjects in their 60s, respectively.

At the 10 year follow-up progressive changes were observed in 81.1% of the initially asymptomatic subjects. In addition to progression;

- disc space narrowing and foraminal stenosis was more frequent in subjects over 50 years
- decrease in signal intensity, posterior disc protrusion and anterior compression of the dura and the spinal cord were higher in subjects 20-49 years old than in those older than 50 years.

Initially asymptomatic patients who developed clinical symptoms during the study period demonstrated significantly more frequent progression of structural disc degeneration on MRI than those without the development of clinical symptoms.

In the most recent study (Matsumoto et al., 2010) the same authors examined age related changes of the thoracic and cervical IVD of 94 asymptomatic Japanese subjects (mean age 48 years) using MRI. Approximately half (46.8%) exhibited positive MRI findings indicating degeneration at one or more intervertebral levels of the thoracic spine. The positive rates of each MRI finding increased with age, suggesting that these positive MRI findings represent age-related changes of the intervertebral discs.

Degenerative MRI findings in the thoracic spine were rarer than those in the cervical spine (90.4%); in particular, a decrease in the signal intensity of the intervertebral discs (37.2% *vs.* 80.9%), posterior disc protrusion (30.9% *vs.* 76.6%), and anterior compression of the dura (29.8% *vs.* 80.9%) were significantly less frequent in the thoracic than in the cervical spine.

The physiology of the aging disc

The maintenance of a healthy fully functional disc requires careful regulation of the ECM. However, little is known about matrix turnover (i.e. matrix synthesis and degradation) in the human IVD.

Recently Mwale et al (Mwale et al., 2008), using quantitative MRI, measured the concentrations of key molecules in matrix turnover and correlated them with aging and grade of degeneration using Thompson's grading system (Thompson et al., 1990). Three matrix turnover phases were identified and illustrated by collagen II changes;

[47] This study may have limited relevance to the New Zealand situation and has been included for completeness.

- *Growth phase (0-15 years):* characterised by active synthesis and denaturation of matrix collagen II molecules.
- *Maturation and ageing phase (15-40 years):* characterised by a progressive reduction in synthetic activity and denaturation of collagen II molecules.
- *Degeneration and fibrotic phase (over 40 years):* characterised by a lack of synthesis of type II procollagen but an increase in collagen II denaturation.

The pattern of type I collagen and aggrecan changes were reported to be similar to that of collagen II (Thalgott et al., 2004).

Matrix synthesis was reported to decrease steadily throughout life but sometimes increase again in old and severely disrupted discs. Reduced synthesis has been partly attributable to decreased cell density, although proteoglycan synthesis rates per cell also decrease. Cell proliferation is reported to occur locally in association with fissures and increased MMP activity. Age-related changes in the types of collagens and MMPs synthesized suggest that cell phenotype can change, possibly in response to altered matrix stress distributions.

With increasing age, the hydrostatic nucleus becomes smaller and decompressed, and so more of the compressive load-bearing is taken by the annulus. To fulfil this functional demand, the inner annulus of the young adult possesses relatively high proteoglycan content. However, with increasing age, the proteoglycan content of the annulus decreases, and it becomes stiffer and weaker. Disc height does not appear to show a major decrease with age, although degenerative changes can cause the annulus to collapse in some old discs.

Classifications and grading systems

Age-related grading systems for the lumbar disc

In order to assist clinical assessment of the intervertebral disc, many studies of disc ageing also classify and grade discs according to age-related features and or the perceived severity of disc changes. In 2006 Kettler and Wilke carried out a systematic review and evaluation of such classification and or grading systems for cervical and lumbar discs and facet joint degeneration (Kettler & Wilke, 2006). In their review a systematic search of Medline identified 32 publications describing 42 different grading systems; 30 applied to the lumbar spine, 10 to the cervical spine and two to both systems. The design of theses grading systems varied considerably as did the method used to grade discs which included:

- macroscopic anatomy
- histology
- plain radiography
- magnetic resonance imaging
- discography

Only four of the 42 systems were recommended [48] by the reviewers (Boos et al., 2002; Lane, Nevitt, Genant, & Hochberg, 1993; Pfirrmann et al., 2001; Thompson et al., 1990). All were for lumbar discs. The system designed by Lane et al (1993) was only recommended for disc narrowing and osteophytes, and summary grades. Of the remaining three, two related the grading to age, **Table 2.3.**

Table 2.3 Three recommended grading systems reported in the systematic review of lumbar disc grading systems carried out by Kettler and Wilke (2006).

Reference	Disc type	View	Method	Age related
Thompson et al (1990)	Lumbar	Sagittal section	Macroscopic anatomy	Yes
Boos et al (2002)	Lumbar	Sagittal paraffin section	Histology	Yes
Pfirrmann et al. (2001)	Lumbar	Sagittal T2 weighted	MRI	No

Thompson first proposed a classification system of the discs of the lumbar spine in 1990. A five-category grading scheme for assessing the gross morphology of mid-sagittal sections of the human lumbar intervertebral disc was developed which reflected the *relationship between age and degree of degeneration* , **Figure 2.12.**

[48] Those systems having interobserver reliability tests with either Kappa or Intraclass Correlation Coefficients >0.60 indicating at least substantial agreement in grading between observers.

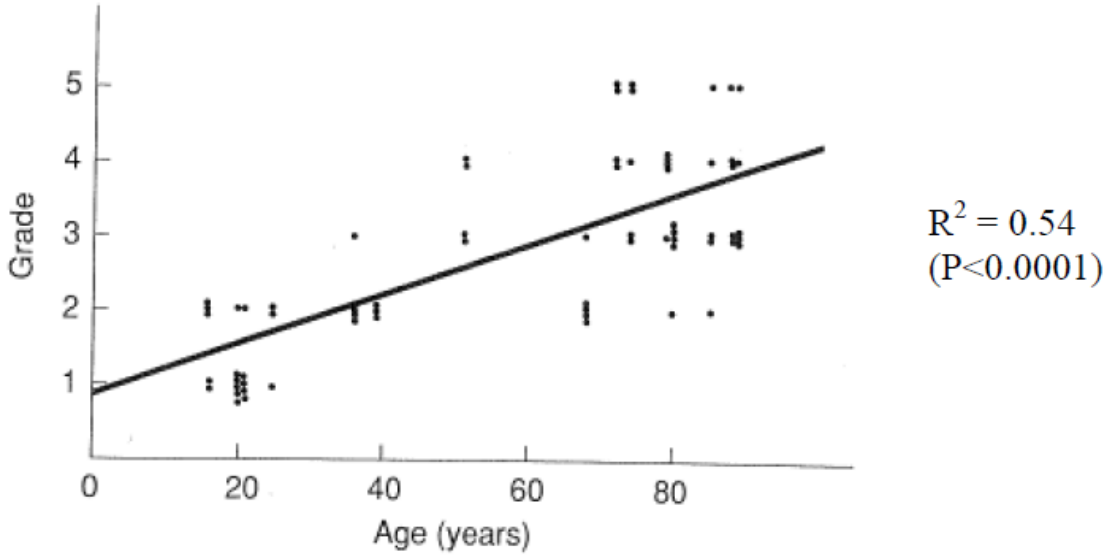


Figure 2.12. The average grades of discs from the spines of donor of differing ages. The line of best fit was calculated by regression. (Thompson et al., 1990)

While the disc grades were regressed against age, grades were not assigned to discrete age groups and the variation in grade at each age point was fairly large and increased with age.

In 2002, Boos et al (Boos et al., 2002) also classified lumbar disc degeneration based on the histology of human cadaver specimens. Discs were classified into eight groups based solely on age and the *general structure of the discs in each age group* described using variables from a macroscopic and histologic assessment of the discs in each age group, see **Table 2.4 and Appendix A.**

Table 2.4. Summary grading of the histological changes in the human intervertebral disc with age. Boos et al (2002).

Grade	age-group	General changes	Changes in the NP	Changes in the EP
0	Foetal disc	No histologic abnormalities Discs are vascularised by thin walled, ectatic (dilated) blood vessels.	Foci of abundant notochord cells	Slightly irregular appearance
1	0 –1 months	Rate of decayed cells is increased,	Slight increase in chondrocyte density Slight mucoid degeneration	Cell density and cartilage disorganization increase
2	0.2-2 years		Mild cleft formation in some discs First granular changes	Regression in the number of physiologic vessels Areas with obliterated vessels are seen Cell density increasing (disorganisation).
3	3-10 years	Abundance of areas with obliterated vessels is increasing.	substantial increase in cell death, chondrocyte density and proliferation, and granular changes	A dramatic decrease of physiologic vessels The first cartilage cracks are seen most pronounced in the central EP.
4	11-16 years	Unequivocal findings of tissue degradation observed with a substantial increase in cell death associated with extensive chondrocyte proliferation. Notochord cells and physiologic vessels disappear from the disc	Structural alteration can be found abundantly in terms of cleft and radial tear formation (most pronounced in the NP)	Frequently observed cartilage cracks
5	17-20 years	Steady increase in structural abnormalities such as clefting and tearing, chondrocyte cloning can be observed adjacent to the structural abnormalities. Obvious decrease in chondrocyte proliferation, cell death, and mucoid degeneration Other abnormalities such as granular changes, clefts, and tears are still increasing in extent and frequency. Rim lesions are seen first in this age group.		Abnormalities in the EP are very similar, but less pronounced.
6	21-30 years	Increase in all histologic changes; cell density, granular changes, mucoid degeneration, clefts and tears. Decaying cells are seen in increasing frequency and extent. Few rim lesions associated with edge neo-vascularity.		Abnormalities very similar to those in younger groups are seen in increasing numbers.
7	31-50 years	Characterized by a continued increasing frequency and extent of abnormalities. Most pronounced is cell proliferation, mucoid degeneration of the extracellular matrix, granular changes.		Increasing frequency and extent of abnormalities Structural disorganisation
8	51-70 years	Tissue alterations become most severe. Adjacent to significant tears and clefts, huge clones of hypertrophic chondrocytes can be found, indicating major cell proliferation. Clefts and tears are filled with granular material (granular changes). Edge neovascularity becomes most pronounced at this stage. In some of the specimens, scar formation and advanced tissue destruction resulting in tissue defects can be found.		Micro fractures and bone sclerosis are seen.
9	>70 years	Structural abnormalities change to scar like tissue formation and large tissue defects. In this age group, frequently a distinction between the anatomic regions is no longer possible. Distinct histologic features such as clefts and tears, cell proliferation, granular changes, cell death, and edge-neovascularity become less pronounced		Cartilage disorganization and new bone remain at the level of abnormalities, as seen in Group 8.

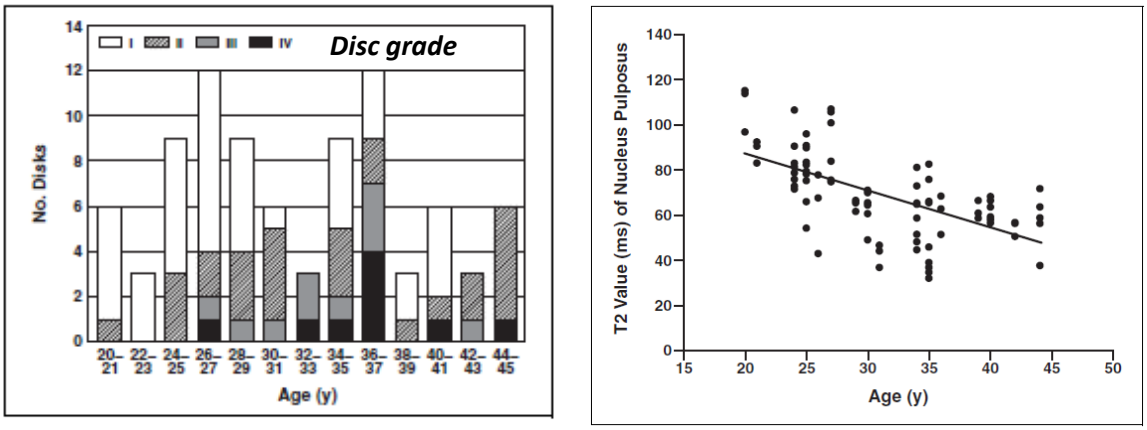
There are a number of notable things about this classification/grading. Firstly changes in the annulus fibrosus did not appear in any of the age group descriptions of changes, secondly, there appeared to be an increasing production of granular tissue, particularly in the areas of tears and fissures, which contrary to other reports, suggests disc tissue repair and/or remodelling. Thirdly, there appear to be two major phases of structural change;

- **Grades 3-4 (3-16 years) when the blood vessels supplying the young disc with nutrients etc. become obliterated, the original cells of the NP (notochord cells or chordocytes) disappear and tears/fissures in the NP become abundant.**
- **Grade 8 (50-<70 years) when the disc appears to be trying to repair disc faults – with major cell proliferation and granular cells filling clefts and tears and neovascularisation at the edge of the disc.**

Since the review by Kettler et al (2006) a number of other grading systems have been published (Puertas et al., 2009; Thalgott et al., 2004; Watanabe et al., 2007). Only one of these grading systems was related to the age of the disc (Duggal, 2009; Watanabe et al., 2007). Watanabe et al developed a grading system based on MRI T2 imaging in order to evaluate *early degeneration* of the IVD. The discs were from 29 healthy volunteers (19 men, 10 women) with no symptoms of back pain or possible sciatica within the past year and with no previous medical treatment for a spinal disorder. Relationships between degenerative grades using axial T2 mapping[49] and subject age, disk level, presence or absence of disk herniation, and type of herniation were evaluated

In axial T2 mapping, degenerative grade of the nucleus pulposus generally increased with age ($p<0.05$) but not the degenerative grade of annulus fibrosus. Among all grade I and II intervertebral disks, no herniation was observed. Among grade III intervertebral disks, three (33.3%) had disk herniation (protrusion in all cases). Among grade IV intervertebral disks, seven (77.8%) had disk herniation; two showed protrusion (22.2%), three (33.3%) showed extrusion, and two (22.2%) showed sequestration.

[49] T2-weighted scans are a basic type of MRI. Like the T1-weighted scan, fat is differentiated from water - but in this case fat shows darker, and water lighter.



A **B**

Figure 2.13. A. Relationship between degenerative grades with axial T2 mapping and participant age. B. Degenerative grade increased with increasing age (Watanabe et al., 2007).

There was huge heterogeneity in the disc grading within and between the different age groups, for example, in four patients between the ages of 23-34 years all *four stages of disc degeneration could be found*, **Figure 2.14.**

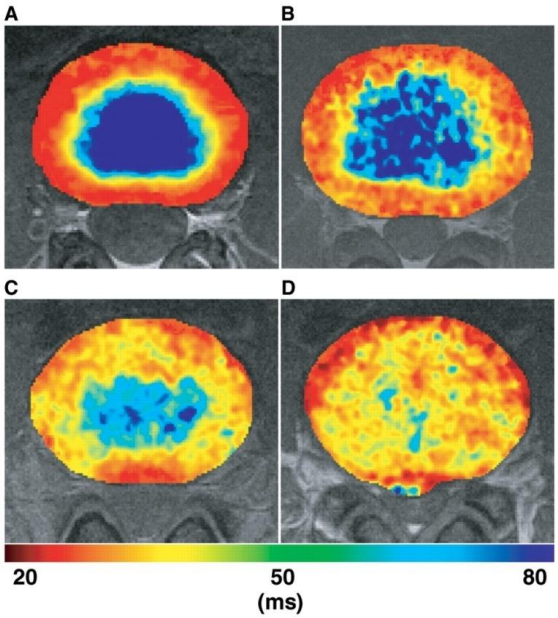


Figure 2.14. Colour-coded maps of intervertebral disks obtained with axial T2 mapping. (A) = grade I in 23-year-old woman, B = grade II in 27-year-old man, (C) = grade III in 25-year-old man, and (D) = grade IV in 34-year-old man (Duggal, 2009).

Hangai et al (2008) used the grading system for MRI images developed by Pfirrmann (Pfirrmann et al., 2001) in univariate and multivariate analyses of variables associated with degeneration. Age ≥ 70years was significantly correlated[50] with MRI grades IV and V, which were considered to be degenerate, **Figure 2.15**. However age was only analysed as a dichotomous variable (i.e. age ≤ 69 years and age ≥70 years).

Figure 2.15. Mid-sagittal view on T2–density-weighted images of discs graded according to a modified Pfirrmann's classification. Grades IV and V were considered degenerated (Hangai et al., 2008).

Mwale et al (2008) used MRI to measure concentrations of *specific molecules* reflecting matrix synthesis and degradation in predetermined regions of human lumbar IVDs. The results were correlated with age and Thompson grade of degeneration in order to detect and quantify matrix composition and integrity and biomechanical changes in *early intervertebral disc degeneration.* Three age-related matrix turnover phases were recognised, **Table 2.5**;

Table 2.5 MRI as a diagnostic tool of intervertebral disc matrix composition and integrity: correlation with age (Mwale et al., 2008).

Phase	Stage	Age	Characteristics
Phase I	Growth	Up to 15 years	Active synthesis of matrix molecules such as type II collagen and active denaturation of type II collagen
Phase II	Maturation and ageing	15-40 years	Distinguished by a progressive drop in synthetic activity and a progressive reduction in denaturation of type II collagen.
Phase III	Degeneration and fibrotic	>40 years	Lack of increased synthesis of type II procollagen, an increase in collagen type II denaturation. The pattern of type I collagen and aggrecan synthesis follows the same pattern.

Age-related grading systems for cervical discs

No publications were identified that reported on the grading of cervical discs in relation to the age of the disc.

[50] Aging was significantly correlated with L1/ 2 (OR 2.14; CI, 1.15–3.99), L2/3 (OR, 3.56; CI, 1.86–7.03), L3/4 (OR, 2.84; CI, 1.50–5.50), and L4/5 (OR, 3.05; CI, 1.55–6.16).

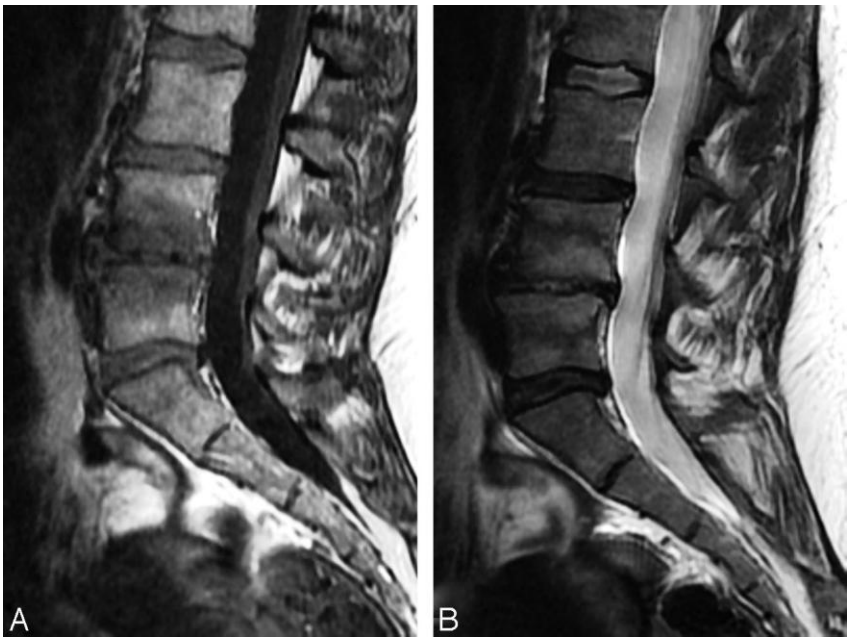
Measuring changes with age using MRI

MR imaging is a specific and sensitive method for detecting the biochemical changes that precede structural changes in the disc. MRI studies of asymptomatic subjects has been a common way of investigating age-related changes in the disc because of the sensitivity of MRI to disc degradation/dehydration marked primarily by decreasing signal intensity (less bright signals) associated with disc dehydration.

However, there are a number of limitations e.g. changes in observed MRI are consequences of alterations in cellular structure that probably occurred months or years earlier; they may not provide much insight to the current functional status of the disc or the current metabolic state of the tissue. Longitudinal MRI studies have shown that disc changes are slow with only 25% of images showing an increase in degenerative grade in 5 years (J. Urban & Winlove, 2007).

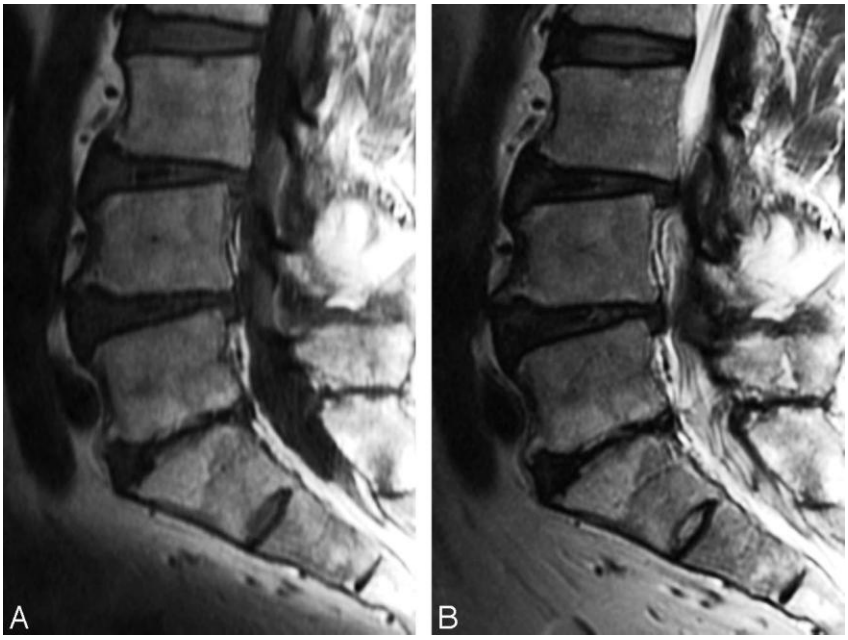
Notwithstanding these comments, most radiologists report changes in the MRI texture of the bone adjacent to the disc (Modic changes) to indicate the acuteness or otherwise of disc changes. Degenerative vertebral endplate and subchondral bone marrow changes were first noted on MR imaging by de Roos et al in 1987. A formal classification was provided subsequently by Modic et al in 1988. Three types of Modic changes are recognised (Rahme & Moussa, 2008);

Figure 2.16. Type 1 changes hypointense (low signal, displayed as dark areas) on T1-weighted imaging (T1WI) and hyperintense (high signal, displayed as light areas) on T2-weighted imaging (T2WI) and represent bone marrow oedema and inflammation



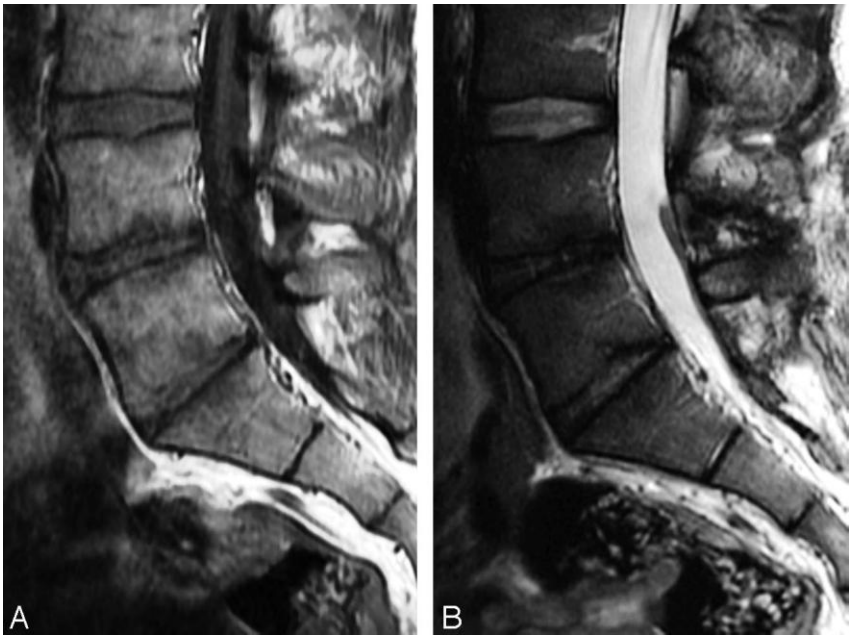
Modic type 1 changes - hypointense on T1WI (*A*) and hyperintense on T2WI (*B*).

Figure 2.17. Type 2 changes hyperintense on T1WI and isointense or slightly hyperintense on T2WI and associated with conversion of normal red hemopoietic bone marrow into yellow fatty marrow as a result of marrow ischemia.



Modic type 2 changes are hyperintense on T1WI (*A*) and isointense or hyperintense on T2WI (*B)*

Figure 2.18. Type 3 changes hypointense on both T1WI and T2WI represent subchondral bone sclerosis.



Mixed-type 1/2 and 2/3 Modic changes have also been reported, suggesting that these changes can convert from one type to another and that they present different stages of the same pathologic process. The absence of Modic changes, a normal anatomic appearance, has often been designated Modic type 0 (Rahme & Moussa, 2008)

Appendix A: Disc classification, Boos et al (2002)

Group	Age (years)	Morphological characteristics of the normal IVD as compared with the previous group
0 (N=9)	Foetal disc	In foetal discs, no histologic abnormalities are seen. However, it is noted that the EP appeared slightly irregular, as compared with hyaline articular cartilage. In the nucleus pulposus, foci of abundant notochordal cells are seen. The foetal discs are vascularised by thin-walled, ectatic (dilated) blood vessels.
1 (N=13)	0 – 1 months	In the IVD of newborns, there is a slight increase in chondrocyte density, particularly in the NP, the rate of decayed cells is increased, slight mucoid degeneration is found in the NP in conjunction with chondrocyte proliferation. EP, cell density and cartilage disorganization increase
2 (N=17)	2 months – 2 years	Very mild cleft formation in the NP occurs in some specimens. Granular changes are first seen in the NP. In the EP, there is a regression in the number of physiologic vessels, and areas with obliterated vessels are seen while cell density is increasing (disorganisation).
3 (N=5)	3-10 years	A dramatic decrease of physiologic vessels in the EP. Conversely, the abundance of areas with obliterated vessels is increasing. With increasing structural alterations of the EP cartilage, the first *cartilage cracks* are seen. This process is most pronounced in the central EP. There is a substantial increase in cell death, chondrocyte density and proliferation, and granular changes, particularly in the NP.
4 (N=8)	11-16 years	Unequivocal findings of *tissue degradation* can be observed. In the IVD, the substantial increase in cell death is associated with extensive *chondrocyte proliferation*. Structural alteration can be found abundantly in terms of *cleft and radial tear formation*. These alterations are most pronounced in the NP. Notochordal cells and physiologic vessels disappear from the disc, and areas of obliterated vessels are therefore most pronounced at this stage. In the EP, cartilage cracks are frequently seen.
5 (N=8)	17-20 years	There is a steady increase in structural abnormalities such as *clefting and tearing*, chondrocyte cloning can be observed adjacent to the structural abnormalities. There is an obvious *decrease in chondrocyte proliferation*, cell death, and mucoid degeneration while other abnormalities such as granular changes, clefts, and tears are still increasing in extent and frequency. Few *rim lesions* are seen first in this age group. Endplate abnormalities are very similar, but less pronounced.
6 (N=32)	21-30 years	This stage is characterized by an increase in all histologic changes in the IVD and EP. In the IVD, cell density, granular changes, mucoid degeneration, clefts and tears, and decaying cells are seen in increasing frequency and extent. There are few rim lesions associated with edge neovascularity. In the EP, abnormalities very similar to those in younger groups are seen, but in increasing numbers.
7 (N=11)	31-50 years	This stage is characterized by a continued increasing frequency and extent of abnormalities in IVD and EP. Most pronounced are cell proliferation, mucoid degeneration of the extracellular matrix, granular changes in the IVD, and structural disorganization of the EP.
8 (N=9)	51-70 years	During this stage, tissue alterations become most severe. Adjacent to significant tears and clefts, huge clones of hypertrophic chondrocytes can be found, indicating major cell proliferation. Clefts and tears are filled with granular material (granular changes). Edge neovascularity becomes most pronounced at this stage. In the EP additionally, microfractures and bone sclerosis are seen. In some of the specimens, scar formation and advanced tissue destruction resulting in tissue defects can be found.
9 (N=38)	>70 years	Structural abnormalities change to scar like tissue formation and large tissue defects. In this age group, frequently a distinction between the anatomic regions is no longer possible (“burnt-out appearance”). Therefore, distinct histological features such as clefts and tears, cell proliferation, granular changes, cell death, and edge-neovascularity become less pronounced. In the EP, cartilage disorganization and new bone remain at the level of abnormalities, as seen in Group 8.

Section 3: Pain generation

(a) An evidence based review of the current knowledge of pain generation in the discs, nerve roots and associated structures of the cervix, thorax and lumbar region (or at least a discussion of their differences), and (b) an evidence based review of the current knowledge of pain generation associated with the facet joints and the causes of radicular pain.

Background

Evaluating pain originating from the spine is challenging. Pain may be generated by pathologies arising in a number of structures including the nerve root, disc annulus, posterior longitudinal ligament, sacroiliac joint, and facet joint. Historical or physical examination findings are generally not sufficiently sensitive or specific enough to identify which of the numerous potential pain generators are at fault. Thus clinical practice guidelines often state that in most cases the tissue source of low back pain cannot be specified (Hancock et al., 2007). Epidemiologic studies suggest that the *intervertebral disc* is the most common pain generator in all patients with low back pain (Beresford et al., 2010). It has been estimated that discogenic low back pain accounts for 28–43% of the patients with low back pain (Baogan Peng, Pang, Wu, Zhao, & Song, 2010)

With a high proportion of *workers* known to suffer back and neck pain, and chronic low back pain reported to be the leading cause of work-related disability in people under age 45 [51], the cost of disc related pain in terms of lost production, personal suffering and treatment is very high. In addition, as the post war "baby boomers" retire and average life expectancy increases, painful disorders of the spine associated with the elderly are expected to increase. These pressures have increased the demand for a better understanding of the nature of common causes of spinal pain to underpin treatment choices.

The innervation of the intervertebral disc and surrounding structures has been extensively studied. However, difficulties surrounding experiments in humans limit research and the establishment of an experimental model with good reliability and reproducibility. To date, most of the pathophysiological data/evidence in this area has been obtained from experiments performed in rat, pigs and dogs[52]. Extrapolation of these animal data to humans must be performed with caution (Connally & Sanders, 1991; Nakamura et al., 1996).

Definition of pain

The Taxonomy Committee of the International Association for the Study of Pain defined pain as

"an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [53]
Shah (2004)

Different types of pain[54]

There are various types of pain and various classification systems. Acute and chronic pain is distinguished by the duration period. Acute pain is usually defined as short-term pain of less than 12 weeks duration[55] and chronic pain as continuous, long-term pain of more than 12 weeks or after the

[51] Workers Compensation Back Claim Study. Boca Raton, Florida. National Council on Compensation Insurance, 1993; pp 1-25.
[52] Recently, the popularity of spinal fusion has led to more opportunities to obtain disc specimens which could be applied to explore the pathogenesis of disc degeneration with modern biologic techniques (Peng 2006).
[53] Mersky H. Classification of chronic pain, descriptions of chronic pain syndromes and definitions of pain terms. Pain 1986; 3:S10-S24.
[54] http://www.pain-management-info.com/types-of-pain.htmTypes of pain http://www.ehow.com/about_5393798_somatic-pain-vs-visceral-pain.html
[55] This may vary with the system used.

time that healing would have been thought to have occurred in pain after trauma or surgery[56]. Chronic pain is the focus of this report.

Chronic pain may be further subdivided into nociceptive pain and neuropathic pain. Nociceptive pain is pain arising from damage to tissues other than nerve fibres. Tissue damage causes stimulation of nerve fibres (pain receptors) that respond only to stimuli approaching or exceeding harmful intensity. Stimuli may be thermal, mechanical or chemical in nature. Undamaged nerve cells called nociceptors carry the pain sensation to spinal cord from where it is relayed to the brain.

Nociceptive visceral pain is reported to originate in the viscera (organs) and is often extremely difficult to locate. Nociception from some visceral regions produces "referred" pain, where the sensation is located in an area distant from the site of the stimulus. Nociceptive somatic pain is reported to result from injury to muscles, tendons and ligaments. Deep somatic nociceptic pain is initiated by stimulation of nociceptors in ligaments, tendons, bones, blood vessels, fasciae and muscles. It is usually described as a dull, aching, poorly-localized pain. Somatic pain is usually well localized whereas visceral pain is usually diffuse and non-localizing.

Neuropathic pain is pain caused by a lesion in the nervous system following structural or functional damage. It is called central neuropathic pain if the lesion is the central nervous system; it is called *peripheral neuropathic* pain if the lesion is in the peripheral nervous system. The neuropathic pain is usually described as severe, sharp, stabbing pain. Neuropathic pain is a clinical description, not a diagnosis; it requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. It is common when investigating neuropathic pain that diagnostic testing may yield inconclusive or even inconsistent data and clinical judgment is required to reduce the totality of findings in a patient into one putative diagnosis or concise group of diagnoses[57].

Nociceptive and neuropathic pain can co-exist in the same patient in conditions such as sciatica.

Intervertebral disc related pain

A tissue can only generate pain if it is innervated. Prior to 1947, it was believed that the disc was a painless (non-innervated) structure. Inman and Saunders in 1947 discovered nerve fibres in the annulus[58]. Following an immense amount of work between 1947 and 2010 this was confirmed by more sophisticated histological techniques, and it is now known that the outer third of the annulus and the posterior longitudinal ligaments (PLL) are supplied by a branch of the sinuvertebral nerve[59] (Alemo & Sayadipour, 2010).

An association between the lumbar disc and low back pain can be traced back to the 1930s. Francis Murphey (1967) later confirmed lumbar disc as a source of low back pain following observations on operating on patients with herniated lumbar discs under conscious sedation and using local anaesthesia.

[56] http://www.britishpainsociety.org/media_faq.htm
[57] http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm#Nociception
[58] Inman VT, Saunders JB (1947) Anatomical and physiological aspects of injuries to the intervertebral disc. J Bone Joint Surg 29:461
[59] Konttinen YT, Gronbald M, Antti-Poika I (1990) Neuroimmunohistochemical analysis of peridiscal nocioceptive neuro elements. Spine 15:383

The innervation of the intervertebral disc and related structures

A tissue can generate pain only if it is innervated. The unravelling of the "wiring diagram" of sensation and pain pathways of the intervertebral disc and associated structures has been a major challenge (Edgar, 2007). By the 1960s the innervation of the structures of the anterior spinal canal was assumed to be well defined; it was generally agreed that the sinuvertebral nerves arose bilaterally and segmentally, with each formed by a fine sympathetic branch usually arising from the grey ramus communicans and a fine sensory branch arising from the ventral ramus. These co-joined sinuvertebral nerves re-entered the vertebral canal through each intervertebral foramen to lay anterior to the nerve root, Figure 3.1.

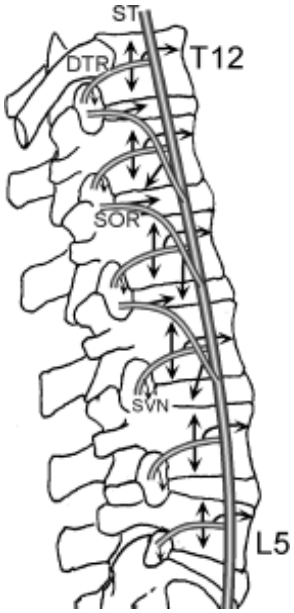


Figure 3.1. Drawing of the lumbar spine innervation, showing the branching patterns of the superficial oblique rami (SOR) and the deep transverse rami (DTR); SVN =sinu-vertebral nerve, ST=sympathetic trunk. T12= 12thr thoracic vertebra, L5= 5th lumbar vertebra.

The sympathetic fibres were considered to be vasomotor efferents and the sensory fibres as proprioceptive and nociceptive. Branches were traced to the posterior longitudinal ligament, to the outer layers of the annulus fibrosus and to the anterior dura. Many were seen to have a fine diameter which was considered to be consistent with pain mediation (Edgar, 2007).

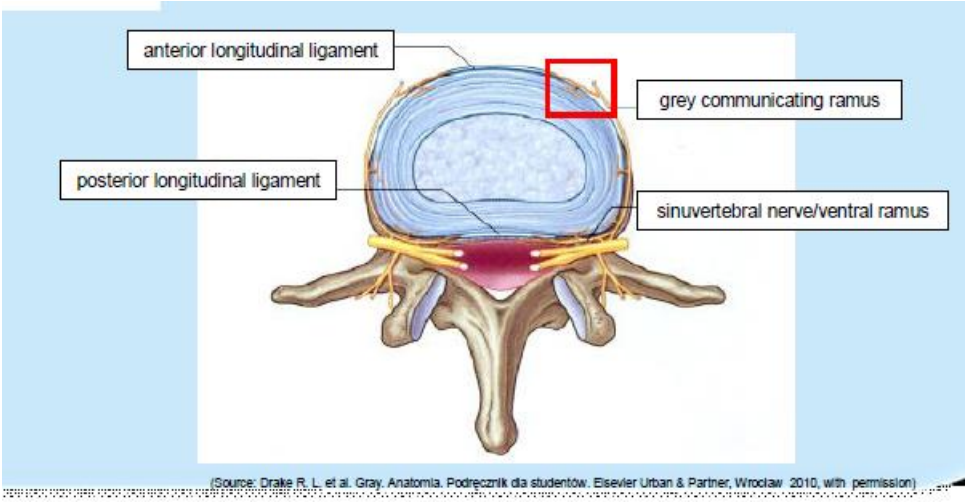


Figure 3.2. Innervation of the normal intervertebral disc

Upon *degeneration*, the IVD becomes densely innervated, even in regions that normally lack innervation. This increased innervation has been associated with pain of IVD origin. Recently, using immunoreactive staining, nerves have been shown to extend as far as the inner third of the annulus in 50% of degenerative discs. These nerves appeared to arise *de novo* from granulation tissue growing into the degenerate disc (neo-innervation[60]) (A. Freemont et al., 1997). More recently, Peng (2005) demonstrated immunoreactive stained nerve fibres in the granulation tissue in the posterior disc which extended *deep into the disc.* The histology of the nerves was consistent with a nociceptive or pain function.

Other recent studies have shown that the endplate (Fagan et al., 2003), and in particular the central region adjacent to the nucleus pulposus, is supplied with a nerve network similar to that of the outer annulus. These studies suggest neo-innervation of the intervertebral disc in response to the pathology of degeneration (Edgar, 2007).

[60] These observations were often limited to the anterior disc only – the main radial tears/crevices containing granulation tissue occur mainly in the posterior disc.

Methods

For a comprehensive description of the searches carried out for this review and the reporting methods see the general methods section. Briefly, a systematic search of the literature for high evidence level studies and overviews (systematic reviews, meta-analyses and clinical guidelines) relating to the pain generation in the intervertebral disc nerve roots and associated structures was carried out.

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews.

In addition to bibliographic databases such as Medline and Embase the following sources/websites were searched for recent (2005 onwards) evidence based guidelines reporting substantially on fusion surgery:

American Academy of Orthopaedic Surgeons (AAOS)

American Society of Neuroradiology (ASN)

American Society of Spine Radiology

Guidelines International Network (GIN)

Institute for Clinical Systems improvement (ICSI)

Medical Services Advisory Committee

National Health and Medical Research Council (NHMRC)

National Institute for Health and Clinical Excellence (NICE)

New Zealand Guidelines Group (NZGG)

NHS Evidence

North American Spine Society (NASS)

Scottish Intercollegiate Guidelines Network (SIGN)

TRIP database

World Health Organisation (WHO)

References

Citations for primary studies quoted in eligible systematic reviews and guidelines are included in footnotes rather than the report references to distinguish them from those identified independently for the current report.

Search results

The search strategy developed for the review of mechanisms of pain generation in the disc and nerve roots identified 115 potentially relevant publications, 95 of these were published between 2000 and 2011. Upon review, *no* systematic reviews or guidelines were identified that focussed on pain mechanisms or that included questions of direct relevance to the topic. A number of non-systematic reviews of the literature were identified.

These studies examined, or included sections reviewing, the pathophysiology of (a) discogenic pain (b) radicular pain and (c) facet joint pain.

Non-systematic reviews pose a number of problems in the context of evidence based medicine. Firstly, the selection of material for review is likely to be biased by the author's personal and conscious/unconscious agenda and possibly limited by his or her range of knowledge and experience. A lack of a formal data extraction process is likely to obscure between-study heterogeneity increasing the chance of spurious comparisons. In addition, the scientific quality of non-systematic reviews is generally lower than that of systematic reviews. Selected studies are generally treated as equally credible or valid as they do not undergo critical evaluation or quality assessments. With no limitations put on the type of evidence reviewed inferences drawn from such reviews may at best be suspect and at worst misleading.

Bearing in mind these limitations, and in the absence of systematic reviews on the topic, the following appraisal of the current knowledge of pain generation in the intervertebral disc and associated structures is taken, for the most part, from non-systematic reviews of experimental studies. Where indicated, primary studies themselves are the information source.

3.1 Mechanisms of discogenic pain

Seven non-systematic reviews were published between 2000 and 2010. Four focussed on sources and patterns of pain (A. J. Freemont, 2009; Hurri & Karppinen, 2004; Sehgal & Fortin, 2000; Solomon, Lutz, Cooke, & Gage, 2004) two focussed on neurological aspects of the intervertebral disc (Edgar, 2007; Garcia-Cosamalon et al., 2010), one focussed on the anatomy and pathophysiology of the disc (Raj, 2008). All of the reviews focussed to a greater or lesser extent on the lumbar disc or spine.

Non-systematic reviews

Seven non-systematic reviews were assessed (Edgar, 2007; A. J. Freemont, 2009; Garcia-Cosamalon et al., 2010; Hurri & Karppinen, 2004; Raj, 2008; Sehgal & Fortin, 2000; Solomon et al., 2004)

Sources and patterns of pain

Seghal and Fortin 2000 "Internal disc disruption and low back pain."

In a review articles entitled " Internal disc disruption and low back pain" Seghal and Fortin (2000) outlined a biochemical/biomechanical model of discogenic pain to explain disabling low back pain in patients with no objective evidence of nerve-root compromise. They suggested that pain was correlated with the extension of annular fissures into the innervated outer third of the annulus fibrosus and that a combination of mechanical and chemical factors combined to make these tears painful. Nociceptive nerve endings in a disc with fissures extending into the annulus and disrupting most of the lamellae were postulated to be mechanically stimulated by even *minor physiological stress*.

In a disrupted disc the *same load* was thought to be absorbed by the *few lamellae that were still intact* and unusually high stresses crossed the threshold for mechanical nociception. It was also argued that the threshold for mechanical stimulation was attained *earlier* with chemical sensitization of the nerve endings through the release of nociceptive substances (Sehgal & Fortin, 2000).

Impaired *cellular function* in the degenerate disc was also noted. This was accompanied by changes in nuclear pH and the release of prostaglandin E, histamine-like substances, potassium ions, lactic acid, polypeptide amines and phospholipase A2[61]. The latter is known to liberate arachidonic acid (from cell membranes) which is a limiting factor in the production of inflammatory mediators, has a direct neurotoxic potential and is implicated in the genesis of pain in herniated discs[62]. Theoretically, interventions directed at inactivating inflammatory mediators can be potentially therapeutic e.g. the use of steroids to counter phospholipase A2 activity.

Quoting a number of studies published in *Spine*[63] published between 1987 and 1997[64], Seghal and Fortin (2000) speculated that leakage of nociceptors from the disc *sensitized* unmyelinated nerve fibres in the annulus and the dorsal root ganglion, lowering the nociceptor threshold for mechanical stimulation.

[61] See for example Franson RC, Saal JS, Saal JA. Human disc phospholipase A2 is inflammatory. Spine 1992; 17: 129-132.
[62] High Phospholipase A2 activity has been reported in herniated discs in comparison to other human tissues (Saal JS, Franson RC, Dobrow R et al. High levels of inflammatory phospholipase A2 activity in lumbar disc herniations. Spine 1990; 15: 674-678.}
[63] Recognized internationally as the leading journal in its field.
[64] For example; McCarron RF, Wimpee MW, HudkinsPG et al. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low back pain. Spine 1987; 12: 760-764. Franson RC, Saal JS, Saal JA. Human disc phospholipase A2 is inflammatory. Spine 1992; 17: 129-132. Saal JS, Franson R, Myers R et al. Human disc PLA2 induces neural injury. A histomorphometric study. From proceedings of the annual meeting. International Society for the Study of the Lumbar Spine, Chicago, 1992.

Physical loading within the physiologic range of the disc could then cause mechanical irritation of sensory nociceptive terminals in the incompetent disc.

For patients presenting with clinical features suggestive of disc prolapsed but with no imaging evidence of prolapse, radial annual tears were thought to provide a route for inflamogenic nuclear fluid to leak out into the epidural space, bathe the dural sac and excite the nerve roots[65]. However, Seghal and Fortin (2000) acknowledged that there was reluctance at that time to acknowledge internal disc disruption as a valid clinical entity.

Hurri and Karppinen 2004 "Discogenic pain."

Hurri and Karppinen (2004) in a brief and relatively superficial topical review entitled "Discogenic pain" noted that the intervertebral disc had been assumed to be a major cause of non-specific low back pain notwithstanding the more specific disc herniation condition (Hurri & Karppinen, 2004). They noted that in a population of chronic low back pain patients 39% had an internal disc disruption, with concordant pain provocation in discography suggesting a discogenic origin of their pain (Schwarzer et al., 1995).

Similar to the earlier review of Seghal and Fortin (2000), Hurri and Karppinen (2004) also reported on studies that had demonstrated the deep innervation of the degenerated discs referring to the study by Freemont et al (1997) which demonstrated that, in highly degenerated discs, nerves may *penetrate the nucleus pulposus*. These structures were reported to express "substance P" and had the morphology of nociceptive nerve terminals (pain receptors).

The role of genetic factors in discogenic pain was also briefly discussed in this topical review, and recent studies were reported that suggested that low back pain was associated with genetic polymorphisms in the interleukin (IL)1 locus (Solovieva et al., 2004). This information was linked with new evidence that cytokines such as IL1 played an important role in discogenic pain. The role of inflammation and cytokines was further discussed with reference to studies that demonstrated that disc cells express tumour necrosis factor α (TNFα) and that topical TNFα caused radicular abnormalities identical to those seen after nucleus pulposus application (Igarashi, Kikuchi, Shubayev, & Myers, 2000). However, clinical trials of a single dose of an anti-TNF agent (infliximab) in the treatment of disc herniation-induced sciatic pain were reported to have been disappointing.

Solomon 2004 "Discogenic low back pain."

Solomon et al (2004) reported that the precise origin intervertebral disc disease had yet to be definitely established. They reported three different models/theories which were supported to varying degrees in the literature;

- The Kirkaldy-Willis' degenerative cascade model[66] in which defects in the annulus fibrosus such as circumferential and radial tears or fissures representing the initial pathological insult.
- The endplate fracture secondary to compressive load on the disc which often results in herniation of the nucleus pulposus into the vertebral body as may be seen in young, athletic

[65] MacMillan J, Schaffer JL, Kambin P. Routes and incidence of communication of lumbar discs with surrounding neural structures. Spine 1991; 16: 167-71.
[66] Kirkaldy-Willis WH. The Pathology and pathogenesis of low back pain. In: Kirkaldy-Willis WH, Bernard TN Jr, editors. Managing low back pain. 4th ed. New York: Churchill-Livingstone; 1999.

spines not yet subjected to disc degeneration, where the herniation follows areas of premorbid structural weakness, the cartilaginous end plate. Injury to the end plate can subsequently interrupt the nutritional process to the disc that normally occurs by diffusion across the end plate, followed by an inflammatory biomechanical degradation of the disc matrix. This process is thought to be bought about through disruption of the disequilibrium between matrix synthesis and destruction as indicated by an abnormally high ratio of the degradative proteinases enzyme MMP-3 to the tissue inhibitor of metalloproteinase-1 (TIMP-1) that normally binds to and inhibits MMP-3. After end plate injury, the originally avascular disc is believed to be invaded by blood vessels from the vertebral body and bone marrow tissue, which activate the disc proteinases through cytokine modulation.

- A combination of mechanical and chemical factors was reported to be another possible theory of the origin of IDD. In this model annular tears extending from the nucleus pulposus to that outer annulus are through to result in a centripetal ingrowth of nerve fibers into the inner annulus. These nerve endings are thought to be nociceptive and express substance P, a nociceptor. The internally disrupted disc releases nociceptive
- substances, which sensitize these nerve endings. Impaired cellular function accompanies changes in nuclear pH and release of prostaglandin E2, nitric oxide, potassium ions, lactic acid, polypeptide amines, and phospholipase A2. Potential mechanisms for pain generation are postulated to include nerve inflammation, direct excitation of annular nociceptors, or nerve injury from enzymatic degradation of phospholipids. While normal physiological loading is distributed equally by the annulus it is postulated that in a disrupted disc, the same load is distributed over fewer annulur fibers, leading to an unusual stressful environment. Therefore, mechanical sensitization is obtained earlier in an abnormal disc environment

Freemont 2009 "The cellular pathobiology of the degenerate intervertebral disc and discogenic back pain.

Freemont published a review of the cellular pathobiology of the degenerate intervertebral disc and discogenic back pain in 2009 (A. J. Freemont, 2009). In this work two key processes were identified as being important in the origins of discogenic back pain;

- disc degeneration
- nociceptive nerve ingrowth into the normally aneural intervertebral disc

In relation to disc degeneration Freemont (2009) focussed on new advances in the understanding of the altered cell biology of the degenerated disc and pain generation. New research on soluble regulators of cell function[67] and nerve ingrowth into the disc was reported. Disturbed cytokine biology, particularly imbalances in various interleukins, appeared to influence a number of key degenerative processes including;

- upregulation of matrix metalloproteinases (MMPs) and A disintegrin and metalloproteinase with thrombospondin Motifs (ADAMTs)

[67] For example: Le Maitre CL, Pockert A, Buttle DJ, Freemont AJ, Hoyland JA. Matrix synthesis and degradation in human intervertebral disc degeneration. Biochem Soc Trans 2007;35:652–5. Jimbo K, Park JS, Yokosuka K, Sato K, Nagata K. Positive feedback loop of interleukin-1beta upregulating production of inflammatory mediators in human intervertebral disc cells in vitro. J Neurosurg Spine 2005;2:589–95. Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. J Bone Joint Surg Am 2006;88(Suppl. 2):68–71.

- abnormal synthesis of aggrecan and collagens
- angiogenesis
- neurogenesis
- apoptosis of native intervertebral disc cells

The factors initiating the imbalance were reported to be unknown; load was reported to be implicated but unproven.
The recently reported activity of tumour necrosis factor alpha (TNF-α), was also reviewed. TNFα has been shown to be expressed by the cells of prolapsed tissue which, in turn, has been shown to be capable of inducing nerve damage[68]. It was hypothesised that TNF-α blockade might have a therapeutic role in nerve root damage and sciatic pain [69] Comparative trials of infliximab (a monoclonal antibody against TNF-α) to date were reported to have been disappointing[70]; explanations included a large placebo effect in patients receiving the saline control injections and further trials on a sub-population of patients were reported to be planned.
An alternative explanation for the role of TNF-α in back pain which was put forward related to its ability to induce sensory nerve growth which is a feature of the painful degenerate intervertebral disc[71].
Anabolic members of the TNF-β superfamily of molecules have also raised some interest, specifically bone morphogenic proteins (BMPs) and their potential for protecting or aiding regeneration of the degenerate disc[72]
In this context Freemont (2009) discussed the therapeutic implications of the recent advances in molecular medicine as they applied to treating degenerative disc disease;

*"Importantly, with the advent of molecular medicine, cytokines and cytokine regulation pathways have the potential to be **key therapeutic targets**, as has happened in rheumatoid disease and OA. Although still relatively nascent, there is no doubt that the next few years will see increasing research focused on translating our understanding of molecular pathways underlying degeneration into novel therapies for managing discogenic pain through prevention of progression or reversal of the pathology of degeneration."*

In relation to nerve ingrowth Freemont (2009) noted that if nociceptive nerve ingrowth was a major cause of discogenic back pain, the processes driving this ingrowth could become key therapeutic targets for its management. Three processes were identified;

[68] Igarashi T, Kikuchi S, Shubayev V, Myers RR. 2000 Volvo Award winner in basic science studies: exogenous tumor necrosis factor-alpha mimics nucleus pulposusinduced neuropathology. Molecular, histologic, and behavioral comparisons in rats. Spine 2000;25:2975–80. Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor- prevents nucleus pulposus-induced thrombus formation, intraneural oedema, and reduction of nerve conduction velocity: possible implications for future pharmacological treatment strategies of sciatica. Spine 2001;26:863–9.
[69] Cooper RG, Freemont AJ. TNF-alpha blockade for herniated intervertebral discinduced sciatica: a way forward at last? Rheumatology 2004;43:119–21.
[70] Korhonen T, Karppinen J, Paimela L et al. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. Spine 2006;31:2759–66. http://www.medscape.com/viewarticle/551809_2
[71] Hayashi S, Taira A, Inoue G et al. TNF-alpha in nucleus pulposus induces sensory nerve growth: a study of the mechanism of discogenic low back pain using TNF-alpha-deficient mice. Spine 2008;33:1542–6.
[72] Wei A, Brisby H, Chung SA, Diwan AD. Bone morphogenetic protein-7 protects human intervertebral disc cells in vitro from apoptosis. Spine J 2008;8:466–74.

- angiogenesis-associated nerve ingrowth
- angiogenesis- altered matrix biology
- angiogenesis- associated with altered cell function

Nerves growing into degenerative intervertebral discs do so in physical association with in-growing blood vessels. Current research suggests that the nerves growing into the disc initially have a vasoregulatory role, but at some stage (and for unknown reasons) they send off nociceptive shoots into the disc tissue. During angiogenesis, endothelial cells of vessels growing into the intervertebral disc synthesize the neurogenic stimulator nerve growth factor (NGF) which is one of a family of neurotrophins that regulate development, maintenance, and function of vertebrate nervous systems[73]. An important aspect of these studies was reported to be the fact that nerves with the structure and biology of nociceptive nerves were only seen in intervertebral discs that had been classified clinically as 'pain level discs'.

Altered matrix biology was reported to have been investigated in "some very elegant experiments" by Johnson and co-workers[74] . Aggrecan removed from normal human annulus fibrosus and nucleus pulposus was found to inhibit the growth *in vitro* of neurites (projections from the cell body of a neuron). Aggrecan that had been deglycosylated to make it more akin to that found in the degenerate intervertebral disc (IVD) was shown to have a *reduced* inhibitory effect. This implied that normal aggrecan was an inhibitor of nerve ingrowth into the IVD, and that in degeneration, nerve ingrowth may occur as a *consequence of changed aggrecan* biology.

In a similar series of experiments, Johnson et al. (2006) [75] examined the effects of cells derived from normal and degenerate intervertebral disc on neurites . They found that the normal inhibition of neurite outgrowth by aggrecan could be reversed by cells derived from degenerate IVD. The extent of the effect was related to the number of IVD cells. It was Freemont's opinion, that as a result of such insights, the clinical management of patients with discogenic back pain would be very different in 10 years time (A. J. Freemont, 2009).

Neurological aspects of the intervertebral disc pain

Edgar 2007 "The nerve supply of the lumbar intervertebral disc."

In 2007 Edgar published a review of the nerve supply of the lumbar disc. He noted that despite 20 years of anatomical and experimental studies relating to the innervations of the normal and degenerative lumbar disc, clinical interpretation and review of the findings had not been carried out. He observed that;

"The unravelling of the 'wiring diagram' of sensation and pain pathways from the lumbar disc and the posterior longitudinal ligament to the dorsal root ganglion and upwards through the spinal tracts has been a challenge beyond the scope of microdiscectomy and histological sections alone."

[73] Freemont AJ, Watkins A, Le Maitre C et al. Nerve growth factor expression and innervation of the painful intervertebral disc. J Pathol 2002;197:286–92.
[74] Johnson WE, Caterson B, Eisenstein SM, Hynds DL, Snow DM, Roberts S. Human intervertebral disc aggrecan inhibits nerve growth in vitro. Arthritis Rheum 2002;46:2658–64.
[75] Johnson WE, Sivan S, Wright KT, Eisenstein SM, Maroudas A, Roberts S. Human intervertebral disc cells promote nerve growth over substrata of human intervertebral disc aggrecan. Spine 2006;31:1187–93.

Edgar (2007) outlined chronologically what he considered to be the most important findings realting to the innervation of the intervertebral disc. These are summarised below.

By the 1960s the innervations of the structures of the anterior part of the spinal canal was assumed to be well defined with;

- the sinuvertebral nerves arising bilaterally and segmentally with each formed by a fine sympathetic branch usually arising from the grey ramus communicans and a fine sensory spinal branch from the ventral ramus i.e. they were *conjoined nerves.*
- the sympathetic nerve fibres considered to be vasomotor efferent nerves and the sensory fibres as proprioceptive and nociceptive with branches traced to the posterior longitudinal ligament, the outer layers of the annulus fibrosus and to the anterior dura
- some nerves comprising very fine fibres consistent with *pain mediation*
- most investigators concluding that the sinuvertebral nerves had up to three segmental levels of overlap which was thought to explain the *poor localisation of low back pain.*

In the early 1980s Bogduk and colleagues further clarified the innervation of the outer layers of the annulus fibrosus. They determined that;

- the posterior part of the lumbar disc was served not only by the sinuvertebral nerve but also received branches posterolaterally directly from the ramus communicans or ventral ramus
- anterior disc nerves were observed to arise solely from the sympathetic plexus surrounding the anterior longitudinal ligament.

In 1990 there was some debate surrounding the dual pattern theory of sensory innervation, Advances in staining and in particular of immunoreactive stains enabled nerves to be better identified and classified according to function and the dual pattern theory supported.

- A number of intricate experimental studies carried out in Japan (mid 1990s to early 2000) on the anterior discs of rats together with contemporaneous reports of local anaesthetic blocks to sympathetic ganglia (L2 level) providing relief in patients with discogenic low back pain suggested that afferent nerve fibres from the annulus passed into the sympathetic chain to re-enter the sensory nerve roots at L1 and L2, the level with white rami comunicantes.
- Parallel experimental studies suggested that the lower lumbar facet joints had similar sensory pathways.
- Cavanaugh et al (1997) confirmed the presence of a nociceptive pathway of sympathetic afferent discharge from the dorsal aspect of the lower lumbar discs to the dorsal root of L2 (in rats) and hypothesised that, unique to the rest of the musculoskeletal system, discogenic pain was a type of visceral pain76.
- It was further suggested that, as in enteric or visceral structures, nociceptive afferents of the disc and related structures may initiate pain in response to ischaemia (narrowing), pressure

[76] Somatic vs visceral pain: Somatic pain is referred to as musculoskeletal pain. It is found in tissue such as skin and muscles as well as in joints, bones and ligaments, often characterized as a sharp pain. Visceral pain originates in the viscera (organs) and often is extremely difficult to locate, and nociception from some visceral regions produces "referred" pain, where the sensation is located in an area distant from the site of the stimulus, it is often characterized as a deep ache with cramping.
Somatic Pain vs. Visceral Pain | eHow.com http://www.ehow.com/about_5393798_somatic-pain-vs-visceral-pain.html#ixzz1PUtyiI6s

changes or inflammatory irritation. The concept of a visceral-type nerve supply to the disc was also compatible with "central sensitisation" as a potential cause of chronic back pain.

The author concluded the review by noting that the mechanism of discogenic pain was still speculative (Edgar, 2007).

Garcia-Cosmalon 2010 "Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain?"

The latest narrative review identified (Garcia-Cosamalon et al., 2010) also focussed on neurological aspects of discogenic pain and in particular the role sensory nerves and neurotrophins[77].

The role of neurotrophic and neurotropic[78] growth factors in IVD hyperinnervation was examined including a recent proposal that the degenerating IVD could synthesize and release 'neurogenic' factors that attract nerve fibres to it (Colombini, Lombardi, Corsi, & Banfi, 2008; A. G. Hadjipavlou, M. N. Tzermiadianos, N. Bogduk, & M. R. Zindrick, 2008). A positive correlation was found between levels of expression of neurotrophins and the density of innervation in the IVD (Yamauchi, Miyamoto, & Murabe, 2007).

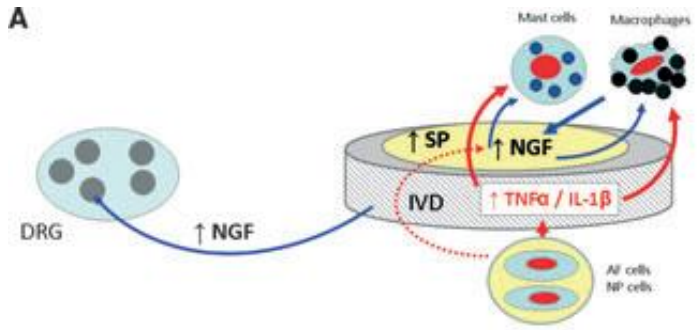
As a result of these and similar studies, neurotrophins *have been proposed mediators in the pathogenic mechanism of pain.* However, to date, it remains unclear whether nerve ingrowth is a consequence of the action of neurotrophic / neurotropic factors in the IVD or a side effect of the normal wound-healing events in injured intervertebral discs (Olmarker, 2005).

The role of neurotrophins and their receptors in inflammatory responses and in pain transmission was also examined in this narrative review. Garcia-Cosamalon et al. (2010) considered that in order to understand the role of neurotrophins in discogenic pain, *four main aspects* needed to be considered, including the role of :

- proinflammatory cytokines as regulators of nerve growth factor synthesis
- neurotrophins , especially nerve growth factor, in regulating nerve ingrowth in intervertebral disc and in inflammation or degenerating pathologies
- the regulation of the synthesis of pain related peptides (such as substance P (SP) and calcitonin gene-related peptide (CGRP)) and pain neuromodulators (such as brain-derived neurotrophic factor (BDNF)) by neurotrophic growth factor (NGF), and the anterograde transport and release of pain-related molecules from dorsal root ganglia to inflamed
- the role of SP, CGRP and BDNF in the transmission of pain in the dorsal horn of the spinal cord, **Figure 3.1.1 A-C**.

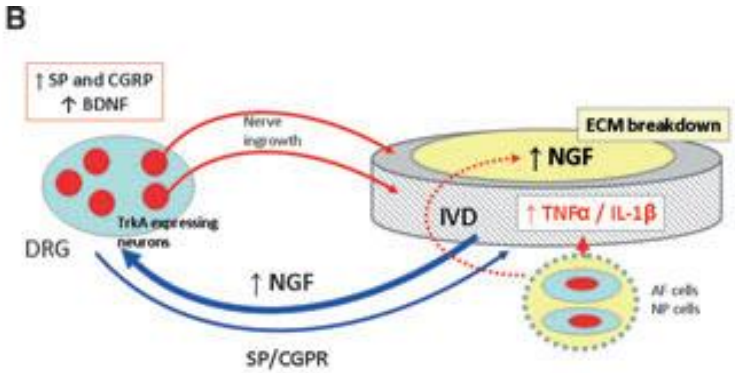
[77] Neurotrophins regulate development, maintenance, and function of vertebrate nervous systems
[78] Among the effects are prevention of neuronal death (neurotrophism) and promotion of axonal growth (neurotropism) after injury.

STEP ONE

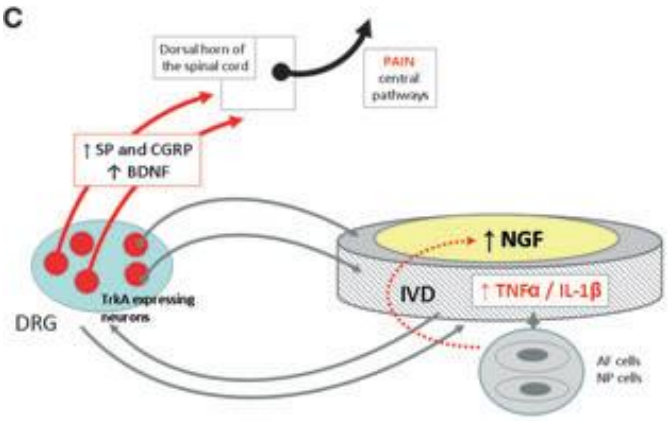


A. Inflammation causes release of proinflammatory cytokines in the intervertebral disc which act on mast cells and macrophages to trigger secretion of nerve growth factor (NFG). Cells in the intervertebral disc (IVD) upregulate expression of NGF and substance P (SP) during inflammation. Increased levels of NGF can be retrogradely transported to dorsal root ganglia (DRGs) or stimulate mastocytes and macrophages locally initiating a positive feedback loop

STEP TWO



B. Increased levels of nerve growth factors (NGFs) reaching the dorsal root ganglia (DRGs) act on TrkA-expressing neurons inducing expression of peptides that mediate pain [substance P (SP) and calcitonin gene-related peptide (CGRP)]. The increased levels of NGF in the IVD, as well as the breakdown of the IVD aggrecans, result in ingrowth of nociceptive nerve fibres and, presumably, in anterograde transport to the IVD, which maintains pain.



C. Synaptic transmission in lamina I and II of the dorsal horn of the spinal cord is mediated by substance P (SP) and calcitonin gene-related peptide (CGRP). In addition, brain-derived neurotrophic factor produced in dorsal root ganglia projects to the same spinal cord laminas and modulates pain transmission.

Figure 3.1.1 A-C. A schematic representation of the possible mechanisms involved in the genesis of the discogenic pain adapted from Garcia-Cosamalon, del Valle et al. (2010).

Neurotrophins are known to activate two different types of receptors – the tyrosine kinase (Trk) family of tyrosine kinase receptors and $p75^{NTR}$. Upon binding to these receptors neurotrophins initiate a variety of signals that lead to the regulation of cell proliferation, differentiation and survival. Neurotrophic signalling has also been reported to increase the expression of pain-related peptides which modulate the synapses of the spinal cord pain pathways[79]. Nerve growth factors TrkA and $p75^{NTR}$ have been reported to be expressed at increased levels in painful discs [80]. In these discs, the levels of proinflammatory mediators are reported to be higher than those in asymptomatic discs, suggesting that an inflammatory state is present (Burke et al., 2002).

Inflammatory cells such as macrophages have been shown to be an additional source of neurotrophins such as nerve growth factor and brain-derived neurotrophic factor (Bonini, Rasi, Bracci-Laudiero, Procoli, & Aloe, 2003; Vega, Garcı´a-Suarez, Hannestad, Pérez-Pérez, & Germanà, 2003); a recent study reported that herniated discs contain massive infiltrations of CD68-positive macrophages (Kokubo et al., 2008).

Inflammation occurs simultaneously with the up-regulation and release of inflammatory cytokines and peptides by the inflamed tissues and the expression of tyrosine kinase A in dorsal root ganglia neurons

[79] Pezet S, McMahon SB (2006) Neurotrophins: mediators and modulators of pain. Annu Rev Neurosci 29, 507–538. Merighi A, Salio C, Ghirri A, et al. (2008) BDNF as a pain modulator. Prog Neurobiol 85, 297–317.
[80] Freemont AJ, Jeziorska M, Hoyland JA, et al. (2002a) Mast cells in the pathogenesis of chronic back pain: a hypothesis. J Pathol 197, 281–285. Freemont AJ, Watkins A, Maitre CL, et al. (2002b) Nerve growth factor expression and innervation of the painful intervertebral disc. J Pathol 197, 286–292.

(Pezet et al., 2001). Nerve growth factor released in inflamed intervertebral discs may act directly on nociceptive fibres and neurons to trigger an increased sensitivity to pain.

In addition to such direct action, nerve growth factor also modulates pain by altering the effectiveness of the central nociceptor signals through brain-derived neurotrophic factor and stimulates mast cells and macrophages to release mediators; thus the interrelationship between nerve growth factor and inflammatory cytokines appears to be both complex and reciprocal[81]

Recent work carried out by Takebayashi et al (2006)[82] was also reported that suggested that mechanical stimulation of the lumbar disc did not always produce pain, but that inflammatory changes could cause the disc to become *sensitive to mechanical stimuli*, and result in nociceptive information being transmitted as discogenic low back pain to the spinal cord through the lumbar sympathetic trunk. It was suggested that this may partly explain the variation in human symptoms of degenerate discs.

Upregulated nerve growth factor expression was reported to occur simultaneously with nerve ingrowth in degenerating discs and the growing literature on the characterisation of nerve fibres in degenerating and painful intervertebral discs was reviewed. However, similar to other reviewers, Garcia-Cosamalon et al. (2010) considered that the mechanisms responsible for nerve growth and hyperinnervation of the lumbar intervertebral had *not yet been fully elucidated*.

In conclusion, Garcia-Cosamalon et al. (2010) considered that the biological evidence strongly suggested that neurotrophins played a role in the both the *genesis* and *maintenance of painful stimuli* from degenerating intervertebral discs. They considered that neurotrophins, together with extracellular matrix modifications and some cytokines, regulated;

- the nerve ingrowth into the intervertebral disc,
- the synthesis of pain-related peptides in the intervertebral disc itself, but especially in dorsal root ganglia,
- the synapses related to pain transmission in the dorsal horn of the spinal cord,
- the biology of the proinflammatory cytokines.

They also considered that a complex network centred on neurotrophins (mainly nerve growth factor and brain-derived neurotrophic factor), could in part rationally explain the cellular and molecular mechanisms of discogenic pain.

From a therapeutic perspective, Garcia-Cosamalon et al. (2010) considered that neurotrophins might be potential targets for therapeutic strategies for discogenic pain and that the disruption of the pathological processes in which neurotrophins are involved could benefit the control of pain and prevention of the degeneration of the intervertebral disc[83].

[81] Spedding M, Gressens P (2008) Neurotrophins and cytokines in neuronal plasticity. Novartis Found Symp 289, 222–233. Uc¸eyler N, Scha¨ fers M, Sommer C (2009) Mode of action of cytokines on nociceptive neurons. Exp Brain Res 196, 67–78.
[82] Takebayashi T, Cavanaugh JM, Kallakuri S, et al. (2006) Sympathetic afferent units from lumbar intervertebral discs. J Bone Joint Surg Br 88, 554–557.
[83] Masuda K, An HS (2004) Growth factors and the intervertebral disc. Spine J 4, 330S–340S. Masuda K, An HS (2006) Prevention of disc degeneration with growth factors. Eur Spine J 15(Suppl 3), S422–S432.

In summary, Garcia-Cosamalon et al. (2010) considered that upon degeneration, the disc became densely innervated even in regions that normally lack innervation and that this increased innervation was associated with pain of intervertebral disc origin. The mechanisms responsible for nerve growth and hyperinnervation of pathological intervertebral discs were considered not yet to have been fully elucidated. Among the molecules that were presumed to be involved in the process were some members of the family of neurotrophins which were known to have both neurotrophic and neurotropic properties and regulate the density and distribution of nerve fibres in peripheral tissues. Neurotrophins and their receptors were known to be expressed in healthy intervertebral discs but much higher levels had been observed in pathological discs suggesting a correlation between levels of expression of neurotrophins and the density of innervation in intervertebral discs. In addition, neurotrophins were believed to also play a role in inflammatory responses and pain transmission by increasing the expression of pain-related peptides and modulating synapses of nociceptive neurons at the spinal cord.

Anatomy and pathophysiology of disc pain

Raj 2008 "Intervertebral disc: anatomy-physiologypathophysiology- treatment."

Raj (2008)focussed on the provocation of pain with discography, reporting that Ohnmeiss et al.[84] studied the typical patterns of pain referral from different degrees of discogram-confirmed, posterior annular tears/ radial fissures.

It was suggested that the disc did *not have to be completely torn, ruptured or bulging* for the patient to suffer from lower limb pain. Outer annulus non-ruptured and non-leaking discs were found to reproduce lower limb pain on discography just as often as bulging, herniated, completely ruptured, and leaking discs.

Raj argued that the *pain pathways for discogenic pain remained very controversial*, noting that while traditionally, pain signals that originated in the nerve roots adjacent to the disc were believed to move from that root, into the corresponding dorsal root ganglion (DRG) and into the spinal cord as shown by the arrows in Figure 3.1.2A, more recent new research suggested that pain signals from the lower lumbar discs (L4 and L5) were *detoured* up the sympathetic nerves (gray ramus communicans) and into the upper lumbar DRGs—especially at the L2 level, Figure 3.1.2B. Thus clinically, some patients with L4 and L5 disc pathology could have L1 or L2 dermatomal pain.

[84] Ohnmeiss DD, et al. Degree of disc disruption and lower extremity pain. Spine. 1997;22:1600–1665.

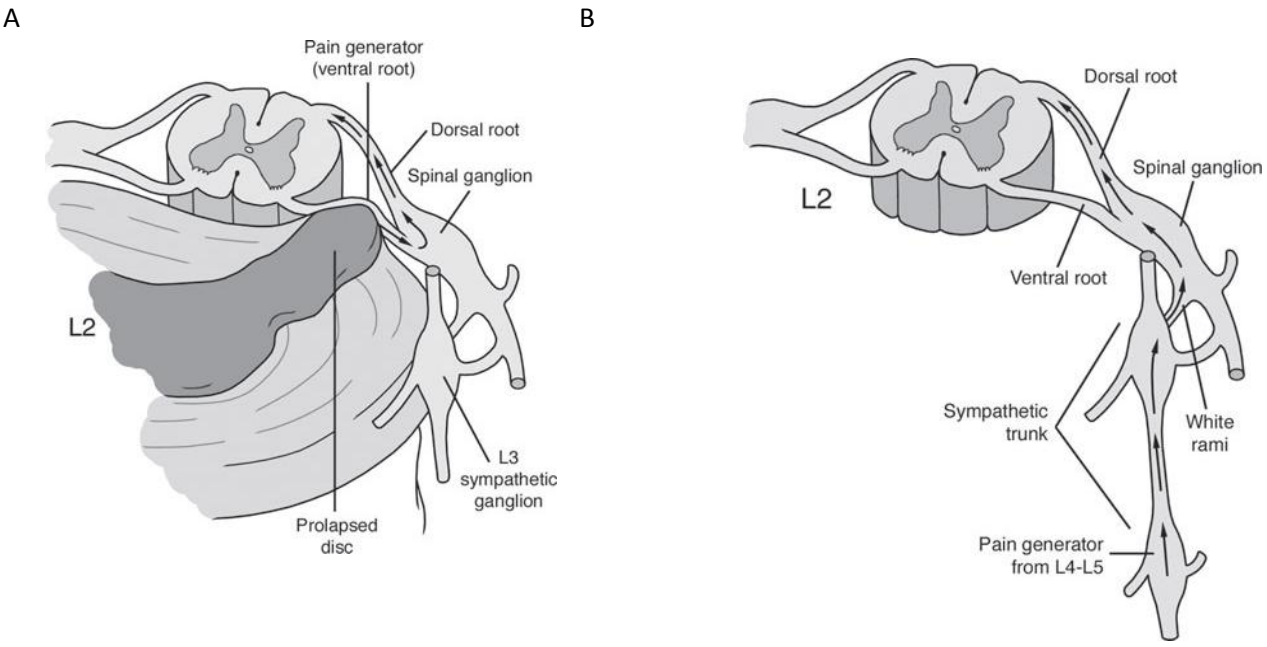


Figure 3.1.2 Pain pathways for discogenic pain. (A) Pain signals generated in the disc pass into the corresponding dorsal root ganglion (DRG) and into the spinal cord. (B) Pain signals from the lower lumbar discs (L4-L5) detour up the sympathetic nerves (grey ramus communicans) into the upper lumbar DRG, especially at the L2 level. DRG, dorsal root ganglion

In summary, Raj (2008) concluded that the nerve supply to the disc was basically through the sinovertebral nerve and that during degenerative changes nociceptive nuclear material tracked and leaked through the outer rim of the annulus. This was believed to be the main source/mechanism of discogenic pain.

Summary of findings for discogenic pain

Innervation of the disc

Research in the 1980s suggested that pain sensation was conducted in part via the sympathetic system and confirmed a *dual pattern of supply* with one route entering the adjacent dorsal root segmentally, the other (non-segmental supply) ascending through the paravertebral sympathetic chain with re-entry through the thoracolumbar white rami communicantes. Sensory nerve endings in the degenerative lumbar disc were reported to penetrate deep into the disrupted nucleus pulposus, which was known to be insensitive in the normal lumbar spine.

It was considered that, for the most part, the disc was innervated by sympathetic nerves and that it was probable that these sympathetic nerves were conveying pain afferent information to the central nervous system.

This suggested that low back pain was a type of *visceral pain,* unique in the musculoskeletal system. It was also considered that the lumbar sinuvertebral nerves had up to three segmental levels of overlap, which might explain the poor localisation of low back pain.

The nature and mechanism of discogenic pain was reported to still be speculative but there was evidence to suggest that in addition to a 'visceral pain' hypothesis, discogenic pain was open to 'peripheral sensitisation' and possibly 'central sensitisation' as a potential cause of chronic back pain.

Biochemical mechanisms

It was reported that during degenerative changes nociceptive nuclear material leaked through the outer rim of the annulus and that this was the main source/mechanism of discogenic pain. While the cellular pathobiology of the degenerate intervertebral disc was yet to be fully elucidated, key roles were postulated for *neurotrophins* such as nerve growth factor and brain derived neurotrophic factor in the neoinnervation of the disc, and for *inflammatory cytokines* such as tumour necrosis factor α (TNFα) and interleukin 6 (IL-6). Immunologically active molecules such as *glycosphingolipids* (GSLs) were also implicated in the generation of pain.

3.2 Mechanisms of facet joint pain

The facet joint has been increasingly recognised as an important source of low back pain with renewed interest resurfacing with the refinement of interventional pain procedures and the development of motion preservation surgical technology (D. S. Binder & Nampiaparampil, 2009; Varlotta et al., 2011).

Nomenclature of the facet Joints

The paired joints at the back of the vertebra are commonly called *facet joints***.** Their official name is *zygapohyseal joints***,** because they are paired joints on the arch; the Greek root *"zyg-"* approximately equals "yoked" or "joined", and "apo-physis" is roughly an out growing knob on a bone. Thus they are the paired or linked joints on the two outgrowths of the arch of the vertebra. The use of the term "facet joint" is common although it has been objected to on the grounds that the term "facet" is used for the flat part of the joint surface on many other joints, where the joint moves against a different bone, but as part of a single joint. The difficulty and obscurity of the term "zygapohyseal joint" appear to have ensured that "facet joint" remains the colloquial term for these joints. The terms are used interchangeable in the current report to allow the preferences in the various review articles to be preserved.

History

The zygapophyseal joint of the lumbar spine first was identified as a potential source of back pain by Goldthwaite in 1911 who suggested that asymmetry of the joints may explain lumbago and nerve pathologies including sciatica and paraplegia[85].

Facet joint "syndrome" was introduced by Ghormley in 1933[86]. His original concept suggested that pain was generated from nerve compression and was radicular in pattern rather than our current understanding of facetogenic pain as a referred pain pattern from nociceptive fibres innervating the facet joint itself. The zygapophyseal joint as a source of *referred pain* was described by Bagley[87] based upon his own clinical and anatomic observations.

In 1963, Hirsch et al.[88] injected hypertonic saline in the region of the facet joints and provoked low back and thigh pain. In the late 1970s facet joint-mediated pain was confirmed as a pain entity in more specific studies involving direct intra-articular injections of hypertonic saline[89].

Although low back pain and sciatica have historically been considered a presentation of pathology of the intervertebral disc, more recent studies indicate that 15 to 40% of chronic low back pain may be generated by pathology in the zygapophyseal joint[90].

[85] Goldthwait JE. The lumbosacral articulation: an explanation of many cases of lumbago, sciatica, and paraplegia. Boston Med Surg J 1911;164:356–372
[86] Ghormley RK. Low back pain with special reference to the articular facets, with presentation of an operative procedure. JAMA 1933; 101:1773–1777
[87] Bagley CE. The articular facets in relationship to low back pain and sciatic radiation. J Bone Joint Surg Am 1941;23: 481–496
[88] 38. Hirsch D, Inglemark B, Miller M. The anatomical basis for low back pain. Acta Orthoscan. 1963;33:1–17.
[89] Mooney V, Robertson J. The facet syndrome. Clin Orthop Relat Res. 1976;115:149–56. McCall IW. Induced pain referral from posterior lumbar elements in normal subjects. Spine. 1979;4:441–6.
[90] Schwarzer AC, Aprill CN, Derby R, Fortin J, Kline G, Bogduk N. The relative contribution of the disc and zygapophyseal joint in chronic low

In comparison to cervical facet joint capsules, the lumbar capsules are shorter and more taught, resulting in a lesser degree of flexion obtained in the lumbar spine in comparison to the cervical spine. The orientation of lumbar facet joints has important functional and clinical consequences. For example, facet joints oriented relatively more parallel to the sagittal plane, such as at L2–L3 and L3–L4, allow limited rotational movements and anatomically favour flexion and extension movements. In contrast, the L4–L5 facet joints, with increased coronal angulations, facilitate greater rotational movements.

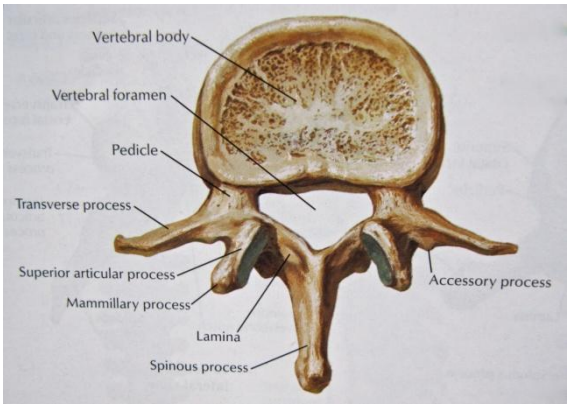


Figure 3.2.1 Facet joints: lumbar vertebra (Netter 2006)

In the lumbar spine, the zygapophyseal joint is oriented sagittally, Figure 3.2.1, effectively protecting the intervertebral disc from axial rotation and loading. In contrast, in the thoracic (Figure 3.2.2) and cervical spine, the facet joints are oriented coronally, offering more effective protection against shearing forces at the level of the intervertebral disc.

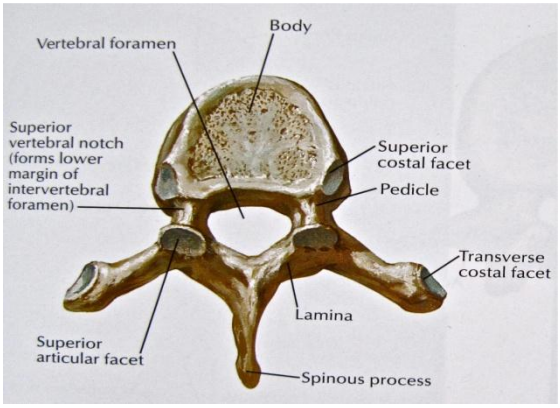


Figure 3.2.2. Facet joints: thoracic vertebra (Netter 2006)

back pain. Spine 1994;19:801–806. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophyseal (facet) joints. Arch Phys Med Rehabil 1996; 77:290–300. Schwarzer AC,Wang S, O'Driscoll D, Harrington T, Bogduk N, Laurent R. The ability of computed tomography to identify a painful zygapophyseal joint in patients with chronic low back pain. Spine 1995;20:907–912

Characteristically, pain from the zygapophyseal joints is worse with standing and lumbar extension and improved with sitting and forward flexion. The pain pattern may be referred to regions including the ipsilateral buttock and posterior thigh, or it may be radicular with more distal radiation.

The orientation of the zygapophyseal joints absolutely and relative to one another may have an important role in the development of degenerative spondylolisthesis and instability within the spinal motion segment (Berven, Tay, Colman, & Hu, 2002).

Non systematic reviews

No systematic reviews were identified that addressed questions relating to the mechanics or generation of facet joint pain.

One systematic review (Kirpalani & Mitra, 2008) of cervical facet joint dysfunction included a section on the pathophysiology of the facet joint, but did not focus on the mechanism of pain generation. Three *non-systematic reviews* were identified published between 2002 and 2011, each reported on the lumbar spine. Only one of these narrative reviews focussed on the role of the facet joint in lumbar spinal pain syndromes (Berven et al., 2002), the remaining two were general reviews of the current state of knowledge of lumbar facet joints which included sections reporting pain pathophysiological studies (D. S. Binder & Nampiaparampil, 2009; Varlotta et al., 2011).

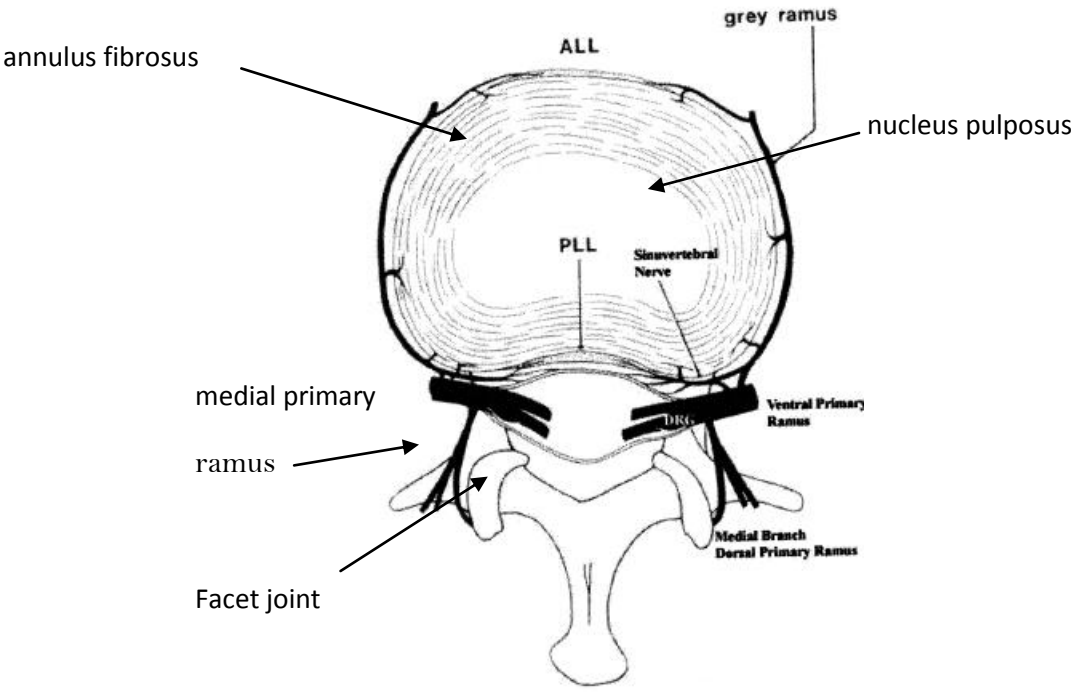
Berven 2002 "The lumbar zygapophyseal (facet) joints: a role in the pathogenesis of spinal pain syndromes and degenerative spondylolisthesis."

In their clinical review of the lumbar zygapophyseal joints, Berven et al (2002) noted that the innervations of the facet joints was the basis for their potential as pain generators (Berven et al., 2002). Bogduk[91], on the basis of an anatomic study, concluded that "the profuse and complex innervation of the capsules of the lumbar zygapophyseal joints invites a sophisticated role for these structures."

Further support for the role of the lumbar facet joint as an important source of low back pain came from (a) clinical observations regarding the generation of pain with injection of hypertonic saline into the facet joints, (b) direct stimulation of the facet joints, and (c) changes in low back pain with facet joint blocks and medial branch ablation procedures[92].

The lumbar facet joints are innervated by nociceptive fibres of the medial branch of the dorsal ramus, Figure 3.2.3. The innervation of the facet joint is distinct from that of the intervertebral disc which is innervated by the sinuvertebral nerve, which is a branch of the ventral primary ramus. The review authors described the role of the facet joints in the generation of low back pain an "incompletely understood" despite being identified as a potential source of back pain as early as 1911.

[91] Bogduk N. The innervation of the lumbar spine. Spine 1983; 8:286–293
[92] Cavanaugh JM, Ozaktay C, Yamashita T, King AI. Lumbar facet pain: biomechanics, neuroanatomy, and neurophysiology. J Biomech 1996;29:1117–1129



ALL = anterior longitudinal ligament. PLL=posterior longitudinal ligament DRG=dorsal root ganglion.

Figure 3.2.3 Innervation of the facet joints and the intervertebral disc.

The authors of the review concluded that while there was good histological evidence that the lumbar facet joints are a significant source of pain of spinal origin, the reliability of provocative techniques (at that time) to identify pathologic levels remained unproved.

The role of the lumbar facet joints in the development of degenerative spondylolisthesis was also highlighted. Thus with the exception of detailing the gross innervation of the facet joint – at the time of publication of this review (2002) no explanation of the mechanism of facet joint pain was forthcoming.

Kirpalani 2008 "Cervical Facet Joint Dysfunction: A Review."

Kirpalani and Mitra (2008) reviewed the relevant literature on cervical facet joint dysfunction to determine its anatomy, aetiology, prevalence, clinical features, diagnosis, and treatment. A short section on the pathophysiology of the facet joint was included (Kirpalani & Mitra, 2008).

They reported that cervical facet joint pain resulted from either traumatic or degenerative processes. Traumatic causes included fracture and/or dislocation injuries and whiplash disorders. They considered that facet dislocations or locked facet injuries occurring with acute cervical trauma may or may not be associated with cervical facet fracture. The authors also noted that the aetiology of whiplash pain was controversial but that facet joints in the cervical spine had been targeted as a possible nociceptive pain generator.

Facet joint injury was hypothesized to result from two different mechanisms during rear-end impact:

(1) Excessive compression of the facet joint

(2) Excessive capsular ligament strain beyond the physiologic limit[93].

Degenerative processes such as osteoarthritis were also reported to cause cervical facet joint pain. Similar to the intervertebral disc, was suggested that early degenerative changes in the articular cartilage in the facet joints were not always symptomatic/pathologic.

In relation to innervation, which is a prerequisite for pain generation, from C3-4 through C8-T1 the cervical joints were reported to be innervated by the medial branches of the cervical dorsal rami above and below the joint, as these branches course around the waist of the articular pillars. The C2-3 facet joint was reported to be innervated by two different branches of the C3 dorsal ramus—a medial branch called the third occipital nerve and a separate articular branch arising from the origin of the communicating branch or from the communicating branch itself[94]. The upper-cervical synovial joints (the atlanto-occipital and atlanto-axial joints) were not innervated by cervical dorsal rami but by branches of the C1 and C2 ventral rami.

In relation pain generation in the facet joints, Kirkpalani and Mitra (2008) noted that the cervical facet joints contained intra-articular inclusions consisting of fibrous connective and adipose tissue[95]. These inclusions were reported to contain well-developed structures known as synovial folds. Since these folds comprised varying amounts of fibrous and adipose tissue, it was suggested that different levels of mechanical stress may be placed on these structures and that they may *play a role in cervical facet joint pain*. Shortly after, peptides known to be involved in pain generation (protein gene product 9.5, substance P and calcitonin gene related peptide) were found in cervical facet joint capsules suggesting that the facet joint capsules may directly be involved in pain generation in the cervical spine[96].

Binder 2009 "The provocative lumbar facet joint"

Binder and Nampiaparampil (2009) provided an overview of the anatomy, pathophysiology, diagnosis, and treatment of facet joint-mediated pain. Further details relating to the innervations of the facet joint of the lumbar spine were described. Nociceptive nerve endings were reported to have been demonstrated in both the capsule and the synovial folds of the facet joint[97] with pain sensation from the capsule and synovium reportedly transmitted through the medial branches of the dorsal ramus of spinal nerves. Each lumbar facet joint was reported to be innervated by the medial branch of the dorsal ramus of the nerve exiting at the *same level* and also the medial branch of the nerve *one level above,* Figure 5.

Binder and Nampiaparampil (2009) noted that both facet joint orientation and facet joint tropism (an asymmetry in the angles of two facet joints at the same level) had been implicated as important

[93] Bogduk N, Yoganandan N. Biomechanics of the cervical spine part 3: minor injuries. Clin Biomech (Bristol, Avon) 2001;16:267-75. Pearson AM, Ivancic PC, Ito S, Panjabi MM. Facet joint kinematics and injury mechanisms during simulated whiplash. Spine 2004;29:390-7
[94] Bogduk N. The clinical anatomy of the cervical dorsal rami. Spine 1982;7:319-30.
[95] Inami S, Kaneoka K, Hayashi K, Ochiai N. Types of synovial fold in the cervical facet joint. J Orthop Sci 2000;5:475-80.
[96] Kallakuri S, Singh A, Chen C, Cavanaugh JM. Demonstration of substance P, calcitonin gene-related peptide, and protein gene product 9.5 containing nerve fibres in human cervical facet joint capsules. Spine 2004;29:1182-6.
[97] Giles LGF, Taylor JR. Human zygapophyseal joint capsule and synovial fold innervation. Br J Rheumatol. 1987;26:93–8.

variables leading to facet joint-mediated pain. They also reported that facet joint tropism had been reported to be much more common in the thoracic spine as compared to the lumbar spine[98].

The development of facet joint-mediated pain was believed to comprise both biomechanical and inflammatory components. It was argued that biomechanically, the facet joints had functions in relation to (a) stabilizing the spine, (b) guiding segmental motion, (c) weight-bearing support during axial loading along with the intervertebral discs[99]. Multiple factors could destabilize the facet joint and its capsule. Disc degeneration with associated narrowing of the disc space altered the mechanical load distribution which was thought to result in a degenerative cascade with increased mechanical stress on the facet joint and joint capsule. The increase in axial rotation and subsequent instability placed additional stressors upon the facet joint capsules which were believed to lead to a molecular response, resulting in fibrocartilaginous metaplasia in the capsules of facet joints. In support of this hypothesis, Boszczyk et al. (2003)[100] reported hypertrophic and fibrocartilagenous changes in the facet joint capsules of patients who had undergone lumbar fusion for degenerative instability.

From a chemical perspective, it was known that changes in load distributions could lead to osteoarthrosis, osteophyte formation, and inflammation[101]. The cartilage and synovium of facet joints were both sources of inflammatory cytokines[102]. Thus it was proposed that painful symptoms may arise not only from mechanical stress but also from the associated *inflammatory response* involving cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) , interleukin 1 beta (IL-1β), oxygen free radicals such as nitric oxide, and inflammatory mediators such as prostaglandins. Some studies suggested that inflammatory cytokines originating from inflamed facet synovia may spread to adjacent nerve roots and produce radicular lower extremity symptoms[103].

As with other diarthrodial joints, it was suggested that the cartilage of facet joints may be sex-hormone sensitive; Ha et al. (2007)[104] have recently found a statistically significant association between the increased expression of oestrogen receptors on the articular cartilage of facet joints and the severity of facet arthritis.

In summary Binder and Nampiaparampil (2009) considered that he development of facet joint-mediated pain involved both *biomechanical and inflammatory* components and that multiple factors could destabilize the facet joint and its capsule.

Varlotta 2011 "The lumbar facet joint: A review of current knowledge."

[98] Masharawi Y, Rothschild B, Dar G, Peleg S, Robinson D, Been E, et al. Facet orientation in the thoracolumbar spine: three-dimensional anatomic and biomechanical analysis. Spine. 2004;29(16):1755–63.
[99] While the intervertebral discs support most of the weight during *flexed postures* (bent postures) the facet joints bear an increasingly greater burden as the lumbar spine is ranged into extension (straightening).
[100] Boszczyk BM, Boszczyk AA, Korge A, Grillhosl A, Boos WD, Putz R, et al. Immunohistochemical analysis of the extracellular matrix in the posterior capsule of the zygapophyseal joints in patients with degenerative L4–5 motion segment instability. J Neurosurg. 2003;99(1 Suppl):27–33.
[101] Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. J Bone Joint Surg Am. 2006;88 (Suppl 2):68–71.
[102] Igarashi A, Kikuchi S, Konno S, Olmarker K. Inflammatory cytokines released from the facet joint tissue in degenerative lumbar spinal disorders. Spine. 2004;29(19):2091–5.
[103] Tachihara H, Kikuchi S, Konno S, Sekiguchi M. Does facet joint inflammation induce radiculopathy?: an investigation using a rat model of lumbar facet joint inflammation. Spine. 2007;32(4): 406–12.
[104] Ha KY, Chang CH, Kim YS, Kim KW, Na KH, Lee JS. Expression of estrogen receptor of the facet joints in degenerative spondylolisthesis. Spine. 2005;30(5):562–6.

The *most recent* review was published in 2011 by Varlotta (Varlotta et al., 2011). In a two-part publication aimed at reviewing the current state of knowledge of lumbar facet joint pathology the authors acknowledged that;

"While MR imaging is widely employed in the evaluation of disc degeneration, there currently is no consensus on how best to evaluate lumbar facet joint arthrosis radiographically."

and that

"Clinicians and researchers alike are still unable to predict with any certainty those patients with degenerative changes in the lumbar facet joints who will become symptomatic and those who will not."

A review of the relevant literature found conflicting evidence in support of a relationship between radiographic facet joint abnormalities and facet-mediated pain. However, the *sagittal orientation of the lumbar facet joint* was again reported to be a risk factor for the development of degenerative spondylolisthesis[105] Kim et al. (1995)[106] showed that patients with narrow facet joint angles (less than 77.9°) had a 2.5 times higher risk of developing degenerative spondylolisthesis than patients with greater facet joint angles (greater than 77.9°).

The authors noted that facet joint tropism was being increasingly studied with respect to degenerative spondylolisthesis. It was suggested that this was partly be due to the poor reliability of the lumbar "facet joint syndrome" diagnosis given to patients presenting with primary lower back pain complaints. It was also noted that the "pseudoradicular" referral patterns of the lumbar facet joints may mimic the pain felt from a herniated disc perhaps making differentiating between the two conditions difficult.

Summary of facet joint related pain generation

The facet joints are true synovial joints with hyaline cartilage surfaces, a synovial membrane, and a surrounding fibrous capsule. The role of facet joints of the lumbar vertebrae in the generation of low back pain remains *incompletely understood.* Because of the unreliability of the relationship between radiographic abnormalities and pain, accurate diagnosis and evaluation of facet joint related pain was reported to be problematic and further exacerbated by the fact that pseudoradicular pain patterns may mimic that produced by herniated discs.

Innervation of the facet joints was reported to be the basis for their potential as pain generators in the lumbar spine with the capsule reported to be innervated by a profuse and complex network of nociceptive fibres of the medial branch of the dorsal ramus. Neurophysiologic studies cited the following in support of facet pain of *capsular origin*: (1) a population of high-threshold, small-diameter sensory neurons in the capsule, (2) sensitization and increased discharge of facet-joint neurons in the presence of inflammation, and (3) demonstration of the effects of substance P on these neurons.

However, the *synovial folds* have also been shown to be innervated and reported to be a source of inflammatory cytokines. Similar to the intervertebral disc, it has been proposed that painful symptoms may arise not only from mechanical stress but also from the associated inflammatory responses

[105] Dai LY. Orientation and tropism of lumbar facet joints in degenerative spondylolisthesis. Int Orthop. 2001;25:40–2.
[106] Kim NH, Lee JW. The relationship between isthmic and degenerative spondylolisthesis and the configuration of the lamina and facet joints. Eur Spine J. 1995;4(3):139–44.

involving cytokines and inflammatory mediators such as prostaglandins. It has also been suggested that inflammatory cytokines originating from inflamed facet synovia may spread to adjacent nerve roots producing radicular symptoms.

In the cervical spine the facet joints have been implicated in the aetiology of whiplash pain. Recently, both facet joint orientation and facet joint tropism (an asymmetry in the angles of two facet joints at the same level) have been implicated as important variables leading to facet joint-mediated pain. Facet joint tropism has been reported to be much more common in the thoracic spine. The sagittal orientation of the lumbar facet joint is reported to be a risk factor for the development of degenerative spondylolisthesis.

3.3 Mechanisms of Radicular pain

Radicular pain has its origins in the nerve root and historically its location was thought to be in the dermatome[107] of the corresponding nerve root (Robinson, 2003).

No systematic reviews were identified that focussed on the pathophysiology of radicular pain or that addressed questions relating to the mechanics or generation of radicular joint pain. Five non-systematic reviews were identified. Two of these focussed on the pathophysiology of pain in the lumbar (A. H. Wheeler & Murrey, 2002) and cervical (Van Zundert et al., 2006) spine. The remaining three reported on various aspects of sciatica (Goupille, Mulleman, Paintaud, Watier, & Valat, 2007; Stafford, Peng, & Hill, 2007) and instability (Leone, Guglielmi, Cassar-Pullicino, & Bonomo, 2007) of the lumbar spine.

Leone et al (2007) suggested that intervertebral disc instability was a possible pathomechanical mechanism underlying sciatica. However, no further details were forthcoming and this review was not considered further.

Similar to reviews of discogenic pain and facet pain, the majority of these reviews were published in the last five years.

Defintions

Radicular pain is defined as 'pain perceived as arising in a limb or the trunk caused by ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots or other neuropathic mechanisms'[108].

Sciatic neuralgia, which is defined as 'pain in the distribution of the sciatic nerve due to pathology of the nerve itself'[55], is a form of radicular pain.

Stafford et al (2007) pointed out that the term 'sciatica' may cause confusion as it has been used to describe any pain referred or otherwise, felt in the leg along the distribution of the sciatic nerve. It was recommended that the use of the term sciatica should be restricted to the above definitions and as such, be distinguished from any or all other forms of pain felt in the leg, particularly referred pain.

History

A recently published text entitled "*Lumbar spine imaging in radicular pain and related conditions."* (Wilmink, 2010a) gave the following introduction to the topic:

"Clinical descriptions of sciatica go back to the times of Hippocrates and Cotugno, and the etiology of this affliction has puzzled medical practitioners for equally long. Much is still unclear. In the course of the twentieth century, surgical techniques and insights improved to a degree in which sciatica was transformed from a symptom related to a "rheumatic" condition causing inflammation of the sciatic nerve to a symptom which could be relieved by an operation. In 1934, Mixter and Barr published their

107 A dermatome is an area of skin that is mainly supplied by a single spinal nerve, see Appendix A. Note: Murphy et al 2009 failed to find much support for the common notion that extremity pain that arises from radiculopathy typically follows along a specific dermatome. In general, the Sensitivity and Specificity of this finding were low, suggesting that this factor is not useful in making the diagnosis of radicular pain.

108 Merskey H, Bokduk N. Classification of Chronic Pain, 2nd Edn. IASP Press, 1994; 13, 15, 198

report on "Rupture of the intervertebral disc with the involvement of the spinal canal". The "dynasty of the disc" had begun! "

Mixter and Barr (1934) described 19 cases of rupture of the intervertebral disc with compression of the spinal cord, cauda equina or exiting nerve root by herniated material. These cases included four cases with a cervical localisation, four cases in the thoracic spine, ten in the lumbar spine and lumbosacral transition, and one in the sacral region. Following this work, the concept of nerve root compression by herniated disc material as a cause of low back and lower extremity pain dominated etiologic and therapeutic thinking on the subject of sciatica for several decades (Wilmink, 2010b). Surgical treatment to relieve the compression thus became the treatment of choice for refractory sciatica.

However, regardless of the technique used, surgery to relieve nerve root compression was not consistently successful. Although short-term success rates were high (80–90%) analysis of long-term success rates showed lower values. In a retrospective study by Loupasis et al. (1999)[109] of 109 patients with a mean follow-up of 12.2 years (range 7–20 years), more than one third of the patients were dissatisfied with the surgical procedure (Mulleman, Mammou, Griffoul, Watier, & Goupille, 2006).

The biochemical model

Lindahl and Rexed (1951)[110] found histological evidence of inflammation in nerve roots inspected during laminectomy. Smyth and Wright (1958)[111] noted that compressed lumbosacral nerve roots were much more sensitive to mechanical stimulation than uncompressed roots. It was concluded that prolonged irritation made the nerve root hypersensitive, and that merely touching such a nerve root was then sufficient to cause severe sciatica (Wilmink, 2010b).

In 1977 Howe et al (1977) reported that repetitive spontaneous firing of nerve fibres took place following minimal compression of the dorsal root ganglia. This work was credited as providing the stimulus for further research into the pathophysiological changes in the dorsal root ganglion as a driving mechanism for pain after injury to the nerve (Van Zundert et al., 2006).

In the 1990s compelling evidence[112] from animal models showed that mechanical compression of a healthy nerve root caused dysesthesia, paresthesia, or motor loss, *but no pain.* In volunteers who underwent disk surgery under local anaesthesia, moderate mechanical stimulation of a nerve root having no contact with the herniated disk merely caused discomfort, whereas the same stimulation applied to a nerve root in contact with a disk herniation often replicated the sciatica. These and other studies demonstrated that nerve root compression *alone* was not sufficient to cause nerve root pain (Mulleman et al., 2006).

[109] Loupasis GA, Stamos K, Katonis PG, Sapkas G, Korres DS, Hartofilakidis G. Seven- to 20-year outcome of lumbar discectomy. Spine 1999;24:2313–7.
[110] Lindahl O, Rexed B (1951) Histologic changes in spinal nerve roots of operated cases of sciatica. Acta Orthop Scand 20(3): 215
[111] Smyth MJ, Wright V (1958) Sciatica and the intervertebral disc; an experimental study. J Bone Joint Surg Am 40-A(6):1401
[112] Cavanaugh JM. Neural mechanisms of lumbar pain. Spine 1995;16: 1804–9.Kulisch SD, Ulstrom CL, Michael CJ. The tissue origin of low-back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. Orthop Clin North Am 1991;22:181–7.

Anatomical considerations

Non-neoplastic compression of nerve roots can have many causes. Besides disc herniation, various types and degrees of narrowing can occur of the spinal canal, of the lateral recesses, or the foramina. There may be deformation of the spinal canal by anterolisthesis or forward slipping of a vertebral body upon its lower neighbour; encroachment upon the spinal canal by ligamentous hypertrophy or synovial cyst formation, or reduction of space within the spinal canal due to abnormal increase in epidural fat (lipomatosis). A disc herniation can produce compression of a single nerve root, while severe stenosis of the spinal canal or spinal lipomatosis can involve the entire cauda equina. Combinations of these factors are common, and in fact such combinations occur more frequently than radicular compression due to a single cause, Figure 3.3.1.

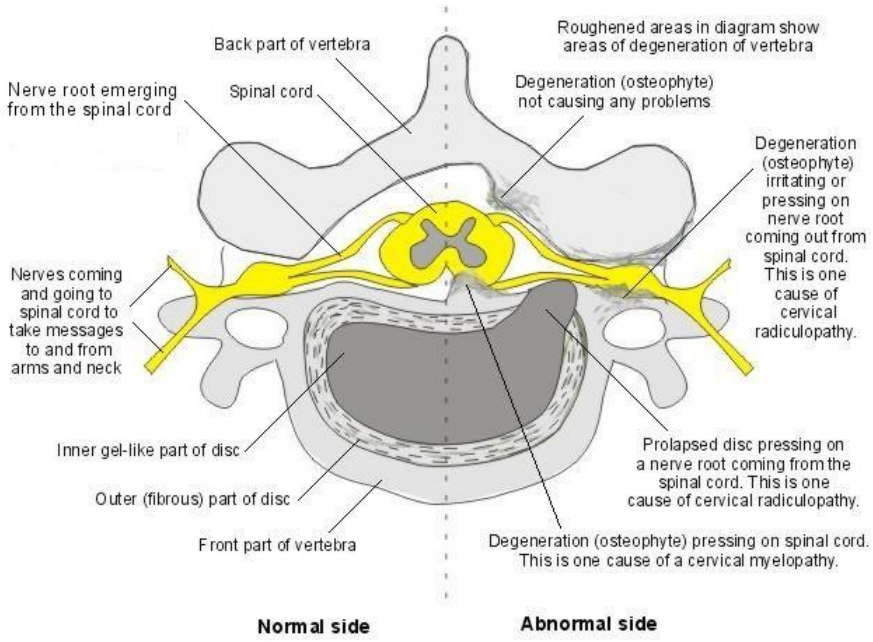


Figure 3.3.1. Examples of nerve compression in the cervical disc; a normal and abnormal disc comparison.

The nature of the herniation is important. Protruded discs are herniated discs in which the *displaced material is still contained or covered by the outer annulus*; the base of the herniation in a protruded disc is always the broadest part because the nucleus has not yet oozed through and out of the annulus, Figure 3.3.2.

Extruded discs are herniated discs in which displaced material is no longer contained by the outer annulus fibrosus having passed through a tear in the annulus and outside the confines of the disc[113]. Extrusions are generally larger than protrusions. In the sagittal imaging plane, extrusion of disc material

[113] In practise it mat be very difficult to distinguish between extruded and protruded discs, personal communication, Gordon Howie, reviewer.

through a ruptured annulus may be deduced from the fact that the height of the herniation outside the disc is greater than the distance between the end-plates of the parent disc Figure 3.9c. The distinction between protrusion and extrusion is more difficult to make in the axial plane; the presence of disc material in axial sections above or below the disc level can be taken as evidence of annular disruption as in Figure 3.3.3.

The clinical importance of the distinction between extruded and protruded disc herniation lies in the fact that extruded discs are *more frequently symptomatic* than protruded discs which can be seen quite often in asymptomatic individuals. The biological importance of the distinction lies in the leakage of nucleus pulposus and its contact with the spinal nerves and other local structures.

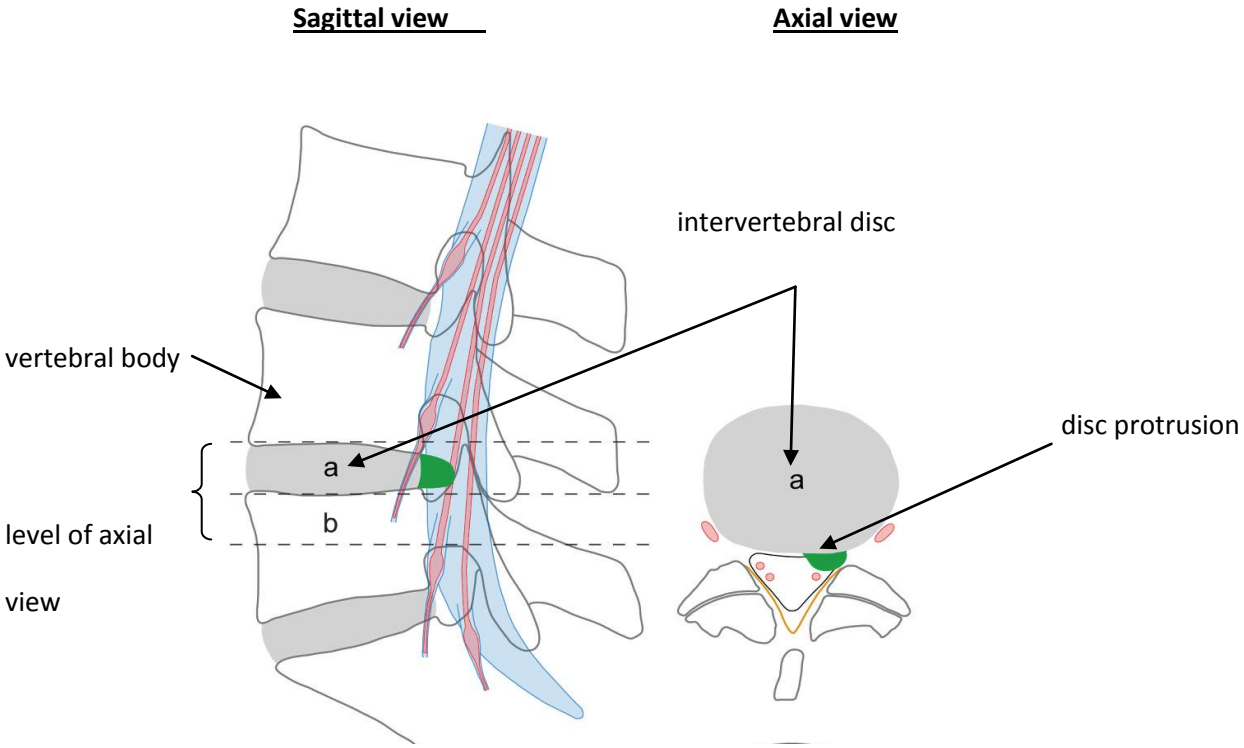


Figure 3.3.2. A protruded disc - L4–5 protrusion shown in green. Sagittal diagram shows dome-shape of protrusion not exceeding levels of end-plates. Axial diagram shows dome-shaped protrusion limited to disc level, not visible in adjacent axial sections.(Wilmink 2010)

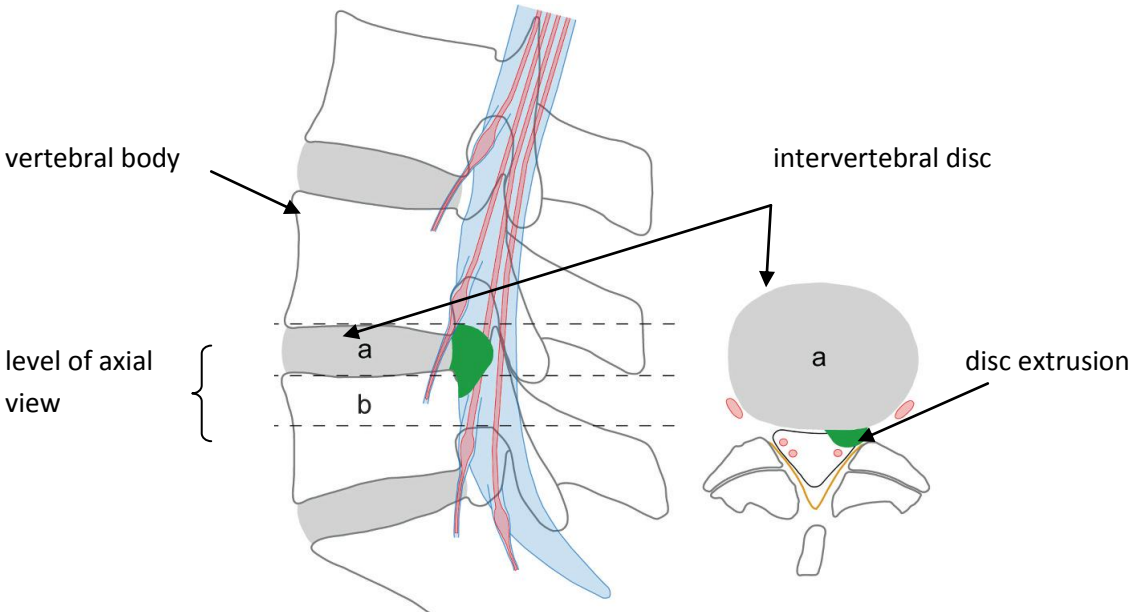


Figure 3.3.3. Extruded disc L4–5 extrusion shown in green. Sagittal diagram shows caudal migration past end-plate indicating annular rupture. Axial images show dome shaped extrusion at disc level (a) extruded material visible below disc level in section through bony lateral recess (b).

Non-systematic reviews

Four studies were reviewed (Goupille et al., 2007; Murata et al., 2011; Stafford et al., 2007; Van Zundert et al., 2006); one reported on cervical radicular pain and three reported on lumbar radicular pain.

Cervical radicular pain

Van Zundert et al (2006) reviewed the role of the dorsal root ganglion (DRG) in the production of cervical radicular pain. In line with the contemporary literature on the pathophysiology of lumbar radicular pain, they considered that two major mechanisms were responsible for the induction of cervical radicular pain;

- nucleus pulposus material leaking onto the nerve root
- compression of the nerve root by anatomical abnormalities.

They considered that *either* of these pathogenic mechanisms was able to produce inflammatory changes in the nerve and changes in ion-channel functioning which eventually lead to hyperexciatbility and spontaneous ectopic activity in the DRG.

Evidence supporting the release of trophic molecules and cytokines notably prostaglandins and nerve growth factor was reported[114]. The potential role of COX-2 (a mediator of prostaglandin synthesis) in the

[114] Kang, JD, Georgescu, HI et al. Herniated Cervical Intervertebral Discs Spontaneously Produce Matrix Metalloproteinases, Nitric Oxide, Interleukin-6, and Prostaglandin E2. Spine. 20(22) Supplement:2373-2378, November 1995.

development of radicular pain was highlighted [115] as well as the involvement of TNF-α and various interleukins. Evidence to suggest that nerve injury modulated adjacent non-injured nerves exposed to an inflammatory environment was also reported. Nerve growth factor had been shown to be linked to the production of brain-derived neurotrophic factor in the lumbar spine[116] and it was proposed that this might also be a major player in the pathophysiology of cervical radicular pain.

In summary, although few studies have addressed this issue directly, indirect evidence suggests that inflammation may well be a major mechanism in the pathophysiology of cervical radicular pain. Inflammation is postulated to occur as a result of injury or exposure of nervous tissue to nucleus pulposus material which induces a cascade of events. Importantly, after nerve injury*, both injured and non-injured fibres* are believed to be involved in this inflammatory process in which nerve growth factor and brain-derived neurotrophic factor are key players.

Nerve injury induced *ion-channel modulation* studies were also reviewed. A number of molecularly and physiologically distinct sodium (Na) channels were reported to be associated with hyperexcitability of dorsal root ganglia neurons[117]. Some channels were known to be drastically reduced in radicular and neuropathic pain[118] with a resulting shift in resting membrane potential. Van Zundert et al (2006) proposed that these data suggested that resting inactivation of nerves could be relieved and that neurons of injured and non-injured nerves could be primed, and in a hyperexcitable state, repeatedly fire leading to cervical radicular pain. Sodium, potassium and calcium channels were thought to be focal points in the generation of the abnormal neuronal discharge. The crux of the pathophysiology of radicular pain was thought to be the elucidation of the specific modulated ion channels which were functional in the generation of pain.

Lumbar radicular pain

Goupille et al (2007) reported at some length on recent evidence that suggested that, contrary to the traditional theory of nerve root compression by a herniated disc (the mechanical theory of sciatica), chemical factors could have a central role to play in the genesis of sciatica (Goupille et al., 2007). Goupille et al (2007) argued that while surgery to relieve pressure on the compressed nerve had a high short-term success rate, the long-term success rate was disappointing and re-intervention was common. Moreover, outcomes had been shown to be *favourable* after conservative treatment and *similar* with *surgical or conservative* treatment. In addition, asymptomatic disc herniation and severe sciatica *without visible disc compression* had been reported and the severity of symptoms and the extent of disc herniation were known to be poorly correlated[119]. These observational data suggested that nerve root compression was unlikely to be the sole cause of radicular pain.

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[115] McCrory, C. and D. Fitzgerald (2004). "Spinal Prostaglandin Formation and Pain Perception Following Thoracotomy." Chest **125**(4): 1321-1327.

[116] Obata, K., H. Yamanaka, et al. (2004). "Activation of extracellular signal-regulated protein kinase in the dorsal root ganglion following inflammation near the nerve cell body." Neuroscience **126**(4): 1011-1021.

[117] Cummins TR, Aglieco F, Renganathan M, Herzog RI, Dib-Hajj SD, Waxman SG (2001) Nav1.3 sodium channels: rapid repriming and slow closedstate inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons. J Neurosci 21:5952–5961.

[118] Abe M, Kurihara T, Han W, Shinomiya K, Tanabe T. (2002). Changes in expression of voltage-dependent ion channel subunits in dorsal root ganglia of rats with radicular injury and pain. Spine (Phila Pa 1976);27(14):1517-24.

[119] Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and non surgical management of sciatica secondary to a lumbar disc herniation: 10-year results from the Maine lumbar spine study. Spine 2005;30:927–35. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SE. Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects: a prospective investigation. J Bone Joint Surg 1990;72A:403–8. Boos N, Rider R, Schade V, Spratt KF, Semmer N, Aebi M. 1995 Volvo Award in clinical sciences: the diagnostic accuracy of

The investigative work of Olmarker et al (1993) in relation to the chemical component in sciatica was reviewed. Olmarker et al (1993)[120] demonstrated a marked deterioration in spinal nerve root fibres following contact with nucleus pulposus material *without* mechanical compression. To provide evidence that the material secreted by the nucleus pulposus was inflammatory in nature Olmarker et al (1994)[121] then investigated whether nerve root abnormalities could be reversed *by treatment with anti-inflammatory agents.* Administration of a high dose of a corticosteroid (30 mg/kg methylprednisolone) 5 minutes, 24 and 48 hours after nucleus pulposus application, restored nerve conduction velocity on day seven. These and other experiments suggested a *proinflammatory* nature for substances secreted by the nucleus pulposus and an ability to induce electrophysiologic changes.

Further experiments to elucidate the nature of the proinflammatory agents secreted by the nucleus pulposus were carried out. In 1998 Olmarker and Larsson [122]published the results of a meta-analysis of observed effects induced by nucleus pulposus material that suggested that these effects might relate to one specific cytokine, tumour necrosis factor alpha (TNF-α). In the same study Olmarker and Larsson (1998) demonstrated that treatment with doxycycline[123] significantly blocked the nucleus-pulposus-induced reduction of conduction velocity. This was the first time, a specific substance (TNF-α), had been linked to nucleus-pulposus-induced nerve roots abnormalities.

The most recent work published by the Olmarker group (Murata et al., 2011) examined the local application of interleukin-6 to the dorsal root ganglion and its ability to induce TNF-α in the dorsal root ganglion resulting in apoptosis of the dorsal root ganglion cells.

Stafford et al (2007) published a broad based overview of sciatica. Similar to Goupille et al (2007), Stafford et al (2007) considered that the evidence suggested that a complex interplay of pressure-related and inflammatory processes were involved in the generation of sciatic pain. Highlighting different experimental studies, Stafford et al (2007) also concluded that:

"TNF-a plays an early and prominent role in the pathophysiological events that lead to nerve dysfunction and pain when nucleus pulposus is approximated to lumbar nerve roots."

Thus Stafford et al (2007) also viewed the inflammatory process as being *exacerbated* by the effects of nerve root pressure. Lumbo-sacral nerve roots, possibly due to the vulnerability of the venous drainage system, seemed to be particularly susceptible to the effects of pressure. Stafford et al (2007) however, added evidence from immunological studies suggesting that *immunological processes* also had a part to play in the reaction between the nerve root and the exposed nucleus pulposus. Raised antibodies to glycosphingolipids (GSLs) found in patients with acute and chronic sciatica[124] and those who had lumbar discectomy for disc herniation and raised neurofilament protein in the CSF of patients presenting for

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magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. Spine 1995;15: 2613–25. Thelander U, Fagerlund M, Friberg S, Larsson F. Straight leg raising test versus radiologic size, shape, and position of lumbar disc herniations. Spine 1992;17:395–9. Weber H. Lumbar disc herniation: a controlled, prospective study with ten years of observation. Spine 1983;8:131–40.

[120] Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine 1993;18:1425–32.

[121] Olmarker K, Byrod G, Cornefjord M, Nordborg C, Rydevik B. Effects of methylprednisolone on nucleus pulposus-induced nerve root injury. Spine 1994;19:1803–8.

[122] Olmarker K, Larsson K. Tumor necrosis factor and nucleuspulposus- induced nerve root injury. Spine 1998;23:2538–44.

[123] Doxycycline inhibits T cell activation and TNF-alpha production.

[124] Brisby H, Balague F, Schafer D, et al. Glycosphingolipid antibodies in serum in patients with sciatica. Spine 2002; 27: 380–6

lumbar disc surgery[125], suggested that an immune reaction to nervous tissue may be involved in the pathogenesis of both acute and chronic sciatica.

From the evidence they presented, Stafford et al (2007) proposed a model in which radicular pain in sciatic nerve roots was viewed as arising from a complex interaction of inflammatory, immune, and pressure-related elements. In this model, potent inflammatory properties of nucleus pulposus provoke an inflammatory reaction, involving the major inflammatory mediators in sciatic nerve roots. This in turn leads to an abnormal immune response with antibodies being formed to normal neural elements that may be related to the development of chronic sciatica.

Summary of radicular pain generation

Two major mechanisms have been proposed for the induction of cervical radicular pain;

- nucleous pulposus material leaking onto the nerve root
- compression of the nerve root by anatomical abnormalities.

It was reported that either of these mechanisms could produce inflammatory changes in the nerve and changes in ion-channel functioning which could eventually lead to hyperexcitability and spontaneous ectopic activity in the dorsal root ganglia. The release of trophic molecules and cytokines, notably prostaglandins and nerve growth factor in the area of the nerve was reported to support this view.

Nerve injury induced *ion-channel modulation* was also reported with modulated sodium, potassium and calcium channels postulated as focal points in the generation of ectopic neuronal discharge. The crux of the pathophysiology of radicular pain was thought to be the elucidation of the specific modulated ion channels which were functional in the generation of pain.

In the lumbar spine the material secreted by the nucleus pulposus had been shown to have an inflammatory nature, with tumour necrosis factor alpha (TNF-α) cited as the key cytokine involved in induced nerve root abnormalities.

Immunological processes were also reported to be involved in the reaction between the nerve root and the exposed nucleus pulposus and a model proposed in which radicular pain in sciatic nerve roots was viewed as arising from a complex interaction of inflammatory, immune, and pressure-related elements. In this model, potent inflammatory properties of the nucleus pulposus provoke an inflammatory reaction, involving the major inflammatory mediators in sciatic nerve roots. This in turn leads to an abnormal immune response with antibodies being formed to normal neural elements that may be related to the development of chronic sciatica.

[125] Brisby H, Olmarker K, Rosengren L, Cederlund CG, Rydevik B. Markers of nerve tissue injury in the cerebrospinal fluid in patients with lumbar disc herniation and sciatica. Spine 1999; 24: 742–6

Summary and conclusions: Pain generation

Fifteen non-systematic reviews describing the findings of experimental and clinical studies on the nature and proposed mechanisms of discogenic (seven studies), facet joint (four studies) and radicular (four studies) pain generation were examined.

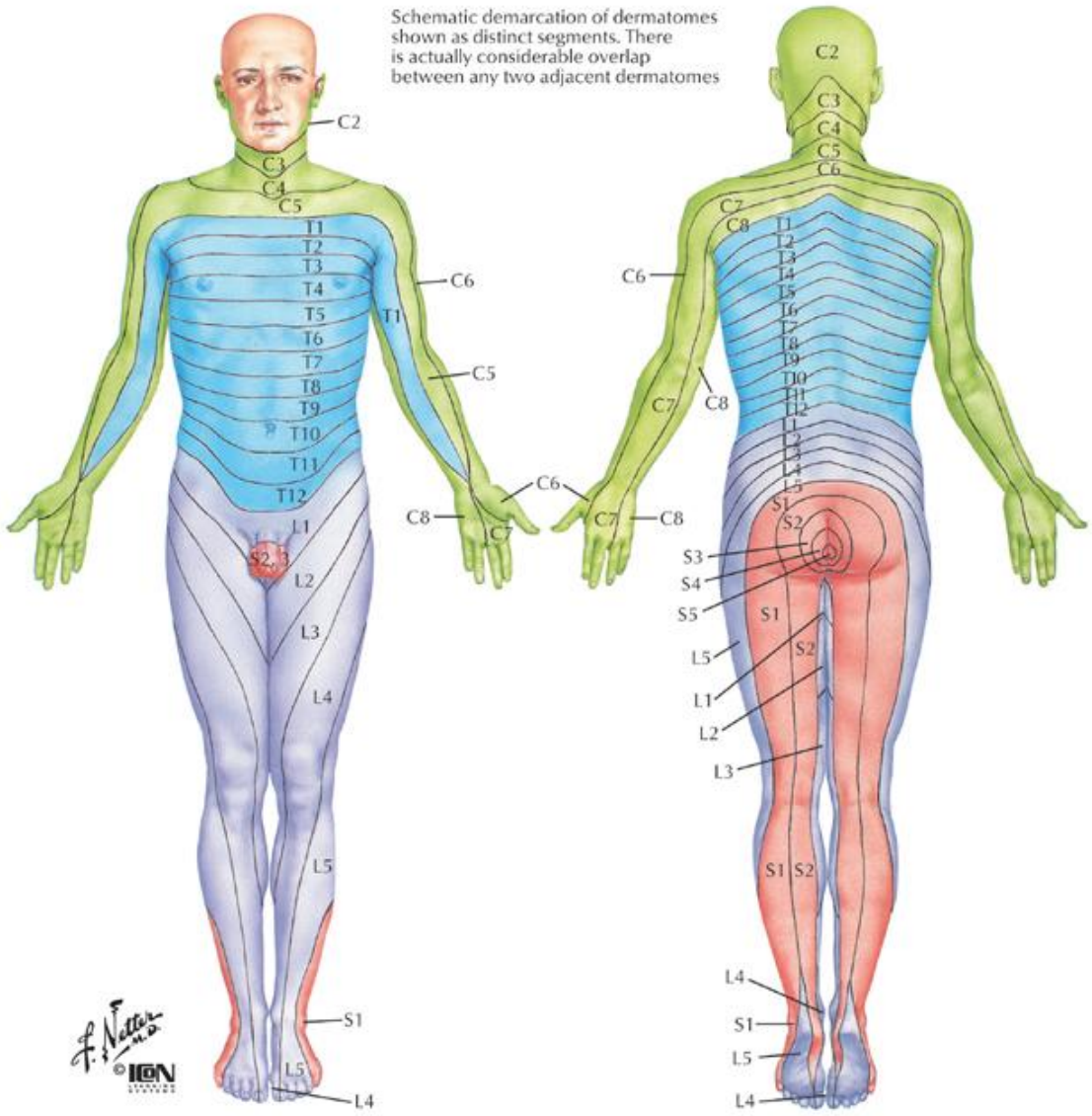
Because of the difficulties associated with human experimentation in this area most of the reported data arose from animal studies and its extrapolation to humans is fraught with problems. Not surprisingly therefore all reviews acknowledged that current knowledge on pain generation in relation to the disc and associated structures in humans was mostly indirect and incomplete.

Within this cautionary framework a number of common themes emerged, these included;

- the multimodal nature of the mechanisms involved
- the potential importance of the facet joints as pain generators
- the inadequacy of purely mechanical pressures to explain discogenic, facet joint or radicular pain
- the importance of an understanding of the innervation of the structures involved and in particular of those structures that in their normal state are sparsely innervated
- the key role of cytokines such as TNF-α and interlukin-6 .
- the involvement of both inflammatory and immunological processes.

These reviews also generally agreed that new insights into the biochemical mechanisms of pain generation were providing new therapeutic targets, a number of which had or were being trialled in humans.

Appendix A: Dermatomes



Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5, S1	Foot
L4	Medial side of great toe
S1, 2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

Section 4: Pain modulation

An evidence based review of the current knowledge on how these causes of pain can be modulated which will focus on the effectiveness of use of local steroid and surgery for pain for certain lesions to include, an assessment of the current state of knowledge on how pain generated in the intervertebral disc, nerve roots and associated structures can be modulated, with the stipulation that this will at least include the use of local steroid and surgery.

This review is complemented by, and links with, a number of other reviews carried out in 2011 for the ACC relating to the effectiveness of fusion surgery and disc replacement surgery for spinal pain [in earlier sections of this report].

Background

In 2008 the Spine Journal devoted its January issue to the publication of articles focussing on evidence informed management of chronic low back pain arising from various sources. Articles covered a wide range of *"popular interventions"* and included;

- surgery
- cognitive behavioural therapy
- trigger point injection
- spinal manipulation
- NSAIDs and muscle relaxants
- physical activity/strengthening exercises/ massage/ lumbar stabilisation exercises
- transcutaneous electrical nerve stimulation
- epidural steroid injections
- intradiscal electrothermal therapy
- traction therapy
- acupuncture
- prolotherapy
- nuclear decompression
- opioid analgesics
- facet joint injection

In the same issue Halderman and Dagenais (2008) indicated that this group of interventions was just the "tip of the iceberg" and tabulated over 200 medications in their "partial list" of therapies, injections, products, and procedures available as treatment options for patients with low back pain. Three main types of *invasive treatments* were listed, injections, minimally invasive procedures and surgical techniques, Table 4.1.

Many of the injection and minimally invasive procedures techniques listed are often considered under the umbrella of "Interventional Pain Management" (IPM)[126] , however, the criteria for distinguishing between some of the IPM invasive procedures and "surgical" procedures are not obvious.

[126] Interventional Pain Management aims to provide a comprehensive approach to chronic pain. According to the American Society of Interventional Pain Physicians (ASIPP), interventional pain management is a "discipline of medicine devoted to the diagnosis and treatment of pain related disorders."

Table 4.1. Invasive treatment options for low back pain: a partial list.

Invasive therapeutic options		
Interventional pain management techniques		**Main surgical interventions & examples**
Injections & examples	**Minimally invasive procedures & examples**[127]	
Epidurals Caudal • corticosteroids Interlaminar • local analgesics • Midazolam • Morphine Transforaminal Facet blocks Prolotherapy • dextrose, • glycerine, • phenol, • lignocaine • dextrose and lignocaine Pyriformis Radio frequency denervation • Dutch technique • ISIS technique Sacroiliac blocks Sciatic nerve block Trigger point • 5HT3 receptor antagonists • botulinum • local anesthetic • saline • steroids	Intradiscal electrothermal treatment (IDET) Intradiscal radio frequency treatment Nuclear decompression • aspiration percutaneous lumbar discectomy • Arthrocare • DeKompressor • laser • SpineJet • MicroResector	Arthoplasty • Charite • ProDisc • Acroflex[128] Progressive disc nucleus replacement † Brain stimulation • thalamus • periventicular gray • internal capsule • periaqueductal gray matter Chemonucleolysis Discectomy Dorsal column stimulator Facet replacement • TFAS • TOPS • Stabilimax NZ Interspinous devises • XSTOP • Wallis • Estendsure • CoFlex • DIAM Laminectomy Morphine pump Pedicle screw fixation • Graf ligament • Dynesys • AccuFlex rod • Medtronic • PEEK Rod • Scient X Isobar Rhizotomy

† Arthrodesis or intervertebral disc fusion appears to be missing from this list as a standalone procedure.

For a number of reasons, not all of the interventions listed in Table 1 are appropriate for consideration in the current review and some interventions are not listed as only interventions for low back pain were

[127] Not all of these are used in New Zealand, personal communication, Gordon Howie, reviewer.
[128] Acroflex was only ever experimental and used in a few cases in Adelaide besides USA but abandoned. Personal communication, Gordon Howie, reviewer.

considered. However, the classification provides a useful (if imperfect) reference framework within which the therapeutic interventions considered in this report can be placed.

In 2002 the ACC undertook a major project to review the available research on a wide range of interventional procedures for the management of persistent pain; evidence-based guidance on their use in New Zealand was included. The Interventional Pain Management (IPM) project was managed by ACC and the recommendations were formulated by an expert advisory group with experience in pain management. The resulting reports were subject to international review.

The IPM interventions reviewed may be used independently or in conjunction with other therapies. Some of the more invasive procedures carry significant risks and tend to be used only when less invasive treatments have failed. Other procedures present relatively low risk and are frequently used in clinical practice, the interventions covered by the IPM guidance were divided into six intervention procedure groups:

1. Infusions
2. Injections
3. Intradiscal electrothermal therapy (IDET)
4. Nerve blocking procedures
5. Neuroablation
6. Neuromodulation

All of these groups included interventions with evidence of effectiveness for the treatment of spinal pain of one sort or another. Invasive surgery such as spinal fusion and disc replacement were not included in the IPM portfolio of interventions.

One of the most commonly recommended IPM interventions for spinal pain is steroid injection therapy and in particular *epidural steroid injection*; evidence of effectiveness relating to this intervention is thus of special interest to the ACC. The IPM project assessed the evidence for epidural steroid injections published up to 2004/2005, to bring its findings in this important area up-to-date, in the current report additional evidence of effectiveness published between 2005 and 2011 was assessed.

Where a specific diagnosis has been made, a number of more *invasive surgical interventions* targeting specific pain generating structures may be advised. Excluding chemonucleosis and IDET which is included in this review under IPM interventions rather a number of more invasive surgical procedures may be considered. These include laminectomy and discectomy (and related procedures), intervertebral disc fusion, with and without instrumentation, and intervertebral disc arthroplasty[129].

[129] Dynamic stabilization has been proposed as a treatment option. However, although there is reported to be some evidence for the use of interspinous spacers for spinal stenosis, there is currently no acceptable clinical evidence available for dynamic stabilization in chronic low back pain (Don & Carragee, 2008) and this intervention is not considered further in this report.

Methods

Computer searches

For a comprehensive description of the searches carried out for this review and the reporting methods see the General Methods section.

Briefly, a systematic search of the literature for systematic reviews, metaanalyses and clinical guidelines relating to the modulation of pain generated in the intervertebral disc nerve roots and associated structures, was carried out. Eligible systematic reviews were required to have carried out (a) a systematic search of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews.

In addition to bibliographic databases such as Medline and Embase the following sources/websites were searched for recent (2005 onwards) evidence based guidelines reporting substantially on fusion surgery:

American Academy of Orthopaedic Surgeons (AAOS)

American Society of Neuroradiology (ASN)

American Society of Spine Radiology

Guidelines International Network (GIN)

Institute for Clinical Systems improvement (ICSI)

Medical Services Advisory Committee

National Health and Medical Research Council (NHMRC)

National Institute for Health and Clinical Excellence (NICE)

New Zealand Guidelines Group (NZGG)

NHS Evidence

North American Spine Society (NASS)

Scottish Intercollegiate Guidelines Network (SIGN)

TRIP database

World Health Organisation (WHO)

All systematic reviews, meta-analyses and guidelines that reported on the use of epidural steroids for painful spinal conditions[130] or undertook comparative assessment of the major surgical treatments for painful spinal conditions were considered potentially eligible. Major surgical treatments included were;

- laminectomy
- discectomy
- intervertebral disc fusion
- disc replacement

Previous evidence reviews

In addition, evidence provided by a comprehensive, internationally peer reviewed analysis of 54 interventional pain management techniques published by the ACC in 2005 (and partially updated in 2011) was examined for evidence-based guidance that was relevant to the current review (New Zealand Accident Compensation Corporation, 2005, 2006).

Interventional pain management (IPM) guidance reviews

The IPM methods included a systematic search to April 2004 of the Medline, Embase, PsycINFO, Cochrane, DARE and TRIP databases and a hand search of key journals (Spine, The Spine Journal, Clinical Journal of Pain , Regional Anaesthesia and Pain Medicine and Pain Research and Management) recommended by an advisory group. A wide range of studies were eligible for inclusion, of the lower level evidence studies (i.e. case series and cohort studies) the minimum number of cases was set at 50. Interventions of interest included invasive procedures for the treatment of persistent pain involving delivery of drugs into targeted areas, or ablation/modulation of targeted nerves. Nerve blocking procedures were also considered where appropriate. All eligible studies were appraised using the Generic Appraisal Tool for Epidemiology (GATE) checklists developed by Professor Rod Jackson of the University of Auckland.

IPM Grading system

The evidence was graded using an adaptation of the methods of New Zealand Guidelines Group (NZGG)[131];

Grade	Description
A	The recommendation (course of action) is supported by good evidence
B	The recommendation (course of action) is supported by fair evidence
C	The recommendation (course of action) is supported by [some][132] expert opinion only.
I	No recommendation can be made because the evidence is insufficient.

[130] In addition to specific conditions producing discogenic pain it is believed that 75% of low back pain lacking a specific diagnosis may be attributed to disc and disc related degenerative conditions and where deemed useful reviews/studies reporting on chronic low back pain have been included.

[131] http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/about-the-ipm-project/WCM1_034235

[132] The qualification [some] has been inserted here to denote the fact that all "experts" do not necessarily agree with the recommendation and/or that not all possible experts in the field may have been consulted. The original wording for the grading is given in Appendix I.

These grades indicate the strength of evidence underlying the recommendation *which may be for or against the intervention e.g. there may be good evidence (Grade A) that an intervention does not work or good evidence (Grade A) that it does work.*

The grading of the recommendation is based on the strength/level of the evidence upon which the recommendation is based. The NHMRC evidence levels are used to assess the strength of the evidence. The particular scheme used depends on the nature of the clinical/research question asked. In the current context, the levels of evidence that apply for therapeutic interventions apply, Table 4.2.

Table 4.2. NHMRC levels of evidence for therapeutic interventions[133].

Level	Intervention studies
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

9This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B). 10 Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

Individual studies considered in the IPM guidance review were assessed using the Generic Appraisal Tool for Epidemiology (GATE) checklists [134] . A quality score was determined for each of the three GATE categories: validity, precision and applicability. For each category, one of three quality scores was assigned based on the extent to which the study design met the quality criteria specified in the relevant section of the checklist. The quality scores were;

+	A strong study where all or most of the validity criteria are met.
~	A study where not all of the criteria are met, but the results of the study are not likely to be affected.
-	A weak study where very few of the validity criteria are met and there is a high risk of bias.

[133] http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf
[134] www.health.auckland.ac.nz/population-health/epidemiology-biostats/epiq/

An overall quality grade was then assigned to each study based on the balance of the scores assigned for validity, precision and applicability. The descriptors applied to the overall quality were;

+	High quality overall.
~	Medium quality overall.
-	Low quality

An alternative quality rating system was used to grade case series [135]. This system applied a score of between zero and three to each case series according to whether it was conducted prospectively, how its participants were selected, and whether follow-up time was adequate and appropriate. Studies appraised as low quality ("-") or case series scoring < 1.5 were not included in the review of effectiveness.

For each intervention a score was also assigned for the weight and consistency of evidence. This was used to qualify the body of evidence as a whole for that intervention. The descriptors applied to the body of evidence were:

+	Good
~	Moderate
-	Poor

Both the overall quality grade and the score for the body of evidence were taken into account when formulating recommendations.

In some instances, although an intervention could not be recommended for general or routine use , the evidence suggested that under particular circumstances or for particular patients some effectiveness had been reported. In these circumstances, the clinical review panel could recommend that an intervention be used under strictly controlled conditions e.g. in a research setting, or be considered on a case by case basis for patients where all other intervention had failed.

Other grading and quality systems used

A number of other grading systems were used on occasion to assess and report additional evidence identified for the effectiveness of epidural steroid injections. These are described below.

[135] Taken from Young et al. (1999). Lung volume surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema (A West Midlands Development and Evaluation Committee Report). Birmingham, UK - University of Birmingham. p51-53.

1. *The US Agency for Healthcare and Quality (AHRQ) system* where the evidence was graded as follows;

- **level I (conclusive):** Research-based evidence with multiple relevant and high-quality scientific studies or consistent reviews of meta-analyses
- **level II (strong):** Research-based evidence from at least 1 properly designed randomized, controlled trial; or research-based evidence from multiple properly designed studies of smaller size; or multiple low quality trials.
- **level III (moderate):** a) Evidence obtained from well-designed pseudorandomized controlled trials (alternate allocation or some other method); b) Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies, case-controlled studies, or interrupted time series with a control group); c) Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- **level IV (limited):** Evidence from well-designed, non-experimental studies from more than 1 centre or research group; or conflicting evidence with inconsistent findings in multiple trial.
- **level V (indeterminate**): opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees.

2. *A grading of recommendations based on Guyatt's criteria*[136]

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Which was based on quality assessments made using the following USPSTF evidence level assessment[137];

[136] Adapted from Guyatt G et al. Grading strength of recommendations and quality of evidence in clinical guidelines. Report from an American College of Chest Physicians task force. Chest 2006; 129:174-181 (70).

Level I: Evidence obtained from at least one properly randomized controlled trial

Level II-1: Evidence obtained from well-designed controlled trials without randomization

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence

Level III: Opinions of respected authorities, based on clinical experience descriptive studies and case reports or reports of expert committees.

3. Levels of evidence and grades of recommendation based on criteria set by Wright (2005)[138] for therapeutic studies are given below.

Levels of evidence:

Level I: Randomized controlled trials with a significant difference or with no significant difference but narrow confidence intervals. Systematic review of Level I randomized controlled trials

Level II: Prospective cohort study. Randomized controlled trials of poor quality (eg, <80% follow-up, low power, poor randomization technique, unblinded evaluators. Systematic review of Level II studies or non homogeneous Level I studies

Level III : Case-control study, retrospective cohort study or systematic review of Level III studies.

Level IV: Case series

Level V : Expert opinion

Grades of recommendations:

A. Treatments that receive an A are supported by good evidence (Level I studies with consistent finding) for or against recommending intervention.

B. Treatments that receive a B are supported by fair evidence (Level II or Level III studies with consistent findings) for or against recommending intervention.

C. Treatments that receive a C have conflicting or poor quality evidence (Level IV or Level V studies) not allowing a recommendation for or against intervention.

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[137] Adapted from the U.S. Preventive Services Task Force (USPSTF) Berg AO, Allan JD. Introducing the third U.S. Preventive Services Task Force. Am J Prev Med 2001; 20:21-35

[138] Wright JG. Levels of evidence and grades of recommendation. AAOS Bull 2005;5:18-19. http://www5.aaos.org/oko/ebp/EBP001/suppPDFs/OKO_EBP001_S8.pdf

I. Treatments that receive an I do not have sufficient evidence to make a recommendation.

4. American Acadamy of Neurology (AAN) classification of evidence for therapeutic interventions (Armon, Argoff, Samuels, & Backonja, 2007).

Class I. Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:
a) primary outcome(s) clearly defined; b) exclusion/inclusion criteria clearly defined; c) adequate accounting for dropouts and cross-overs with numbers sufficiently low to have minimal potential for bias; and d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.

Class IV. Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Classification of recommendations

A. Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies).

B . Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C . Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U . Data inadequate or conflicting; given current knowledge, treatment is unproven.

Surgical interventions

Since a comprehensive review of the effectiveness of fusion and other contemporary surgical techniques for the amelioration of painful spinal conditions has been submitted in a previous report, (see http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-managment/index.htm) only a descriptive introduction to techniques not detailed previously is included here.

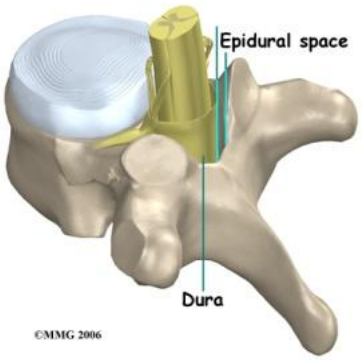
References

Citations for primary studies quoted in eligible systematic reviews and guidelines are included in footnotes rather than the report references to distinguish them from those identified independently for the current report.

The techniques and procedures

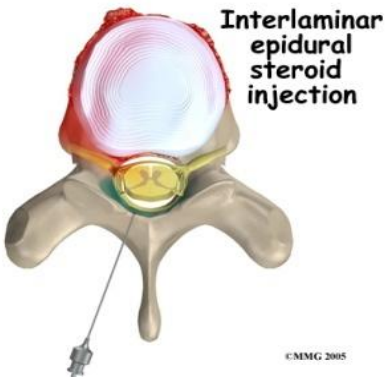
Epidural injection procedure

There are several approaches available to access *the lumbar epidural space*; transforaminal, caudal, and interlaminar. Substantial differences have been described between these three approaches. The transforaminal approach is reported to have the advantage of being target specific and using the smallest volume. Thus the transforaminal route to the lumbar epidural space for steroid injection has gained rapid and widespread acceptance for the treatment of lumbar and leg pain. There are, however, few well-designed randomized, controlled studies to determine the effectiveness of epidural injections. The role and value of transforaminal lumbar epidural steroid injections is still questioned (Buenaventura, Datta, Abdi, & Smith, 2009).



The epidural space is area between the bony ring of the spine and the covering of the spinal cord or dura. This space is normally filled with fat and blood vessels. Fluids such as lignocaine and cortisone that are injected during an epidural steroid injection (ESI) are free to flow up and down the spine in the epidural space to coat the nerves that run inside the spinal canal. There are several openings in the bones that surround the epidural space where a needle can be placed thus giving rise to different types of epidural steroid delivery methods. Each of these types of ESI has advantages and disadvantages.

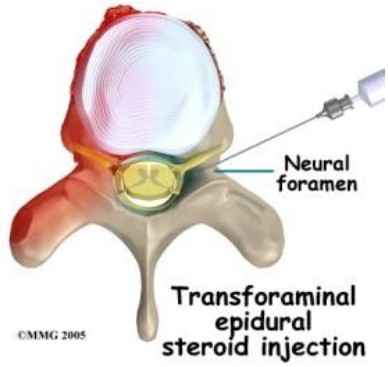
Interlaminar epidural steroid injection procedure[139]



An interlaminar injection carried out from the back of the spine. It is performed by placing the needle between the laminae of two adjacent vertebrae. This places the tip of the needle in the back of the spine and is thus easy to perform without the guidance of a fluoroscopic x-ray machine. The injectate is usually placed between the two vertebrae that are believed to be causing the pain thus placing the steroid as close as possible to the pain source. One disadvantage of this type of epidural steroid injection is that the injectate may not reach the source of the pain particularly if the source is the intervertebral disc[140].

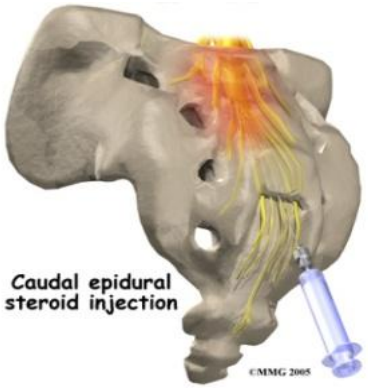
[139] http://www.spine-health.com/video/epidural-steroid-injections-back-pain-and-leg-pain-video (hold control/click and wait)
[140] This is not easy to perform, it takes training. Is usually carried out without fluoroscopy. Personal communication, Gordon Howie, reviewer.

Transforaminal epidural steroid injection procedure [141]



A transforaminal injection is carried out from the side of the spine, through the *neural foramen* (the opening where the nerve root exits the spine). The tip of the needle is placed into the neural foramen under fluoroscopic guidance. The advantage to this type of injection is that it places the medication in the front of the spinal canal, very near to the intervertebral disc. The disadvantage is that transforaminal injections require fluoroscopic guidance[142].

Caudal epidural injection procedure



A caudal injection is performed through a small opening in the bones of the tip of the sacrum. This opening leads directly to the epidural space. Fluid injected through this opening can flow upward through the epidural space to coat the nerves throughout the lower lumbar spine. Fluoroscopy is not required but there is a problem is variability of proximal spread.

Figure 4.1. Epidural injections.

Cervical epidural steroid injection procedure[143]

Cervical epidural steroids may be delivered via the interlaminar or the transforaminal route. Under fluoroscopy guidance the needle is inserted into the epidural space. Contrast dye is injected into the space to check positioning. A combination of corticosteroids and anaesthetic is injected into the epidural space (Hutson, 2009).[144]

[141] http://spinepaindocs.com/procedures/lumbar-transforaminal-epidural-steroid-injection (hold control/click and wait)
[142] Transforaminal injection besides fluoroscopic can also be done with CT guidance. The other disadvantage is a higher incidence of nerve puncture and it is difficult at L5s1. Personal communication, Gordon Howie, reviewer.
[143] http://www.spine-health.com/video/cervical-epidural-steroid-injection-video, http://www.spine-health.com/video/cervical-transforaminal-epidural-steroid-injections-video
[144] There is the potential for catastrophic complications. Personal communication, Gordon Howie, reviewer.

Rationale for steroid injections

The rationale behind injecting glucocorticoid into the epidural space adjacent to a spinal nerve is that it will combat the inflammatory response associated with disc herniation and will reduce or modulate pain. The medications that are normally injected include an anaesthetic such as novocaine, lignocaine or bupivacaine and cortisone. The effect of cortisone injected in the proximity of the pain producing lesion (e.g. a herniated disc) is to reduce inflammation and reduce pain and reduce swelling which allows the nerves to function properly reducing numbness and weakness, Figure 4.2.

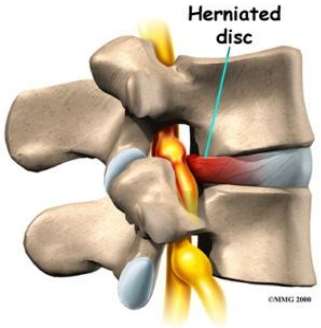


Figure 4.2. The hernatiated disc (http://www.eorthopod.com/content/epidural-steroid-injections).

When steroid injections are used to treat spinal stenosis the inflammation and swelling caused by narrowing of the spinal canal is the target. Reduction of swelling reduces pressure on the spinal nerves which in turn relieves pain symptoms numbness and weakness, Figure 4.3.

Figure 4.3. Lumbar stenosis (http://www.eorthopod.com/content/epidural-steroid-injections).

Mode of action

Herniated disk specimens have demonstrated increased levels of matrix metalloproteinase activity, nitric oxide, prostaglandin E2, and interleukin-6. The enzyme phospholipase A2 which also plays a role in the inflammation of the nerve root is believed to be neurotoxic.

Epidural steroids have been shown to inhibit phospholipase A2 activity, mitigate nerve conduction slowing caused by inflammation, and affect cell-mediated activity and cytokines, which may be involved in the pathogenesis of radicular pain. Other reported modes of action of corticosteroids include the stabilisation of nerve membranes inhibiting ectopic impulses, inhibition of ion conductance, hyperpolarisation of spinal neurons, and inhibition of C fibre transmission. These latter properties of corticosteroids may explain the relief of symptoms in non-inflammatory states.

Local anaesthetic which is normally mixed with corticosteroid may have additional benefits beyond the direct anaesthetic affects. Lignocaine has been shown to have an anti-inflammatory effect on nucleus pulposus induced nerve injury and to increase intra-radicular blood flow in an animal compressed nerve root model. This may improve intra-neural metabolism and reduce inflammatory mediators (Hutson, 2009).

Surgical techniques

Surgical procedures are commonly used as a treatment for chronic low back pain assumed to originate from the intervertebral disc (Bogduk & Andersson, 2009). Because it is difficult to conduct true placebo-controlled trials of surgical procedures, most studies compare the pain relief obtained with surgery to that obtained with non-operative care or one surgical procedure with another. The most popular surgical techniques employed for pain modulation in this area are;

- laminectomy – surgical removal of the lamina of a vertebra
- discectomy - surgical removal of herniated disc material
- intervertebral fusion – removal of disc and fusion of adjacent vertebral bodies
- disc replacement- removal of problematic disc and replacement with a prosthetic disc.

These procedures may be carried out alone, or in conjunction with each other, or together with other related procedures including;

- facetectomy -removal of the articular facet of a vertebra.
- foraminotomy – surgical enlargement or opening up of the foramen
- laminotomy – removal of part of the lamina of the vertebral arch
- laminoplasty – procedure involving the lamina to relieve pressure on the spinal cord
- corpectomy – removal of part of the vertebral body.

Laminectomy, laminotomy, laminoplasty facetectomy and foraminotomy are similar surgical procedures in that they all require removal of vertebral bony structures that are impinging upon soft tissue such as nerves or to gain access to protected parts of the spine.

Facetectomy and foraminotomy are two examples of spine surgeries that may be recommended to patients who suffer from chronic pain as a result of nerve compression in the spinal column.
For patients suffering from chronic back or neck pain as a result of spinal stenosis, a laminectomy or laminotomy may be recommended when more advanced treatment is required. These surgical procedures have a number of similarities and are often completed at the same time during open spine surgery. Most of these procedures may be illustrated using the video links located in the footnote area or shown in Appendix II.

Laminectomy

The vertebral lamina is the thin flattened posterior wall of vertebral arch that forms the vertebral foramen through which pass the spinal cord and nerve roots. The lamina protects the spinal cord.

Laminectomy is a surgical procedure in which all (laminectomy/open decompression) or part (laminotomy) of the selected vertebral lamina is removed to relieve mechanical pressure on the spinal cord and/or spinal nerve roots. Laminectomy opens up the spinal canal so the spinal nerves have more room. The procedure may be combined with a discectomy, foraminotomy, and spinal fusion, where laminectomy may be done for access rather than treatment.

Laminectomy is typically performed to alleviate pain caused by neural impingement that can result from spinal stenosis arising from arthritis, chronic inflammation herniated disc or spinal injury, Figure 4.6 and video link[145]

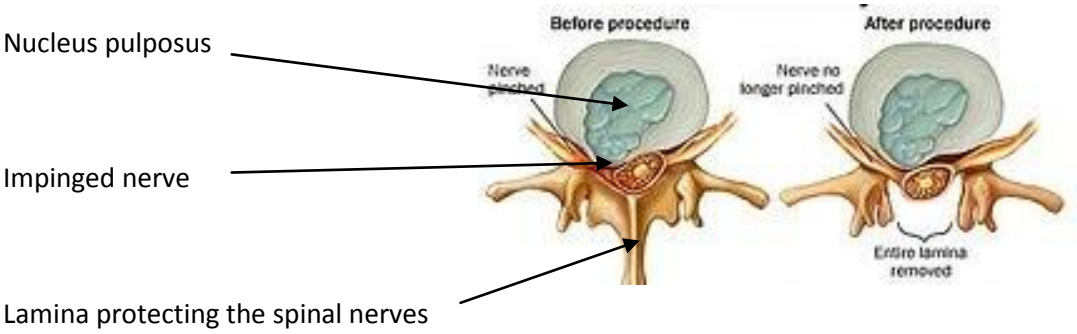


Figure 4.4. Lumbar laminectomy

Historically, a laminectomy required complete excision of the lamina. By removing this bone, the spinal cord or cauda equina would be given more room with in the spinal canal. A minimally invasive version of laminectomy has been developed which involves careful removal of part of the lamina, leaving the supporting soft tissue largely intact.

Laminotomy

Laminotomy is the partial removal of the lamina, Figure 7. The terms laminotomy and laminectomy are sometimes used interchangeably.

[145] Laminectomy Back Surgery for Spinal Stenosis Video (control/click and wait)

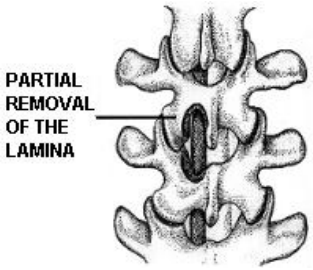


Figure 4.5. Laminotomy

Laminoplasty[146]

Laminoplasty is a surgical procedure for treating spinal stenosis by relieving pressure on the spinal cord. The procedure involves cutting the lamina on both sides of the affected vertebrae. After cutting through the lamina on one side and merely cutting a groove on the other, the freed flap of bone is "swung" open like a trapdoor thus relieving the pressure on the spinal cord. The spinous process may be removed to allow the lamina bone flap to be swung open. The bone flap is then propped open using small wedges or pieces of bone such that the enlarged spinal canal will remain in place. This technique contrasts with vertebral laminectomy in the amount of bone and muscle tissue that has to be removed, displaced, or dissected in the procedure (see videolink below).

Discectomy[147]

A traditional discectomy involves the surgical removal of herniated disc material. The procedure involves removing the disc material stressing the spinal cord or radiating nerves. Alternatives to traditional discectomy procedures include microdiscectomy[148], endoscopic discectomy, and laser discectomy.

Discectomy may be performed in conjunction with a laminectomy to permit access to the intervertebral disc and fusion of the vertebrae to immobilise the motion segment. It is also performed with fusion. Anterior discectomy is performed in the cervical region and almost always anteriorly in the thoracic spine, but rarely as a primary procedure in lumbar region.

Facetectomy

A facetectomy or excision of the articular facet of a vertebra is similar to a laminectomy in that a portion of bone is removed from the spinal column to provide additional room in the spinal column to decompress nerve roots. The procedure involves exposing the affected vertebra and removing one or both of the facet joints that are rubbing against the nerve. However, because the facet joint provides the spine with mobility and stability, removing this joint in its entirety may require fusion surgery to ensure structural integrity, Figure 4.9.

[146] http://www.spine-health.com/video/laminaplasty-back-surgery-videos (videolink: "control", "click" wait)
[147] Anterior Cervical Discectomy Video (control/click and wait)
[148] Microdiscectomy: Lumbar Microdecompression Spine Surgery Video (control/click and wait)

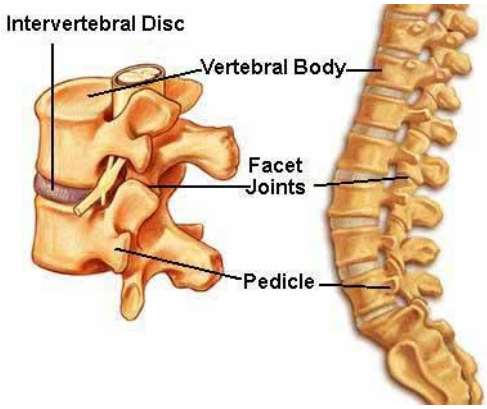


Figure 4.6. The facet joints

Foraminotomy [149]

The intervertebral foramina are passages or tunnels through which spinal nerves from the spinal cord, pass through the vertebrae and out into our body. The nerve passageways are called neuroforamen. Thirty-one different pairs of spinal nerve roots pass through these foramen, Figure 4.10.

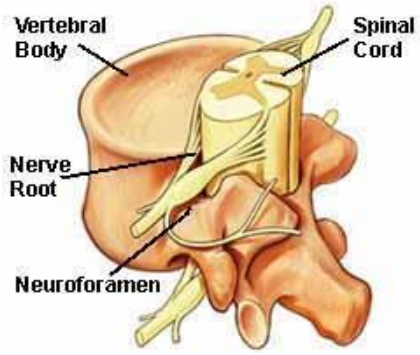


Figure 4.7 Vertebra and main spinal nerves exiting the spinal cord via the neuroforamen.

A foraminotomy is usually performed to relieve the symptoms of nerve root compression in cases where the foramen is being obstructed by bony outgrowths, disc material, scar tissue, or excessive ligament growth, resulting in a pinched nerve.

During a foraminotomy, the surgeon removes any obstructing bone or tissue releasing the spinal nerve root. The procedure is may be performed as a minimally invasive procedure in which an incision is made, the muscle peeled away to reveal the bone underneath, and a small hole cut into the vertebra itself. Through this hole, using an arthroscope, the foramen can be visualized, and the impinging bone or disk

[149] Cervical Posterior Foraminotomy Video (control/shift)

material removed. Foraminotomy may be combined with other procedures such as a laminotomy or laminectomy.

Corpectomy[150]

Corpectomy is a surgical procedure that involves removing part of the vertebral body or corpus. It is usually performed to decompress the spinal cord and nerves. Corpectomy is often performed in association with some form of discectomy. Corpectomy is always performed from the front because the spinal cord and nerve roots are in the way, if coming from behind it is a big operation and has more risks than many other operations.

[150] Lumbar Corpectomy Surgery Video (control/click and wait)

Interventional pain management (IPM) procedures

In pain medicine, diagnostic procedures are used to either identify the source of pain or to determine the cause of pain; some diagnostic interventions are used to determine the mechanism of the pain. Diagnostic interventions generally involve introducing a needle at the location of a nerve going to a painful area usually under x-ray guidance or other type of imaging to precisely locate the position of the needle or probe. These types of interventions are called diagnostic blocks and attempt to briefly anesthetize the nerve thought to be involved in mediating the pain. They are most commonly used in the diagnosis of spine-related pain such as low back pain, thoracic, or neck pain. Often single nerves are blocked with a local anaesthetic agent such as lignocaine (short acting) or bupivacaine (long acting). While the anaesthetic is working, the patient should experience pain relief if the treated nerve is the one involved in sending pain messages.

In interventional pain management, many of the diagnostic interventions are used to provide long-term pain relief by increasing the amount or type of material injected. Such interventions include, for example, epidural steroid injections (ESI), facet joint injections, single nerve root blocks, peripheral nerve injections, and sacroiliac joint injections. The most frequently used substance injected for temporary relief of pain due to swelling and inflammation is the anti-inflammatory steroid hormone cortisone.

Other interventions require the application of chemicals, heat, and cold or use surgical procedures to destroy nerves (neuroablation) to achieve relief of the pain mediated through specific nerves as shown by previously performed diagnostic blocks. The use of radiofrequency heating and cryogenic cooling is common. Radiofrequency waves generated into tissue by a probe cause the tissue to heat. The heating can be sufficient to cause temporary or permanent shut-down of nerve fibres. An increasing area of therapeutic interventional pain medicine is known as neuromodulation. This involves applying electricity or administering medications directly to the nervous system to relieve pain[151].

The Accidental Compensation Corporation (ACC) Interventional Pain Management (IPM) review and guidance published in 2005 and updated in part in 2011 assessed a number of the procedures described above to treat and manage pain. The ACC Guidance covered six groups of interventional procedures:

- IDET (intra-discal electrothermal therapy)
- Infusion
- Injection
- Nerve blocking procedures
- Neuroablation
- Neuromodulation
- IPM interventions relevant to the current review of therapies to modulate pain generated by the intervertebral discs and related spinal structures are listed below.
- For chronic pain in the low back/leg region;

[151] http://www.nationalpainfoundation.org/articles/158/interventional-pain-management

- chemonucleolysis
- common peroneal nerve block
- epidural clonidine - lumbar
- epidural steroid - caudal-sacral
- epidural steroid - lumbar
- epidural steroid - transforaminal
- intra-discal electrothermal therapy (IDET)
- intravenous (IV) amantadine
- intravenous (IV) colchicine
- prolotherapy injections
- radiofrequency (RF) neurotomy: lumbar medial branch
- radiofrequency (RF) neurotomy: lumbosacral dorsal root ganglion
- spinal nerve block
- steroid for lumbar facet joint pain
- sympathetic ganglion block
- therapeutic lumbar medial branch block.

For chronic pain in the *neck/arm region*;

- epidural steroid and anaesthetic - cervical
- radiofrequency (RF) neurotomy: cervical medial branch
- radiofrequency (RF) neurotomy: cervicobrachial dorsal root ganglion
- steroid or local anaesthetic for cervical facet joint pain

The full details of the Guidance including evidence tables are available at the IPM website[152]. A brief synopsis of the assessments for 23 interventions assessed for the treatment of back, neck or non cancer chronic pain which were considered to be relevant to the current review is given below followed by a final summary highlighting only interventions for which positive recommendations of one sort or another were made.

It perhaps worth noting at the outset that most of the above pain syndromes have somewhat vague definitions and overlapping diagnoses. Moreover, trial candidates may include minimal cases with a high rate of spontaneous resolution and placebo response. Given these difficulties small trials may not be able to demonstrate reliable effects.

[152] http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/index.htm.

Intra-discal electrothermal therapy (IDET)

IDET is a procedure that is performed to treat pain of lumbar intervertebral disc origin. High heat is applied directly to the inside of the disc with the aim of shrinking the collagen of the disc wall and cauterizing associated small nerve fibres and blood vessels. This procedure is considered when a diagnosis of internal disc disruption has been made with disc stimulation and CT discography.

Evidence was reviewed which assessed the use of IDET for;

- chronic low back pain originating from internal disc disruption,
- chronic discogenic pain in the low back,
- chronic low back pain due to annular disruption of contained herniated discs.

These syndromes overlap heavily, have a naturally high spontaneous remission rate and are not naturally occurring distinct entities

Two health technology assessments, one guideline, one systematic review, three experimental studies and five observational studies provided information on the effectiveness of IDET for internal disc disruption. The experimental studies included between 37 and 56 participants; the longest period of follow-up was 24 months and was of medium quality. Seven additional studies informed the safety and harm section.

There was conflicting evidence about the effectiveness of IDET for internal disc disruption; some studies reported short term benefit and some reported evidence that suggested that there was no benefit. There appeared to be a small risk of harm with this procedure. IDET was therefore only recommended for use in a research setting for adults with internal disc disruption[153]. (Grade of recommendation = B, i.e. supported by fair evidence).

Infusions

Eight pain mediators delivered by infusion for the alleviation of six painful conditions were examined, Table 3. These conditions included refractory non-cancer pain of any origin, pain arising from spinal injury, complex regional pain syndrome*, neuropathic pain, sciatica and low back pain.* The outcomes of the evidence review for therapeutic interventions for the last three indications are of particular relevance to the current report. Seven interventions were assessed;

- epidural opioids
- intrathecal baclofen
- Intrathecal opioids
- intravenous amantadine
- intravenous colchicine

[153] Since this report the Adelaide spine group reported outcomes from an RCT with a needle in the back and a sham video of the procedure. They stopped at 50 patients because it lacked efficacy compared to placebo. A sheep model showed extensive necrosis of half the disc at 6 months.(Freeman, Fraser, Cain, Hall, & Chapple, 2005)

- Intravenous ketamine
- intravenous lignocaine

Table 4.3. ACC interventional pain management project: evidence based recommendations for infusions.

Infusion	Conditions used for in the studies appraised?	Recommendation	Summary
Epidural opioids	Refractory non-cancer pain	Epidural infusion of opioids and/or opioids and bupivacaine is not recommended for the treatment of adults with persistent pain, due to the low quality of the evidence of effectiveness and the adverse effects profile. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	X
Intrathecal baclofen	Spasticity of spinal origin caused by multiple sclerosis or spinal cord injury.	Intrathecal infusion of baclofen is not recommended for the treatment of pain without spasticity. Grade of recommendation = C, i.e. supported by [some] opinion only.	X
Intrathecal opioids	Refractory non-cancer pain.	Intrathecal infusions of opioids are not recommended on their own for the treatment of adults with persistent pain of non-cancer origin because of significant side effects from the procedure and a lack of evidence of relative benefit over systemic opioids. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	X
Intravenous (IV) amantadine	Sciatica	Intravenous infusion of amantadine is not recommended for the treatment of adults with sciatica. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	X
Intravenous (IV) colchicine	Low back pain of less than 6 months duration.	Intravenous infusion of colchicine is not recommended in the treatment of adults with low back pain. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	X
Intravenous (IV) ketamine	Persistent pain of non-cancer origin	The general use of intravenous infusion of ketamine is not recommended in the treatment of adults with persistent non-cancer pain. Grade of recommendation = B, i.e. supported by fair evidence.	X
Intravenous (IV) lignocaine	Neuropathic pain	The general use of intravenous infusion of lignocaine is not recommended for the treatment of neuropathic pain. Grade of recommendation = B, i.e. supported by fair evidence.	X

X = negative recommendation. ✓ = positive recommendation. CC case-by-case consideration.

Intravenous infusion of amantadine

There was high quality evidence from a single randomised trial (n=30) that intravenous infusion of amantadine was not effective for the treatment of adults with sciatica. The follow-up time reported in this study was only three hours; it was unclear whether there was sufficient power to detect a difference between the treatment and control group. No adverse effects were reported. Intravenous infusion of amantadine was therefore not recommended for the treatment of adults with sciatica. Grade of recommendation = C, i.e. supported by [some] expert opinion only.

Intravenous infusion of colchicine

There was low quality evidence from a single randomised controlled trial (n=48) that intravenous infusion of colchicine was effective in the treatment of adults with *low back pain of less than six months* in the very short term (1-2 days). The procedure was reported to have the potential to cause severe adverse effects and was *not recommended* in the treatment of adults with low back pain. Grade of recommendation = C, i.e. supported by [some] expert opinion only.

Intrathecal baclofen

One health technology assessment, one guideline and one experimental study provided information on the effectiveness of intrathecal infusion of baclofen. Follow-up was reported to be up to 12 months. The number of study participants was small. There was conflicting evidence of the effectiveness of intrathecal infusion of baclofen from studies of medium quality. It was not effective in reducing neuropathic pain. Reported complications were those associated with intrathecal drug administration in general. These occurred in approximately 20% of patients. Intrathecal infusion of baclofen was *not recommended* for the treatment of pain without spasticity. Grade of recommendation = C, i.e. supported by [some] expert opinion only.

Intravenous ketamine

In 2005, the IPM guidance highlighted a lack of evidence for the 'long term' effectiveness of ketamine infusion in the treatment of persistent non-cancer pain and questioned the clinical relevance of the very short term relief reported in the studies reviewed. A high incidence of psychomimetic adverse effects was reported and ketamine has been shown to be addictive and cause kidney damage with chronic use. The guidance noted that use of S+ isomer ketamine may provide additional clinical benefits with fewer adverse effects.

The 2011 evidence update identified two randomised double blind, placebo controlled trials that attempted to address the weaknesses of previous studies. The general use of intravenous infusion of ketamine is not recommended in the treatment of adults with persistent non-cancer pain Grade of recommendation =B, i.e. supported by fair evidence[154].

Intravenous infusion of lignocaine

The 2005 IPM review found conflicting evidence about the effectiveness of intravenous (IV) infusion of lignocaine for the treatment of non-cancer pain. Some studies reported short term benefit (up to three weeks) in the treatment of neuropathic pain; others suggested it was not as effective as ketamine infusion. A consistent positive effect was reported in the treatment of fibromyalgia, although the relevance of these studies is questionable. Lignocaine can have serious side effects, particularly in patients with some cardiac conditions. Central nervous system effects may be expected. The general use of intravenous infusion of lignocaine was not recommended for the treatment of neuropathic pain [155] .Grade of recommendation = B, i.e. supported by fair evidence.

Injections

A wide range of interventions and indications were reviewed, those of relevance to the current report are listed and described below and recommendations summarised in Table 4.4;

- Botulinum toxin for low back pain (lumbago)
- Botulinum toxin for neck pain

[154] Carefully titrated ketamine infusion delivered in a hospital setting with concomitant medication to control or moderate psychomimetic adverse effects may be appropriate for cases of persistent pain arising from complex regional pain syndrome (CRPS) in patients where other treatments have failed Grade of recommendation =B.

[155] The 2011 evidence update found that overall there is conflicting evidence on the short term effectiveness of lignocaine infusion for neuropathic pain. The four new studies identified provided no additional evidence and, similar to the evidence examined in 2005, report on short term intervention and relief. The conclusion was therefore that the 2005 clinical recommendation should remain in place.

- Chemonucleolysis
- Epidural clonidine - lumbar
- Epidural steroid - caudal-sacral
- Epidural steroid - lumbar
- Epidural steroid - transforaminal
- Epidural steroid and anaesthetic - cervical
- Prolotherapy injections
- Steroid for lumbar facet joint pain
- Steroid or local anaesthetic for cervical facet joint pain

Table 4.4. ACC interventional pain management project: evidence based recommendations for injections.

Infusion	Conditions used for in the studies appraised?	Recommendation	Summary
Botulinum toxin lumbar	• Low back pain	The routine use of botox injections for the treatment of low back pain is not recommended due to insufficient evidence. Grade of recommendation =I. However, in rare circumstances where conventional treatment has failed, it may be considered on a case-by-case basis	I CC
Botulinum toxin cervical	• Neck pain	The routine use of botox injections for the treatment of neck pain cannot be recommended due to conflicting evidence. Grade of recommendation = C, i.e. supported by [some] expert opinion only. However, in rare circumstances where conventional treatment has failed, it may be considered on a case-by-case basis.	X CC
Chemonucleolysis	• Back pain and sciatica • Lumbar disc prolapse (herniated lumbar disc)	Chemonucleolysis is not recommended for the treatment of herniated lumbar disc because of the incidence of adverse effects (particularly allergic reactions). Grade of recommendation = B, i.e. supported by fair evidence.	X
Epidural clonidine - lumbar	• Back pain	A single lumbar epidural injection of clonidine is not recommended for the treatment of adults with persistent non-cancer pain. Grade of recommendation = C, i.e. supported by expert opinion only.	X
Epidural steroid - caudal-sacral	• Sciatica • • Low back pain	Epidural caudal/sacral injection of steroid may be used for the short-term treatment of sciatica or radicular pain. Grade of recommendation = B, i.e. supported by fair evidence. Epidural caudal/sacral injection of steroid is not recommended for the treatment of low back pain. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	✓ X
Epidural steroid - lumbar	• Low back pain and/or sciatica. • Lumbar disc herniation.	Lumbar epidural injection of steroid may be used for the short-term treatment of adults with radiating leg pain (sciatica). Grade of recommendation = B, i.e. supported by fair evidence. Lumbar epidural injections of steroid are not recommended for the treatment of adults with chronic low back pain. Grade of recommendation = B, i.e. supported by fair evidence.	✓ X
Epidural steroid - transforaminal	• Lumbosacral radiculopathy • Sciatica • Failed back surgery syndrome • Herniated nucleus pulposus • Lumbar radicular pain	Transforaminal injection of steroid with local anaesthetic may be considered for the short-term treatment of adults with sciatica. Grade of recommendation = B, i.e. supported by fair evidence.	✓
Epidural steroid and anaesthetic - cervical	• Cervicobrachialgia or neck, shoulder and arm pain	Cervical epidural steroid and anaesthetic injection is not recommended for the treatment of adults with cervicobrachialgia. Grade of recommendation = C, i.e. supported by expert opinion only.	X
Prolotherapy injections	• Low back pain	Prolotherapy alone is *not recommended* for the treatment of low back pain. Grade of recommendation = B, i.e. supported by fair evidence.	X

Infusion	Conditions used for in the studies appraised?	Recommendation	Summary
Steroid for lumbar z-joint pain	• Low back pain • Lumbar or lumbosacral pain	Injection of steroid with or without local anaesthetic into the lumbar facet joints are not recommended for the treatment of adults with low back pain. Grade of recommendation = B, i.e. supported by fair evidence.	X
Steroid or local anaesthetic for cervical z-joint pain	• Zygapophyseal joint pain following automobile accidents	Intra-articular injection of steroid or local anaesthetic is not recommended for the treatment of adults with cervical zygapophyseal joint pain following automobile accidents. Grade of recommendation = C, i.e. supported by [some] expert opinion only.	X

X = negative recommendation. ✓ = positive recommendation. CC case-by-case consideration

Botulinum toxin injection for low back pain

In 2009 ACC commissioned Adelaide Health Technology Assessment (AHTA) to review the evidence for botox injections for chronic low back pain. The review concluded that the published evidence was insufficient at that time for ACC to routinely fund the intervention.

The 2011 IPM evidence update found one additional study, a well conducted case series with a reasonable (24 weeks) follow up. However, due to its relatively weak design and lack of blinding it provided only low level evidence for effectiveness and the routine use of botox injections for the treatment of low back pain could not be recommended due to insufficient evidence (Grade of recommendation I). However, in rare circumstances where conventional treatment had failed, it was determined that botulinum injection for low back pain may be considered on a case-by-case basis.

Botulinum toxin for neck pain

The IPM 2011 evidence update identified a number of eligible studies on neck pain, including 15 randomised controlled trials (RCTs). The RCTs consistently reported greater improvement in pain relief compared with the control but generally failed to demonstrate statistically significant differences between the intervention and control groups. Small study size, a large placebo effect and concomitant pain medication were believed to have contributed to the failure of some trials to demonstrate significant differences between the study groups. The authors of the two largest trials came to opposing conclusions in relation to the effectiveness of botulinum injections. A head-to-head comparison of these two trials, suggested that one trial was superior in terms of design, reporting and quality; this trial provided evidence of effectiveness however the estimated effect size was small.

The routine use of botox injections for the treatment of neck pain was not recommended due to conflicting evidence (Grade of recommendation C). However, in rare circumstances where conventional treatment had failed, it was determined that botulinum injection for neck pain may be considered on a case-by-case basis.

Chemonucleolysis

Chemonucleolysis is a method of treating pain caused by lumbar disc herniation. An enzyme such as chymopapain is injected into the nucleus pulposus of the herniated disc in order to dissolve it. Chemonucleolysis is a conservative alternative to disc surgery.

One high quality systematic review of 15 studies (Gibson & Waddell, 2007) was identified. In five high quality trials chymopapain was reported to be more effective than a placebo. In five poor quality trials comparing chemonucleolysis to surgical discectomy, all of the analyses showed consistently poorer results for chemonucleolysis although this did not reach statistical significance. In the remaining trials there was no significant difference between chymopapain and the study comparators. Three additional randomised controlled trials (Gogan & Fraser, 1992; Hedtman, Steffen, & Krämer, 1987; Wittenberg, Oppel, Rubenthaler, & Steffen, 2001) and a low to medium quality systematic review (Stevens, Dubois, Larequi-Lauber, & Vader, 1997) reported results which were consistent with those of the systemic review by Gibson (2007). Three case series of reasonable or good quality reported that chymopapain was an effective treatment for radicular complaints and displaced or recurrent herniated discs.

With regard to the safety of chymopapain injections, one RCT (Wittenberg et al., 2001) reported that 12% of patients had allergic reactions including one slight anaphylactic reaction to chymopapain. Another RCT of 86 patients (Hedtman et al., 1987) reported that five patients developed slight and transient cutaneous reactions that were treatable with antihistamines. Hadjipavlou (1992) reported on adverse events in 66 of 115 patients: one patient suffered nerve root damge and one patient developed discitis; no patients suffered allergic or CNS complications. In a case series of 85 patients receiving a second injection of chymopapain for recurrent disc herniation (van de Belt, Franssen, & Deutman, 1999), four patients had a Type 1 and one had a Type 2 sensitivity reaction. There were no life-threatening Type 3 anaphylactic reactions.

Chemonucleolysis was not recommended for the treatment of herniated lumbar disc because of the high incidence of adverse effects (particularly allergic reactions). Grade of recommendation B.

Epidural clonidine - lumbar

Clonidine is a centrally acting alpha-2 agonist that has mainly been used to treat high blood pressure and migraine. It has been found to activate pain-inhibiting mechanisms in the spinal cord, especially in patients with acute pain. Clonidine may be injected into the epidural space (the space between the spinal column and the dura (covering) around the spinal cord).

Two low to medium quality randomised crossover trials of 30 patients reported that lumbar epidural injection of clonidine was effective for the treatment of adults with chronic pain below the waist. However, it appeared to be no better than intravenous clonidine and had a greater effect if combined with lignocaine. Unpleasant side effects were reported in six out of 20 patients using clonidine alone.

A single lumbar epidural injection of clonidine is not recommended for the treatment of adults with persistent non-cancer pain. Grade of recommendation C.

Epidural steroid - caudal-sacral

A steroid solution may be injected into the epidural space (the space between the spinal column and the dura or covering around the spinal cord). Caudal/sacral epidural injections are mostly used to give pain relief for the leg pain that can occur when a disc in the lower back is damaged, but are probably only useful for damage to the lowest two lumbar vertebrae (L4 and L5). Ideally they are given within three months of the disc injury as this is when they are most likely to be useful.

The IPM evidence review determined that there was medium quality evidence from one health technology assessment (HTA), four systematic reviews, four randomised controlled trials (RCTs) and three case series that epidural caudal/sacral injection of steroid was effective for the treatment of sciatica or radicular pain in the short term (i.e. up to 60 days). In some patients there was evidence of modest long term (i.e. up to one year) pain relief with a number-needed-to-treat (NNT) of 11. A recent American guideline document which included an economic assessment presented similar findings(Manchikanti et al., 2003).

The evidence of *short-term* effectiveness was reasonably consistent. Pooled estimated NNTs of six (75% pain relief) and 3 (50% pain relief) were reported. The size of the RCTs was generally modest, i.e. 45-65; 318 patients were treated in the case series.

Most of the high quality studies reporting effectiveness were placebo controlled; there was little or no evidence that epidural steroid injection (caudal or lumbar) was *more effective* than epidural injection of local anaesthetic. There was no conclusive evidence for the effectiveness of lumbar epidural steroid injection for chronic low back pain.

The procedure was reported to be relatively safe with few, relatively minor, adverse effects[156]. Forceful injections of large quantities of fluid into the epidural space may be associated with more serious adverse effects.

Epidural caudal/sacral injection of steroid was recommended for use for the short-term treatment of *sciatica or radicular pain.* Grade of recommendation B. Epidural caudal/sacral injection of steroid was *not recommended* for the treatment of *low back pain.* Grade of recommendation C.

Epidural steroid - lumbar [157]

A steroid solution may be injected into the epidural space (the space between the spinal column and the dura covering the spinal cord). The commonest reason for the performance of this injection was to relieve leg pain that can occur with lumbar disc injury. Ideally the intervention should be carried out within three months of the disc injury because this is when the intervention is most likely to be effective. It may also be useful in more chronic conditions such as spinal stenosis.

In the studies reviewed, epidural steroid injections were used to moderate pain caused by low back pain and/or sciatica and lumbar disc herniation. There was medium quality evidence from one health technology assessment (HTA), six systematic reviews, four randomised controlled trials (RCTs) and three observational studies that lumbar epidural steroid injection for the treatment of adults with sciatica with or without back pain was effective in the *short term (up to 60 days).* The RCTs reporting on this procedure included between 36 and 100 patients. The total number of patients treated in the reported case series was 811. The size of the reported effect was variable. The evidence on *long term effectiveness was conflicting* and there was no conclusive evidence that lumbar epidural steroid injection was effective for chronic low back pain.

[156] Most protagonists of epidural steroid injections make light of side effects which can be significant, including loss of diabetic control, Cushingoid symptoms including hirsutism, menstrual irregularity, even avascular necrosis of the hip. Personal communication, Gordon Howie, reviewer.

[157] http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/interventions/intervention-index/WCM1_033801

Accidental dural puncture and transient blindness was reported in a small number of cases. Other transient and less serious side effects have also been reported.

Lumbar epidural injection of steroid *was recommended* for the short-term treatment of adults with *radiating leg pain (sciatica).* Grade of recommendation B. Lumbar epidural injection of steroid *was not recommended* for the treatment of adults with chronic low back pain. Grade of recommendation B.

Epidural steroid – transforaminal[158]

Transforaminal epidural injection is a procedure during which drugs (e.g. steroid, local anaesthetic or a mixture of both) are injected adjacent to a spinal nerve root at the point where it enters the spinal canal via the foramen.

Transforaminal epidural injections of steroid were used to treat a variety of conditions in the assessed studies including;

- lumbosacral radiculopathy
- sciatica
- failed back surgery syndrome
- herniated nucleus pulposus
- lumbar radicular pain.

There was medium quality evidence from five randomised controlled trials and four observational studies that transforaminal injection of steroid with local anaesthetic was effective for the treatment of adults with sciatica, in the short term (up to 12 weeks). The primary studies included a total of 631 patients.

A 2003 guideline document of limited quality made a strong recommendation in favour of transforaminal epidural injection with steroid, which was not supported by the strength of the evidence. Little safety information was reported. One RCT reported that there were no complications. It was noted in a further study that there were no complications in cases where injections were performed under fluoroscopic control Only one randomised controlled trial (Vad, Bhat, Lutz, & Cammisa, 2002), n=50) reported on safety. The authors noted that there were no complications such as dural puncture, excessive bleeding, headache or infection in either of the study groups. A case series by Lutz et al. (1998), n=69) reported no complications of dural puncture, nerve root injury or infection after 94 procedures where all injections were performed under fluoroscopic control.

Transforaminal injection of steroid with local anaesthetic was recommended for the short-term treatment of adults with sciatica. Grade of recommendation B.

Epidural steroid and anaesthetic - cervical

Steroid is injected into the epidural space at one of the lowest two vertebrae in the neck (C7 or C6). These injections are mainly used to relieve the neck or arm pain that can occur when a disc in the neck is

158 http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/interventions/intervention-index/WCM1_033825

damaged. The commonly accepted mechanism of action is that the local application of steroid provides an intense anti-inflammatory effect in the epidural space for a period of days to weeks. This reduces the inflammation seen in the epidural space after disc injury and hence reduces pain. Other mechanisms have been suggested. These procedures are not as commonly performed as lumbar epidural steroid injections, as cervical discs are not as frequently damaged as lumbar discs and the link between cervical disc damage and pain is less reliable.

In the studies appraised, cervical epidural steroid and anaesthetic injections were used to treat cervicobrachialgia or neck, shoulder and arm pain.

There was evidence from one medium quality randomised controlled trial (RCT) of 42 patients that cervical epidural steroid and anaesthetic injection was more effective than intramuscular steroid injection for the treatment of adults with cervicobrachialgia. Effectiveness was reported for up to one year after the injection, with a high recovery of capacity to work in treated patients.

There are several reports of very rare but serious side effects from this procedure, including death and quadriplegia. Two cases of unintentional dural puncture and three cases of vasovagal syncope were reported from 790 consecutive cervical epidural steroid nerve blocks administered to 215 patients (Waldman, 1989). A late complication of infection was reported in a single patient following his fourth block. All patients recovered from their adverse events and there were no long-term effects. Five additional case studies reported a number of rare but serious adverse events attributed to cervical epidural steroid injection. Brouwers et al. (2001) reported a case of cervical anterior spinal artery syndrome resulting in complete paralysis with loss of pain and temperature sense. Huang et al. (2004) reported a patient with cervical epidural abscess, while Stoll & Sanchez (2002)reported a case of epidural haematoma with severe neurological impairment. Two cases of spinal cord damage were reported by Hodges et al. (1998) and Kao (1998) reported on a case of bilateral retinal detachment following epidural steroid injection. Infection was rare but had significant consequences and may present days or weeks after the procedure is carried out.

Cervical epidural steroid and anaesthetic injection was *not recommended* for the treatment of adults with cervicobrachialgia. Grade of recommendation C.

Prolotherapy injections

Prolotherapy is a treatment that involves a protocol of injections, exercises, and vitamin and mineral supplements. Tissues such as ligaments are injected with an irritant substance, usually 20% glucose, which causes localised inflammation with the aim of stimulating blood flow and promoting healing. Low back pain was one of the conditions treated with prolotherapy injections in the appraised studies.

There was evidence from one medium quality systematic review of four high quality randomised controlled trials (RCTs) of no effect of prolotherapy alone for the treatment of low back pain. The overall number of patients assessed in the systematic review was 344.

Prolotherapy alone was *not recommended* for the treatment of low back pain. Grade of recommendation B.

Steroid for facet joint pain

The joints between the vertebrae of the spine are known as the zygapophyseal (z-) or facet joints. Injections of steroid and local anaesthetic are used to treat pain that is arising from the facet joints. In the appraised studies steroid with/without local anaesthetic injections were used to treat;

- low back pain
- lumbar or lumbosacral pain

One high quality systematic review (Nelemans, de Bie, de Vet, & Sturmans, 2001), one randomised controlled study (Revel et al., 1998) and one observational study (R. Jackson, Jacobs, & Montesano, 1988) informed the review of effectiveness.

The single high quality systematic review of three medium quality trials (n=411) reported a non-significant trend towards benefit and one medium quality randomised controlled study of 80 patients reported a significant benefit for some patients after lignocaine injection of the lumbar zygapophyseal (z- or facet joint) compared to a placebo saline[159] injection. A medium quality observational study (454 patients) of prognostic factors could not predict which patients would benefit.

Facet joint injections were considered to be generally safe. A rare but significant complication (paraspinal abscess) was reported.

Injection of steroid with or without local anaesthetic into the lumbar facet joints is *not recommended* for the treatment of adults with low back pain. Grade of recommendation B.

Steroid or local anaesthetic injection for cervical facet joint pain

The joints between the vertebrae of the spine are known as the zygapophyseal, z- or facet joints. Injections of steroid and/or local anaesthetic are used to treat pain arising from the cervical z-joints.

In the appraised study steroid or local anaesthetic injection for cervical z-joint pain was used to treat zygapophyseal joint pain following an automobile accident.

There was medium quality evidence from a single randomised controlled trial (RCT) of 41 patients that intra-articular injection of steroid or local anaesthetic is not effective in the treatment of adults with cervical zygapophyseal pain following automobile accidents. Injections were guided by fluoroscopy. Some minor adverse reactions were reported but it was unclear which of the study interventions were implicated.

- Intra-articular injection of steroid or local anaesthetic was not recommended for the treatment of adults with cervical zygapophyseal joint pain following automobile accidents. Grade of recommendation C.

[159] Saline is not an innocuous substance. It has an acid pH and has effects of it's own. Plasmalyte may be a better control. Personal communication, Gordon Howie, reviewer.

Nerve blocking procedures

Four nerve block interventions for a variety of spinal pain types were reviewed, those of relevance to the current report are listed and described below and recommendations summarised in Table 4.5.

Table 4.5. ACC interventional pain management project: evidence based recommendations for nerve blocks.

Nerve block	Conditions used for in the studies appraised?	Recommendation	Summary
Common peroneal nerve block	• Sciatic radicular pain	Common peroneal nerve block is not recommended for the treatment of adults with sciatic radicular pain. Recommendation = C, i.e. supported by [some] expert opinion only.	**X**
Spinal nerve block	• Osteoporotic vertebral fractures • Radicular pain unresponsive to conservative treatment	There is insufficient evidence to support or refute the use of spinal nerve block in the management of persistent non-cancer pain. Recommendation = I, i.e. no recommendation can be made because the evidence is insufficient.	**I**
Sympathetic ganglion block	• Chronic low back pain	Lumbar sympathetic ganglion block is *not recommended* for the management of adults with chronic low back pain. Recommendation = B, i.e. the recommendation is supported by fair evidence.	**X**
Therapeutic lumbar medial branch block	• Chronic persistent low back pain • Zygapophyseal joint pain	The *general use* of therapeutic lumbar medial branch blocks is *not recommended* for the treatment of adults with low back pain, however these blocks may be considered in the research setting. Recommendation = B, i.e. the recommendation is supported by fair evidence.	**R**

X = negative recommendation. ✓ = positive recommendation. CC case-by-case consideration. R= research setting only- this recommendation may be made when the intervention cannot be recommended for routine or general use. I= insufficient information to assess.

Common peroneal nerve block

The common peroneal nerve arises at the upper part of the popliteal fossa (back of the knee). It is one of the two terminal branches of the sciatic nerve, which is a nerve supply to the lower leg. This nerve may be blocked with a single injection of local anaesthetic at the back of the knee.

Peroneal nerve block was used to treat sciatic radicular pain in the appraised study.

There was medium quality evidence from one randomised placebo controlled experimental study of 19 patients that common peroneal nerve block is effective in the very short term for the treatment of adults with sciatic radicular pain. Pain relief was only measured for 15 minutes after the procedure. The RCT did not report on safety, however, it is known that this technique may carry an increased risk of nerve injury (peripheral neuritis) compared to other nerve blocks.

Common peroneal nerve block was *not recommended* for the treatment of adults with sciatic radicular pain. Grade of recommendation C.

Spinal nerve block

A fine needle is inserted into the spine and is guided towards the spinal nerve under x-ray guidance. Radiographic contrast is injected first and, after satisfactory distribution of contrast has been confirmed; local anaesthetic is injected around the nerve.

One of the conditions that spinal nerve block was used to treat in the appraised articles was radicular pain which was unresponsive to conservative treatment.

One medium quality case series provided information on the effectiveness of lumbar spinal nerve block in the treatment of patients with acute and chronic osteoporotic vertebral fractures and radicular pain unresponsive to conservative treatment (D. J. Kim, Yun, & Wang, 2003). The nerve root reproducing the characteristic pain was injected with lignocaine, bupivacaine and DepoMedrol, repeated at 2-week intervals (maximum 3 times) until there was symptomatic improvement. On a pain scale of 0 to 100, the mean pain score dropped from 85 (pre-treatment) to 17.4 at final follow-up (mean 14 months). There was no significant difference in the mean scores between the acute and chronic groups at final follow-up. Nerve root injections appeared to be effective in the treatment of pain resulting from osteoporotic vertebral fractures.

Overall, there was insufficient evidence to support or refute the use of spinal nerve block in the management of persistent non-cancer pain (I).

Sympathetic ganglion nerve block

Sympathetic block can be produced with local anaesthetic deposited at the sympathetic ganglia, e.g. stellate ganglia and lumbar sympathetic ganglia.

In the appraised studies sympathetic ganglion nerve block was used for a number of different conditions including;

- cervical spondylotic radiculopathy
- chronic low back pain.

There was evidence from two medium quality randomised placebo-controlled trials of 87 patients that lumbar sympathetic ganglion block with bupivacaine and/or saline is associated with short term pain relief in adults with chronic low back pain. There were reports of rare, severe complications from this procedure.

Lumbar sympathetic ganglion block was *not recommended* for the management of adults with chronic low back pain. Grade of recommendation B.

Therapeutic lumbar medial branch block

The zygapophyseal (facet) joints of the lumbar spine receive their nerve supply from nerves called the medial branches of the lumbar dorsal rami. Each joint is supplied by two medial branches. Therapeutic lumbar medial branch blocks are used to treat zygapophyseal joint pain by targeting the nerves that

supply the joints. Agents that have been administered with this procedure include corticosteroids and sarapin[160], combined with local anaesthetic.

In the appraised studies therapeutic lumbar medial branch block was used to treat chronic or persistent low back pain.

One guideline (medium quality), three randomised controlled trials (RCTs) (one medium to good, one medium and one low to medium quality) of 226 patients and two non-randomised comparative studies of 680 patients (medium quality) provided information on the effectiveness of therapeutic lumbar medial branch block.

Two early RCTs reported that facet nerve block with anaesthetic or anaesthetic and steroid was not effective treatment for low back pain. A more recent RCT reported that medial branch nerve block with anaesthetic and sarapin, with and without steroid, was effective and cost-effective in the treatment of chronic low back pain. Two non-randomised comparative studies reported pain relief with lumbar nerve blocks and anaesthetic alone or in combination with steroid and/or sarapin; there were conflicting conclusions on the incremental value of sarapin. A recently published guideline (Manchikanti et al., 2003) concluded that there was strong evidence of short term relief and moderate evidence of long term relief of pain of facet joint origin. However this was considered to be an overly positive interpretation given the evidence.

No serious adverse events were reported. Interventions were noted to be 'painful and unpleasant' for patients, with transient symptoms of headache, nausea and paresthesia.

The general use of therapeutic lumbar medial branch blocks was *not recommended* for the treatment of adults with low back pain; however it was considered that these blocks may be considered in the research setting. Grade of recommendation B.

Neuroablation

Radiofrequency (RF) neurotomy (also known as RF denervation) is a procedure in which the heated tip of an electrode is placed beside a nerve to coagulate the proteins inside that nerve. Successful treatment temporarily prevents the nerve from conducting impulses. Recovery of the nerve typically takes about a year.

The IPM reviewed four relevant radiofrequency neurotomy procedures;

- Radiofrequency (RF) neurotomy: Cervical medial branch
- Radiofrequency (RF) neurotomy: Cervicobrachial dorsal root ganglion
- Radiofrequency (RF) neurotomy: Lumbar medial branch
- Radiofrequency (RF) neurotomy: Lumbosacral dorsal root ganglion

[160] Sarapin is a biological medicine – it is derived from a naturally occurring organism (the Pitcher plant). It works by inhibiting pain signals in the nerves of the spine where they exit the spinal column.

These are described below and recommendations summarised in Table 4.6.

Table 4.6. ACC interventional pain management project: evidence based recommendations for radiofrequency neurotomy.

RF neurotomy of	Conditions used for in the studies appraised?	Recommendation	Summary
Cervical medial branch	• Whiplash injury with or without specifically diagnosed zygapophyseal (z-) joint pain. • Painful cervical z-joint attributed to a motor vehicle accident and experienced > 3 months following that accident. • Neck pain > 3 months after a motor vehicle accident. • Cervical z-joint pain in patients involved in a motor vehicle accident ≥ 20 weeks earlier. • Neck pain with or without radiation to the head or shoulder girdle.	Radiofrequency neurotomy of the cervical medial branch should only be performed in a research setting. Recommendation = B, i.e. the recommendation is supported by fair evidence.	**R**
Lumbar medial branch	• Chronic non-specific low back pain • Chronic low/mid/thoracic back pain • Chronic spinal pain. • Mechanical pain of spinal origin.	The general use of radiofrequency neurotomy of the lumbar medial branch is not recommended for the treatment of adults with lower back pain. Recommendation = C, i.e. supported by [some] expert opinion only. However, the procedure may be considered in the research setting.	**R**
Lumbosacral dorsal root ganglion	• Chronic lumbosacral back pain.	Radiofrequency neurotomy of the dorsal root ganglion is not recommended for the treatment of adults with lumbosacral pain. Recommendation = B, i.e. the recommendation is supported by fair evidence.	**X**

X = negative recommendation. ✓ = positive recommendation. CC case-by-case consideration. R= research setting only. I= insufficient information to assess.

Radiofrequency (RF) neurotomy: Cervical medial branch

The zygapophyseal (facet or z-) joints of the cervical spine receive their nerve supply from nerves called the medial branches of the cervical dorsal rami. RF neurotomy is applied to the medial branches to treat neck pain, with or without radiation to the head or shoulder girdles, when its source is one of the cervical z-joints. Each joint, except C2-3, is supplied by two medial branches and treatment of two nerves is therefore required to relieve pain from one joint.

In the appraised studies RF neurotomy of the cervical medial branch was used to treat;

- whiplash injury with or without specifically diagnosed zygapophyseal (z-) joint pain

- painful cervical z-joint attributed to a motor vehicle accident and experienced > 3 months following the accident
- neck pain > 3 months after a motor vehicle accident
- cervical z-joint pain in patients involved in a motor vehicle accident ≥ 20 weeks earlier
- neck pain with or without radiation to the head or shoulder girdle.

There was medium quality evidence that radiofrequency neurotomy of the cervical medial branch was effective (for a median period of nine months) in the treatment of adults with persistent neck pain due to a motor vehicle accident. The evidence was provided by one health technology assessment, one guideline, two systematic reviews and two case series (n=50 and n=122 respectively). However, it should be noted that most of the evidence presented by the four secondary studies was taken from a single randomised controlled trial (n=24). A further case series (n=49) provided additional evidence on the safety of the procedure.

Radiofrequency neurotomy of the cervical medial branch should only be performed in a research setting. Grade of recommendation B.

Radiofrequency (RF) neurotomy: Lumbar medial branch

The facet joints of the lumbar spine receive their nerve supply from nerves called the medial branches of the lumbar dorsal rami. RF neurotomy is applied to the medial branches to treat low back pain originating from one of the lumbar z-joints. Each lumbar z-joint is supplied by two medial branches and two nerves therefore have to be treated in order to relieve pain originating from one joint.

In the appraised studies RF neurotomy of the lumbar medial branch was used to treat;

- chronic non-specific low back pain
- chronic low/mid/thoracic back pain
- chronic spinal pain
- mechanical pain of spinal origin.

RF neurotomy of the lumbar medial branches was only indicated in cases where pain had been completely relieved by controlled diagnostic lumbar medial branch blocks

The evidence on the effectiveness of radiofrequency neurotomy of the lumbar medial branch for the treatment of adults with lower back pain was conflicting. One guideline, three systematic reviews and four observational studies provided information on the effectiveness of this procedure. The observational studies included a total of 570 patients.

The general use of radiofrequency neurotomy of the lumbar medial branch was not recommended for the treatment of adults with lower back pain. Grade of recommendation C. However, the procedure may be considered in the research setting.

Radiofrequency (RF) neurotomy: Lumbosacral dorsal root ganglion

The dorsal root ganglion (DRG) is a collection of nerve cells located close to the spinal cord. There is one DRG for each nerve segment level in the body. The lumbosacral DRG carries nerve signals from the lower part of the back to the spinal cord, which in turn carries them to the brain. RF neurotomy of the lumbosacral DRG creates lesions in the nerve pathways before they reach the spinal cord, thus interrupting the transmission of pain impulses from the lower back.

In the appraised studies RF neurotomy of the lumbosacral dorsal root ganglion was used to treat;

- chronic lumbosacral back pain

There was medium quality evidence from one RCT and a case series study that radiofrequency neurotomy of the dorsal root ganglion is not effective in the treatment of adults with chronic lumbosacral pain with or without lumbosacral radicular pain. There was evidence that discrete or irritating loss of motor function may result from insertion of the electrode alone, with or without application of the RF current.

The information on safety and effectiveness was provided by one experimental and one observational study involving a total of 359 patients. In the randomised controlled trial there was severe treatment-related pain in 43% of the RF neurotomy group and 31% of the sham treatment group. There was discrete or irritating loss of motor function in 14% and 20% of the participants respectively.

Radiofrequency neurotomy of the dorsal root ganglion was not recommended for the treatment of adults with lumbosacral pain. Grade of recommendation B.

Neuromodulation

The IPM reviewed one relevant neuromodulation procedure, spinal cord stimulation. This procedure is described below and recommendations summarised in Table 4.7.

Table 4.7. ACC interventional pain management project: evidence based recommendations for neuromodulation.

Neuromodulation	Conditions used for in the studies appraised?	Recommendation	Summary
Spinal cord stimulation	• Chronic neuropathic pain due to traumatic spinal cord injury • Failed back surgery syndrome • Chronic back pain / extremity pain	The general use of spinal cord stimulation is not recommended for the treatment of adults with pain due to failed back surgery syndrome or chronic neuropathic pain following traumatic spinal cord injury. However, the procedure may be considered in the research setting.	R

X = negative recommendation. ✓ = positive recommendation. CC case-by-case consideration. R= research setting only. I= insufficient information to assess.

Spinal cord stimulation

Spinal cord stimulation is a procedure in which one or more electrical leads are placed in the epidural space over the dorsum of the spinal cord. The leads are attached to an impulse generator, which delivers a small electrical current. An electrode at the end of the leads thus provides stimulation to the dorsal part of the spinal cord.

In the appraised studies spinal cord stimulation was used to treat a number of different conditions including;

- chronic neuropathic pain due to traumatic spinal cord injury.
- failed back surgery syndrome.
- chronic back pain / extremity pain.

There was conflicting evidence of the effectiveness of spinal cord stimulation for the treatment of adults with pain due to failed back surgery syndrome or chronic neuropathic pain following traumatic spinal cord injury. The procedure was associated with a wide range of adverse events, mechanical complications are common and additional surgeries are frequently required.

Two guidelines, two health technology assessments, three systematic reviews, four randomised controlled trials and five observational studies provided evidence on the safety and effectiveness of spinal cord stimulation. Further information on safety was obtained from eight additional studies. Most of the included secondary studies concluded that there is insufficient evidence to draw definitive conclusions about the effectiveness of this procedure. All agreed that the quality of the primary research was poor. Clinical trials reported varying results and most observational studies concluded that spinal cord stimulation provided pain relief in a portion of patients with a variety of conditions.

The general use of spinal cord stimulation was not recommended for the treatment of adults with pain due to failed back surgery syndrome or chronic neuropathic pain following traumatic spinal cord injury. However, the procedure may be considered in the research setting. Grade of recommendation C.

Other interventions

The IPM review listed a number of procedures that were not *in common use or which at the time of the review only isolated studies were found*. A number of these interventions had been used to treat various types of spinal pain and included;

Infusion

- Intravenous infliximab – Karppinen et al. (2003)

Injection

- Botulinum toxin (chronic back pain) – Foster (2001)
- Botulinum toxin (chronic neck pain) – Wheeler et al. (2001)
- Botulinum toxin (lateral epicondylitis) – Keizer et al. (2002)

- Collagenase (lumbar disc herniation) – Bromley at al. (1984)
- Glycerol (intradiscal) – Kotilainen et al. (1997)
- Oxygen/ozone (lumbar spine disc abnormalities) – Torri et al. (1999); Andreula et al. (2003)
- Steroid (intradiscal) – Simmons et al. (1992)
- Steroid (perineural: for sciatica) – Kramer et al. (1997), Parts I & II
- Steroid (sacroiliac joint) – Luukkainen et al. (2002)

Neuroablation

- Radiofrequency neurotomy for discogenic pain - Oh & Shim (2004)
- Radiofrequency neurotomy of the thoracic medial branch –Manchikanti et al. (2002);

Recommendations *were not made* on their usage.

Summary of IPM recommendations

For the moderation of painful conditions of the spine 28 separate interventional pain management procedures were assessed. Following an examination of relevant systematic reviews, guidelines and primary research studies; one of five recommendations was made for each intervention.

- Recommendation for general use (3 interventions)
- Consideration for use in a research setting only (4 interventions)
- Consideration on a case-by-case basis where other treatments have failed (2 interventions)
- Not recommended (15 interventions)
- Insufficient evidence to support or refute usage (3 interventions)

Of the *positive recommendations*, three interventions were recommended for the short-term moderation of radicular pain/sciatica:

- Epidural caudal/sacral injection of steroid for the short-term treatment of sciatica or radicular pain
- Lumbar epidural injection of steroid for the short-term treatment of radiating leg pain (sciatica).
- Transforaminal injection of steroid with local anaesthetic for the short-term treatment of sciatica

Four interventions were recommended for use in a *research setting* only:

- Lumbar medial branch block for chronic persistent low back pain and zygapophyseal (facet) joint pain
- Radiofrequency neurotomy of the cervical medial branch for (a) whiplash injury with or without zygapophyseal (facet) joint pain, (b) painful cervical z-joint attributed to a motor vehicle accident (c) neck pain > 3 months after a motor vehicle accident (d) cervical z-joint pain in patients involved in a motor vehicle accident ≥ 20 weeks earlier and (e) neck pain with or without radiation to the head or shoulder girdle.
- Radiofrequency neurotomy of the lumbar medial branch for chronic non-specific low back pain, chronic low/mid/thoracic back pain, chronic spinal pain and mechanical pain of spinal origin.
- Spinal cord stimulation for chronic neuropathic pain due to (a) traumatic spinal cord injury, (b) failed back surgery syndrome, or (c) chronic back pain / extremity pain

Two treatments were recommended for consideration only on a case-by-case basis where other treatments had failed (2011 IPM update):

- Botulinum toxin injections for the treatment of low back pain
- Botulinum toxin for neck pain

Further evidence: epidural steroid injections (2005-2011)

Background

Epidural injection of corticosteroids is one of the most commonly used interventions for the management of chronic spinal pain. Reports of epidural corticosteroid injections to treat sciatica date back to the 1950s and their use has increased over time despite limited quality data and conflicting reviews of their efficacy and safety[161]. These reviews varied in terms of criteria for inclusion of patients, study design, types of interventions, outcome measures, and use of additional treatments.

In 2005 the ACC reviewed the available evidence relating to the use of lumbar, caudal/sacral, transforaminal and cervical steroid injections to modulate spinal pain (New Zealand Accident Compensation Corporation, 2005, 2006). The recommendations arising from the review were positive for caudal/sacral, lumber and transforaminal steroid injections however the evidence was not conclusive or uniform. The use of cervical epidural steroid injections was not supported.

With the continuing publication of a large volume of literature on the subject, debate continued in the medical literature as to the value of epidural steroid injections in managing spinal pain with the pros and cons argued in journal editorials, reviews, health technology assessments and medical society association guidelines. Importantly, a number of these publications listed questions that remained to be answered regarding the use of epidural steroids for spinal pain conditions. For example, in a report from the American Academy of Neurology, Armon et al (2007) posed 10 questions for consideration in their assessment of the use of epidural steroid injections in the treatment of radicular lumbosacral pain (Armon et al., 2007):

- Q1 Who is being treated? Diagnosis for treatment, demographics (age, gender), who should be treated?
- Q2 Factors which predict outcome (good/bad); factors which predict who should not be treated.
- Q3 What is the expected duration of benefit?
- Q4 What is the appropriate technical approach? Direction of the needle, type of needle, dose of medication, fluoroscopy vs. no fluoroscopy?
- Q5 Competency of the treater?
- Q6 Is the epidural injection sufficient, or should there be therapy of another kind with it? How does it compare to or add to other treatment modalities? Should it be combined with other treatment modalities?
- Q7 Can we differentiate treatment for acute, sub-acute, chronic patients, and is there a difference in outcome?
- Q8 How is efficacy measured? What measurement tools are used to measure efficacy? What measurement should be used to measure efficacy? How is success defined?
- Q9 Is there evidence for efficacy?
- Q10 Safety: How safe is this method of treatment? Are there any associated risks?

[161] Koes BW, Scholten RJPM, Mens JMA, Bouter LM: Effi cacy of epidural steroid injections for low-back pain and sciatica:a systematic review of randomized clinical trials. Pain 1995, 63:279–288. Watts RW, Silagy CA: A meta-analysis on the effi cacy of epidural corticosteroids in the treatment of sciatica. Anaesth Intensive Care 1995, 23:564–569. Nelemans PJ, de Bie RA, de Vet HCW, Sturmans F: Injection therapy for subacute and chronic benign low-back pain. Cochrane Database Syst Rev 1999, CD001824.

In the same year, the complexity of the medical choices relating to the different types of epidural steroid injections for these conditions was highlighted and included;

- the use of different delivery routes (e.g. interlaminar, transforaminal, and caudal)
- effectiveness in modulating specific types of spinal pain (e.g. axial, radicular)
- different areas of delivery (e.g. lumbar, cervical, thoracic) of the spine
- the use of appropriate controls in trials of effectiveness
- decisions relating to the type and amount of steroids and concomitant anaesthetic to be given .

Given the complexity of the problem it is not perhaps surprising that there has been ongoing debate and additional systematic reviews of the evidence to try to define more precisely the patient populations that may benefit from specific types of steroid injections.

The search results

The search procedure designed for the current review of the modulation of discogenic and related pain identified seven potentially relevant systematic reviews published between 2005 and 2011 (Abdi et al., 2007; Benyamin et al., 2009; Buenaventura et al., 2009; Conn, Buenaventura, Datta, Abdi, & Diwan, 2009; DePalma, Bhargava, & Slipman, 2005; Parr, Diwan, & Abdi, 2009; S. T. Roberts, Willick, Rho, & Rittenberg, 2009). Two guidelines were also identified, one published by The Institute for Clinical Systems Improvement (ICSI, 2010), the other by American Academy of Neurology (Armon et al., 2007).

Additional systematic reviews: (2005-2011).

Upon assessment two of the additional seven systematic reviews were determined to be ineligible and were not considered any further. The evidence reviewed by DePalma et al (2005) overlapped with the 2005 IPM review of transforaminal steroid interjections reported earlier in this report and with evidence presented in the more recent systematic review by Abdi et al (2007). The systematic review carried out by Parr et al (2009) only assessed blind lumbar interlaminar epidural injections; these were not considered to represent contemporary IPM practice.

Of the remaining five reviews, Conn et al (2009) focussed on epidural injections *per se* for chronic back pain; steroid injections were not the focus of this review and their comparative effectiveness was not assessed directly by the reviewers. This review is reported separately. The main features of the four remaining reviews (Abdi et al., 2007; Benyamin et al., 2009; Buenaventura et al., 2009; S. T. Roberts et al., 2009) and the author's conclusions are summarised in Table 4.8, and reported in more detail below.

Table 4.8. Systematic reviews of epidural steroid injection for painful spinal conditions (2005-2011)

Systematic review/ Indications Short-term/long-term Quality and grading systems used	Epidural steroid interventions	RCTs included			Author's conclusions
Abdi (2007) Chronic spinal pain Short-term = ≤6 weeks Long-term = ≥ 6 weeks Observational studies =AHRQ RCTs =Cochrane Review Group Levels of evidence= adapted from 6 studies	Interlaminar (lumbar) (controls=intramuscular, interspinous, saline, caudal, anaesthetic) Interlaminar (cervical) (Controls=aesthetic, neck muscle injections) Transforaminal (Lumbar) (Controls = anaesthetic, saline, trigger point injection, interspinous injection) Transforaminal (cervical) (no controls) Caudal (controls=epiduroscopy, lumbar injection, anaesthetic, saline)	**Interlaminar (lumbar)** Wilson-McDonald (2005) Arden (2005) Carette (1997) McGregor (2001) Pirbudack (2003) Snoek (1977) Cuckler (1985) Dilke (1973) Ridly (1988) Rogers (1992) Kraemer (1997)	**Interlaminar (cervical)** Castagnera (1994) Stav (1993) **Transforaminal (Lumbar)** Riew (2000) Ng Karppinen (2001/02) Vad (2002) Devulder (1999) Thomas (2002)	**Transforaminal (cervical)** Bush (1991) Cyteval (2004) Kolstad (2005) Lin (2006) **Caudal** Bush (1991) Mattews (1987) Helsa (1979) Revel (1996) Meadeb (2001)	**Interlaminar** In managing lumbar radicular pain with interlaminar lumbar epidural steroid injections, the level of evidence is *strong* for short-term relief and limited for long-term relief. In managing cervical radiculopathy with cervical interlaminar epidural steroid injections, the evidence was *moderate* for short-term improvement and long-term improvement. The evidence is indeterminate in the management of axial neck pain, axial low back pain, and lumbar spinal stenosis. **Transforaminal** The evidence for lumbar transforaminal epidural steroid injections in managing lumbar nerve root pain is *strong* for short-term and moderate for long-term improvement. The evidence for cervical transforaminal epidural steroid injections in managing cervical nerve root pain is *moderate* for short-term and long-term improvement. The evidence is *limited* in managing lumbar radicular pain in post-lumbar laminectomy syndrome. The evidence is indeterminate in managing axial low back pain, axial neck pain, and lumbar disc extrusions. **Caudal** The evidence of caudal epidural steroid injections with randomized trials and non-randomized reports is *strong* for short-term relief and *moderate* for long-term relief in managing chronic pain of lumbar radiculopathy and post-lumbar laminectomy syndrome. The evidence is *moderate* in managing chronic low back pain for short-term and long-term improvement.
Roberts (2009) Lumbosacral radicular pain Short-term = not defined Long-term = not defined Quality checklist modelled after the 2001 CONSORT Statement.	Transforaminal (controls =saline trigger point, anaesthetic, saline, interlaminar)	**Transforaminal vs control** Vad (2002) Devulder (1999) Riew (2000) Karppinen (2001) Ng (2005)		**Transforaminal vs interlaminar** Kolsi (2000) Thomas (2002) Ackerman (2007) Candido (2008)	There is *fair* evidence supporting transforaminal epidural steroid injections as superior to placebo for treating radicular symptoms. There is *good* evidence that transforaminal epidural steroid injections should be used as a surgery sparing intervention, and that transforaminal epidural steroid injections are superior to interlaminar ESIs (ILESIs) and caudal ESIs for radicular pain. In patients with sub-acute or chronic radicular symptoms, there is *good* evidence that a single transforaminal epidural steroid injection has similar efficacy as a single transforaminal injection of bupivacaine or saline

Systematic review/ Indications Short-term/long-term Quality and grading systems used	Epidural steroid interventions	RCTs included	Author's conclusions
Buenaventura (2009) Low back and lower extremity pain Short-term = ≤ 6 months Long-term = > 6 months Observational studies =AHRQ RCTs =Cochrane Review Group Grading recommendations =Guyatt	Transforaminal (Controls = saline, anaesthetic, trigger point injection, ganglia/pre-ganglia)	Karppinen (2001) Riew (2000,2006) Vad (2002) Jeong (2007)	The results of this systematic evaluation of lumbar transforaminal epidural injections showed that they have significant effect in relieving chronic pain of lumbar disc herniation and radiculitis with indicated evidence levels of Level II-1 to II-2 with a 1C/*strong recommendation.*
Benyamin (2009) Chronic neck pain Short-term = ≤ 6 months Long-term = > 6 months Observational studies =AHRQ RCTs =Cochrane Review Group Grading recommendation=Guyatt	Interlaminar Cervical (controls =anaesthetic, neck muscle injection, single injection versus continuous epidural)	Castagnera (1994) Stav (1993) Pasqualucci (2007)	The results of this systematic evaluation of cervical interlaminar epidural injections showed that they have a significant effect in relieving chronic intractable pain of cervical origin and also provide long-term relief with indicated evidence of Level II-1 with a 1C/*strong recommendation.*

Abdi et al (2007) "Epidural steroids in the management of chronic spinal pain: a systematic review"

In an update of an earlier (2005) systematic review of the effectiveness of epidural steroids for chronic spinal pain Abdi et al (2007) commented that, despite the publication of multiple systematic reviews and guidelines, a meta analysis, health technology assessments by insurers and local medical review policies, controversy continued regarding their effectiveness (Abdi et al., 2007).

The authors reported that the rationale for their update was that several important studies and complications had been reported since the previous (2005) systematic review. A flow chart showing the number of articles retrieved, reviewed and included in each category of interlaminar, transforaminal, and caudal techniques together with a breakdown of the types of studies was included Figure 4.11.

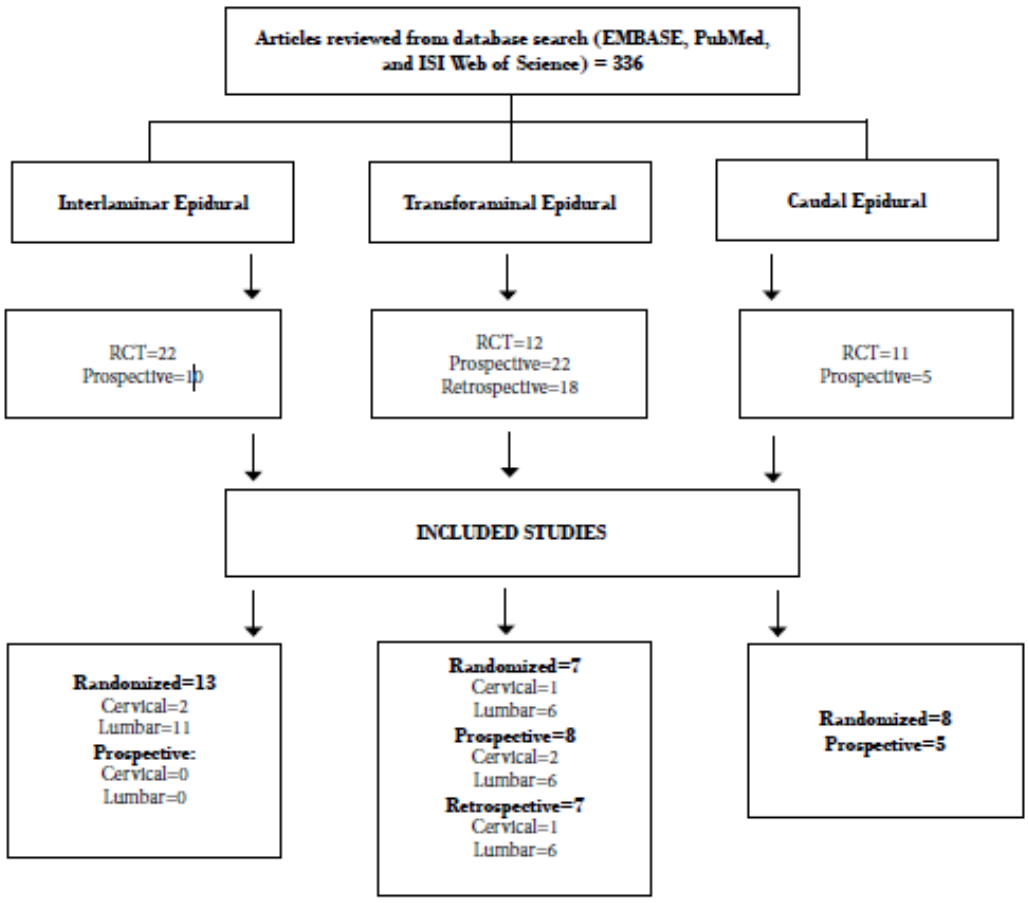


Figure 4.8. Systematic review flow chart (From: Abdi, S., S. Datta, et al. (2007). "Epidural steroids in the management of chronic spinal pain: a systematic review." Pain Physician 10(1): 185-212).

Following a systematic search of the literature and a review and quality evaluation by three of the authors, studies evaluating steroid injection in patient populations suffering *chronic* spinal pain for at least three months were submitted to a *best evidence review*.

The strength of the evidence was judged using the Agency for Health Care and Policy Research (AHCPR) rating schema (see methods section).

A study was judged to be positive if the authors concluded that epidural steroid injection was more effective than the reference treatment in randomised trials, or simply concluded that it was effective. Pain relief was described as "short-term" if it lasted six weeks or less and "long-term" if it lasted six weeks or more. The steroid preparations used varied and were delivered mixed with and without anaesthetics such as bupivacaine.

The best available evidence was reported to be determined as follows; where there were 10 or more RCTs lower level studies were not included in the evidence evaluation. However, it was not always clear that this procedure had been followed. For some of the sub-set analyses, discrepancies between the information in the text and the figures made it difficult to determine exactly which studies, in addition to RCTs, had formed the basis for the determination of the strength and level of the evidence.

A summary of the strength of the evidence for the different modes of delivery and pain presentations is given in Table 4.9, and followed by further details of the review findings.

Table 4.9. Summary of the strength of the evidence for different modes of delivery of steroid injection.

Delivery rout/patient pain group	RCTs	Short term	Long term
Interlaminar injections			
For patients with *lumbar radiculitis*	11	strong	limited
For patients with cervical pain and radiculopathy	2	moderate	moderate
Transforaminal injections			
For patients with lumbar disc herniation and radiculopathy	6	strong	moderate
For patients with axial neck pain, axial low back pain, and lumbar spinal stenosis/disc extrusions.	-	indeterminate	indeterminate
For patients undergoing cervical transforaminal injections for neck pain, radiculopathy, and herniated disc	0	moderate	moderate
Caudal epidural injection			
For patients with lumbar radiculopathy and post lumbar laminectomy syndrome	8	strong	moderate
For patient with chronic low back pain	-	moderate	moderate

Strong= Research-based evidence from at least 1 properly designed randomized, controlled trial; or research-based evidence from multiple properly designed studies of smaller size; or multiple low quality trials. Moderate = a) Evidence obtained from well-designed pseudorandomized controlled trials (alternate allocation or some other method); b) Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies, case-controlled studies, or interrupted time series with a control group); c) Evidence obtained from comparative studies with historical control ,two or more single-arm studies, or interrupted time series without a parallel control group. Limited= Evidence from well-designed, non-experimental studies from more than 1 centre or research group; or conflicting evidence with inconsistent findings in multiple trials.

Interlaminar epidural injections

For patients with *lumbar radiculitis,* 11 RCTs formed the evidence base.

- Eight studies were positive and three negative for short term pain relief, two studies were positive and nine negative for long-term pain relief.
- In managing lumbar radicular pain with interlaminar lumbar epidural steroid injections,
- the evidence was assessed as "strong" for short-term relief and "limited" for long-term pain relief.

For patients with *cervical pain and radiculopathy,* two RCTs formed the evidence base.

- Both RCTs were positive for short- and long-term pain relief
- In managing cervical radiculopathy with cervical interlaminar epidural steroid injections, the evidence was assessed as "moderate".

Note: it was not clear why the evidence was determined to be "moderate", it must be assumed that the RCTs were considered to be of low quality.

Transforaminal epidural injections

For patients with *lumbar disc herniation and radiculopathy*, six RCTs and five non-randomised studies formed the evidence base.

- Four RCTs were positive and two negative for short term pain relief, four RCTs were positive and negative for long-term pain relief.
- Five non-randomised studies were positive for short-term relief, four non-randomised studies were positive and one negative for long-term relief.
- In managing lumbar radicular pain with lumbar transforaminal epidural steroid injections the evidence was assessed to be "strong" for short-term and "moderate" for long-term pain relief.
- The evidence is indeterminate in the management of axial neck pain, axial low back pain, and lumbar spinal stenosis/disc extrusions.\

For patients undergoing *cervical* transforaminal injections for neck pain, radiculopathy, and herniated disc, four non-randomised studies formed the evidence base.

- Four non-randomised studies were positive for both short and long-term pain relief
- In managing *cervical nerve root pain* the evidence was assessed to be "moderate"

Caudal epidural injection

For patients with a variety of pain presentations, including chronic low back and leg pain, sciatica, and nerve root comprise undergoing caudal epidural injection, eight RCTs and five non-randomised studies formed the evidence base for effectiveness.

- Five RCTs were positive and three negative for short-tem pain relief, four RCTs were positive and four negative for long-term pain relief.
- Five non-randomised studies were positive for both long and short-term pain relief.
- In managing chronic pain arising from lumbar radiculopathy and post lumbar laminectomy syndrome, the evidence for caudal epidural steroid injections was assessed as “strong” for short-tem pain relief and “moderate” for long-term relief.
- The evidence was considered to be moderate in managing chronic low back pain for short-term and long-term improvement.

The most common and worrying complications of caudal, interlaminar, and transforaminal epidural injections were reported to be those related to the needle placement and drug administration and included;

- dural puncture,
- spinal cord trauma,
- infecradiol;oion,
- hematoma formation,
- abscess formation,
- subdural injection,
- intracranial air injection,
- epidural
- lipomatosis,
- pneumothorax,
- nerve damage,
- headache,
- death,
- brain damage,
- increased intracranial pressure,
- intravascular injection,
- vascular injury,
- cerebral vascular or pulmonary embolus,
- effects of steroids

Spinal cord trauma and spinal cord or epidural hematoma formation were regarded as catastrophic complications that were rarely seen following interventional procedures in the cervical spine, thoracic spine, or upper lumbar spine. Side effects related to the administration of steroids were attributed either to the chemistry or to the pharmacology of the steroids.

The major theoretical complications of corticosteroid administration were reported to include suppression of pituitary-adrenal axis, hypercorticism, Cushing's syndrome, osteoporosis, avascular necrosis of bone, steroid myopathy, epidural lipomatosis, weight gain, fluid retention, and hyperglycemia. However, the most commonly used steroids in neural blockade in the United States, (methylprednisolone acetate, triamcinolone acetonide, betamethasone acetate, and phosphate mixture) were all noted to have all been shown to be safe at epidural therapeutic doses in both clinical and experimental studies. It was also noted that the use of fluoroscopy was a potential problem with damage to eyes, skin, and gonads from exposure to ionizing radiation.

Comment

This was an update of an earlier systematic review by the same author which was undertaken because of the publications of "significant" new studies. The impact of these studies on the assessment of the evidence and their significance was not reported and it was not made clear how the conclusions based on the updated evidence differed from the earlier assessment. The RCTs included in the review varied in their robustness. Five studies were prospective, randomized, and double-blinded; three of these studies incorporated a placebo-control group. The other two trials compared transforaminal with interlaminar corticosteroid injections without a placebo-control group. The sixth study could not blind its subjects, who were randomized to transforaminal epidural steroid injections (TFESIs) or trigger point injections (TPIs). Inconsistencies were noted in the reporting of the evidence assessments in the text of the 2007 publication.

Benyamin et al (2009) "Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain"

The objective of this systematic review was to evaluate the effect of cervical interlaminar epidural injections in managing various types of chronic neck and upper extremity pain emanating as a result of cervical spine pathology. The primary outcome measure was pain relief (short-term relief = up to 6 months and long-term > 6 months). Secondary outcome measures were improvement in functional status, psychological status, return to work, and reduction in opioid intake.

The authors noted that while cervical epidural injections were commonly used for managing chronic neck pain in the United States, the literature supporting the practice was scant and no systematic review dedicated to the evaluation of the intervention been performed in the past.

The review focused on randomized trials, observational studies and reports of complications. The population of interest was patients suffering chronic mechanical or whiplash-related neck pain with or without radicular findings for at least three months The quality of RCTs was assessed using the modified Cochrane review criteria with weighted scores, the quality of observational studies was assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria. Only the studies scoring at least 50 of 100 on weighted scoring criteria and fulfilling set clinical relevance criteria were utilized for analysis. A

study was judged to be positive if the epidural injection therapy was clinically relevant and effective*, either with a placebo control or active control* in randomized trials.

Following a systematic search of the literature three randomized or double-blind trials and 17 observational studies were identified. Only the three RCTs met the quality and clinical relevance criteria for inclusion in the analysis, only one of the trials was recent. Of the three randomized trials evaluating cervical interlaminar epidural steroid injections, all showed positive results for short-term relief, two were positive for long-term relief; the results of long-term relief were not available for one study.

The indicated evidence for cervical interlaminar epidural steroid injections was reported as Level II-1 based on U.S. Preventive Services Task Force (USPSTF) criteria (see methods section) with a grading recommendation (based on Guyatt's criteria) of 1C i.e. a strong recommendation, low-quality or very low-quality evidence, with benefits clearly outweighing risk and burdens, or vice versa (see methods section).

Comment

It is not clear why a level of evidence of II-1[162] was assigned for three RCTs . The Grading of recommendations used was designed for guidelines and takes into *account clinical experience and expert opinion*; it may be argued that it is inappropriate to use it to evaluate RCTs.

Buenaventura et al (2009) "Systematic review of therapeutic lumbar transforaminal epidural steroid injections"

Buenaventura et al (2009) also published a systematic review of therapeutic lumbar transforaminal epidural steroid injections in 2009. The objective of the review was to evaluate the effect of TFESIs in managing low-back and leg pain (sciatica). The authors noted that there had been a number of previous systematic reviews and guidelines[163] reporting on the effectiveness of lumbar TFESIs reporting conflicting conclusions and recommendations and suggesting that;

"neither the effectiveness nor the superiority of transforaminal epidural injections has been proven clearly. Further, the underlying mechanism of action of epidurally administered steroid and local anaesthetic injections is still not well understood".

Furthermore, recent studies of interforaminal injection of oxygen-ozone were reported to have shown better relief than interforaminal injection of steroids[164].

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[162] II-1 =evidence obtained from well-designed controlled trials without randomization.

[163] Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4: European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 2006; 15:S192-S300. Abdi S, Datta S, Trescot AM, Schultz DM et al. Epidural steroids in the management of chronic spinal pain: A systematic review. Pain Physician 2007; 10:185-212. Boswell MV, Trescot AM, Datta S, et al. Interventional techniques: Evidencebased practice guidelines in the management of chronic spinal pain. Pain Physician 2007; 10:7-111. DePalma MJ, Bhargava A, Slipman CW. A critical appraisal of the evidence for selective nerve root injection in the treatment of lumbosacral radiculopathy. Arch Phys Med Rehabil 2005; 86:1477-1483. American College of Occupational and Environmental Medicine. Low Back Disorders Chapter. In: Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery of Workers, Second Edition. American College of Occupational and Environmental Medicine, Elk Grove Village, 2007. Manchikanti L, Singh V, Derby R, Helm S, Trescot AM, Staats PS, Prager JP, Hirsch JA. Review of occupational medicine practice guidelines for interventional pain management and potential implications. Pain Physician 2008; 11:271-289. Manchikanti L, Singh V, Derby R, Schultz DM, Benyamin RM, Prager JP, Hirsch JA. Reassessment of evidence synthesis of occupational medicine practice guidelines for interventional pain management. Pain Physician 2008; 11:393- 482.

[164] Gallucci M, Limbucci N, Zugaro L, Barile A, Stavroulis E, Ricci A, Galzio R, Masciocchi C. Sciatica: Treatment with intradiscal and intraforaminal injections of steroid and oxygen-ozone versus steroid only. Radiology 2007; 242:907- 913. Bonetti M, Fontana A, Cotticelli B, Volta GD, Guindani M, Leonardi M. Intraforaminal O(2)-O(3) versus periradicular steroidal infiltrations in lower back pain: Randomized controlled study. AJNR Am J Neuroradiol 2005; 26:996- 1000.

The systematic review was undertaken to evaluate transforaminal lumbar epidurals injections *with or without steroids.* The search identified 42 studies (11 RCTS and 31 observational studies) for review. Pain relief ≤ 6 months was defined as "short-term" relief; pain relief > 6 months was defined as "long-term" relief. In the randomized trials, a study was judged to be positive if the transforaminal epidural injection therapy was clinically relevant and effective, either with a placebo control or active control. The systems for grading recommendations and assessment of the quality of the evidence which underpinned them were the same as those used by Benyamin et al (2009).

Following a quality and clinical relevance assessment four RCTs were included in a best evidence synthesis (Jeong et al., 2007; Karppinen et al., 2001; Riew et al., 2006; Riew et al., 2000; Vad et al., 2002). All but one of these RCTs (Jeong et al., 2007) was also reviewed by Roberts et al (2009). The additional RCT (Jeong et al., 2007) essentially compared transforaminal epidural injections to themselves and only altered the level (preganglionic vs. ganglionic) that was injected. The question the authors sought to answer was where best to inject; at the site where the disc is contacting the presumed affected nerve or at the foramen where that nerve exits? Positive short-term relief was observed with both techniques.

All four randomized trials evaluating lumbar transforaminal epidural steroid injections showed positive results for short-term relief and two were positive for long-term relief; the results of long-term relief were not available for one study the other was negative. The indicated level of evidence for lumbar transforaminal epidural steroid injections was reported as U.S. Preventive Services Task Force (USPSTF) Level II-1 for short-term pain relief (evidence obtained from well-designed controlled trials without randomization) and USPSTF Level II-2 for long-term relief in managing chronic low back and lumbar nerve root pain (evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group). The overall recommendation for lumbar transforaminal epidurals based on this evidence was **1C** i.e. strong recommendation, moderate or low quality evidence, with a caveat that the recommendation could change if higher quality evidence became available in the future (adapted from Guyatt et al. (2006), see methods section).

Roberts et al (2009) "Efficacy of lumbosacral transforaminal epidural steroid injections: a systematic review."

Roberts et al (2009) reported on the effectiveness lumbosacral transforaminal epidural steroid injections (TFESI) . Clinically based outcome measures were assessed. The objective of the study was to review the best available evidence relating to the use of TFESIs in the treatment of radicular pain.

The authors posed three questions:

A. Are transforaminal epidural steroid injections more effective than interlaminar epidural steroid injections for radicular pain?
B. Are transforaminal epidural steroid injections more effective than placebo?
C. Are transforaminal epidural steroid injections a surgery-sparing intervention?

Following a systematic search of the literature for relevant RCTs of fluoroscopically guided transforaminal epidural steroid injections eleven studies were identified as suitable for review. Each

study was then assigned a level of evidence (I-V) based on criteria set by Wright (2005)[165] for therapeutic studies (see methods section).

Following a quality assessment, nine studies were eligible for a "best evidence" review. Five RCTs compared transforaminal epidural steroid injections to a control intervention and four RCTs compared the effectiveness of transforaminal epidural steroid injections to interlaminar epidural steroid injections. A grade of recommendation (A, B, C, or I) was assigned to each statement based on the grades of recommendation set by Wright et al in 2005. The criteria for a "positive result" were not clear.

Transforaminal epidural steroid injection (TFESI) vs. control

Three trials were considered to be of high quality[166] (Level 1) and two trials were considered to be of poorer[167] (Level II) quality. The controls used in the trials varied and included;

- steroid
- bupivacaine alone
- saline transforaminal injections
- paraspinal trigger point injections of saline

The results and recommendation of the review are summarised below.

- Only the trial employing saline trigger point injections was considered to be placebo controlled[168]. In this trial 1-3 TFESIs with lignocaine and betamethasone was found to be superior to paraspinal trigger point injections of saline in patients with radicular symptoms from herniated nucleus pulposus for both short- and long-term (follow-up 1.4 years) pain reduction and disability [169]
- Grade of recommendation = B (Fair evidence for or against recommending intervention i.e., Level II or III studies with consistent findings)

The remaining four trials compared transforaminal epidural steroid injection (TFESI) to transforaminal injection (TFI) of another substance. Three of these trials were considered to be good quality RCTs providing A grade evidence.

The recommendations from studies comparing TFESI to TFI of another substance are summarised below.

- In patients with radicular pain secondary to herniated nucleus pulposus or spinal stenosis who are surgical candidates, *TFESI is a surgery sparing intervention* when compared to TFI of bupivacaine[170]. Grade of Recommendation = A (Good evidence for or against recommending intervention i.e., Level I studies with consistent findings).

[165] Wright JG. Levels of evidence and grades of recommendation. AAOS Bull 2005;5:18-19. http://www5.aaos.org/oko/ebp/EBP001/suppPDFs/OKO_EBP001_S8.pdf
[166] Randomized controlled trials -with a significant difference or with no significant difference but narrow confidence intervals
[167] eg, <80% follow-up, low power, poor randomization technique, unblinded evaluators
[168] A therapeutic effect has been demonstrated with the epidural injection of saline
[169] Vad VB, et al. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. Spine 2002;27:11-16.
[170] Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. J Bone Joint Surg Am 2000;82-A:1589-1593.

- In patients with sub-acute to chronic radicular symptoms, a single TFI of bupivacaine or saline alone *has similar effects* on both short-term and long-term pain and disability as a single TFESI[171]. Grade of Recommendation = A (Good evidence for or against recommending intervention i.e., Level I studies with consistent findings).

- In patients with chronic nerve fibrosis and failed back surgery syndrome, pain relief *is similar* with a TFI of bupivacaine and hyaluronidase, a TFI of bupivacaine and methylprednisolone, and a TFI of bupivacaine, hyaluronidase, and methylprednisolone[172]. Grade of Recommendation = B (Fair evidence for or against recommending intervention i.e., Level II or III studies with consistent findings).

Transforaminal epidural steroid injection (TFESI) vs interlaminar epidural steroid injections (ILESI)

Roberts et al (2009) noted that no placebo controlled trials evaluating the efficacy of fluoroscopically guided lumbar ILESIs or caudal epidural steroid injections (ESIs) had been published and no studies comparing the efficacy of *blind* injections with *fluoroscopically guided* injections had been found. Despite this, lumbar interlaminar epidural administration of steroids, both with and without fluoroscopic guidance, continued to be a common practice.

Four trials comparing TFESI and ILESI were identified[173] , one was considered to be a good quality RCT, the remaining three were considered to be poor quality RCTs.

- In patients with S1 radicular pain from an L5-S1 herniated nucleus pulposus, TFESI provided superior pain relief compared with fluoroscopically guided ILESI and caudal ESI. Grade of Recommendation: A (Good evidence for or against recommending intervention i.e.,Level I studies with consistent findings).
- In patients with radicular pain from herniated nucleus pulposus, TFESI was superior to blind ILESI for both short-term and long-term pain and function. Grade of Recommendation: B (Fair evidence for or against recommending intervention i.e.,Level II or III studies with consistent findings).
- In patients with low back pain and unilateral radiculopathy, parasagittal ILESI had similar effects on both short term and long-term pain compared with a "posterior" TFESI. Grade of Recommendation: B (Fair evidence for or against recommending intervention i.e., Level II or III studies with consistent findings).

[171] Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: a randomized controlled trial. Spine 2001;26:1059 1067. Ng L, Chaudhary N, Sell P. The efficacy of corticosteroids in periradicular infiltration for chronic radicular pain: A randomized, doubleblind, controlled trial. Spine 2005;30:857-862.
[172] Devulder J. Transforaminal nerve root sleeve injection with corticosteroids, hyaluronidase, and local anesthetic in the failed back surgery syndrome. J Spinal Disord 1998;11:151-154.
[173] Kolsi I, Delecrin J, Berthelot JM, et al. Efficacy of nerve root versus interspinous injections of glucocorticoids in the treatment of diskrelatedsciatica. A pilot, prospective, randomized, double-blind study. Joint Bone Spine 2000;67:113-118. Thomas E, Cyteval C, Abiad L, et al. Efficacy of transforaminal versus interspinous corticosteroid injection in discal radiculalgia—A prospective, randomised, double-blind study. Clin Rheumatol 2003;22:299- 304. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. Anesth Analg 2007;104:1217-1222. Candido KD, Raghavendra MS, Chinthagada M, Badiee S, Trepashko DW. A prospective evaluation of iodinated contrast flow patterns with fluoroscopically guided lumbar epidural steroid injections: The lateral parasagittal interlaminar epidural approach versus the transforaminal epidural approach. Anesth Analg 2008;106:638-644.

A number of general observations were also made. In studies favouring TFESI, more than one injection was allowed if relief with the initial injection was temporary or partial. In the negative studies only one injection was allowed, for example of the four Level I studies reviewed, two were positive with more than one injection and two were negative with only one injection allowed. One study revealed a need for fewer injections when the TFESI approach was used compared with the ILESI or caudal approach.

The authors of the systematic review considered that the greatest measurable effect of transforaminal epidural steroids might be that they are a *surgery-sparing* intervention for patients with radicular pain. It was also argued that since the natural history of lumbar disk herniation was generally favourable and symptomatic improvement tended to occur more rapidly than improvements seen on imaging studies, if the initial period of pain and incapacity could be treated, surgery may not be necessary in many cases of lumbosacral radicular pain.

Roberts et al (2009) also noted that the ideal route of an epidural steroid injection for the treatment of radicular pain was often questioned. Only two RCTs were identified that compared TFESIs with other fluoroscopically guided approaches: Ackerman et al (2007) and Kolsi et al (2000). The strongest support for the use of TFESIs over fluoroscopically guided ILESIs or caudal ESIs was reported from the Ackerman study which provided Level I evidence that the TFESI approach was superior for both short -term and long-term pain relief. The Kolsi study (Level II evidence) revealed no differences between TFESI and ILESI for short-term pain relief and the authors concluded that of the current literature available, stronger evidence supported the use of TFESI.

In recommendations for future studies, it was noted that a number of questions remained unanswered and that despite growing evidence in favour of TFESIs from RCTs, further studies were needed to shape future best practice. In particular high quality studies were required to determine

- the ideal number of injections required to treat any given patient
- the ideal volume and type of medication injected
- differences in cost, side effects, and risks, in addition to efficacy of the injectate
- differences in the rate and type of complications between the different injection approaches.

Further placebo-controlled blinded studies were required to eliminate the therapeutic effect of epidural saline or local anaesthetic, and, because of the extreme variations in the pathology of patients that undergo epidural steroid injections, future efficacy studies should involve the most homogenous patient groups possible.

Author's conclusions

"There is fair evidence supporting TFESIs as superior to placebo for treating radicular symptoms. There is good evidence that TFESIs should be used as a surgery sparing intervention, and that TFESIs are superior to interlaminar ESIs (ILESIs) and caudal ESIs for radicular pain. In patients with subacute or chronic radicular symptoms, there is good evidence that a single TFESI has similar efficacy as a single transforaminal injection of bupivacaine or saline."

Conn et al (2009) "Efficacy of lumbosacral transforaminal epidural steroid injections: a systematic review."

Conn et al (2009) published a systematic review of caudal epidural injections with or without steroids in the management of chronic pain secondary to lumbar disc herniation or radiculitis, post-lumbar laminectomy syndrome, spinal stenosis, and discogenic pain without disc herniation or radiculitis.

The objective was to evaluate the effect of caudal epidural injections with or without steroids in managing these conditions. The review was undertaken to try to resolve the multitude of conflicting opinions and controversy relating to the clinical effectiveness of caudal epidural steroid injections.

The authors prefaced their review with the following observations;

"Caudal epidurals are considered as the safest and easiest, with minimal risk of inadvertent dural puncture, even though requiring relatively high volumes. They have also been shown to be significantly effective compared to interlaminar epidural injections. Even then, controversy continues with regards to the medical necessity and indications of lumbar epidural injections. Multiple systematic reviews, guidelines, health technology assessments, and local medical review policies and coverage decisions, have been published. The evidence is highly variable from indeterminate to strong in various publications. Further, the benefit and most effective route of administration for epidural steroids remain controversial."

The quality of RCTs was assessed using the Cochrane Musculoskeletal Review Group Criteria, the quality of observational studies was assesses using the Agency for Healthcare Research and Quality (AHRQ) criteria. The level of evidence was classified as Level I, II, or III based on the U.S. Preventive Services Task Force (USPSTF) criteria (see methods section). Clinical relevance of the included studies was evaluated according to five questions recommended by the Cochrane Back Review Group. The primary outcome measure was pain relief (short-term relief = up to 6 months and long-term ≥ 6 months). Secondary outcome measures of improvement in functional status, psychological status, return to work, and reduction in opioid intake were utilized. Following a systematic search of the literature for eligible studies 18 RCTs and 20 observational studies were assessed for inclusion in an analysis. The characteristics and findings of the review are summarised in Table 4.9.

Table 4.10. Summary of the evidence for caudal steroid injection for different types of chronic lumbar pain from Conn et al (2009).

Systematic review/ Long-term/ short-term Assessment tools	Indications	ESI Interventions	RCTs included		Author's conclusions
Conn (2009) Short-term = ≤ 6 months Long-term = > 6 months Observational studies =AHRQ RCTs =Cochrane Review Group criteria Evidence levels=USPSTF	Disc herniation and radiculitis	Caudal	Manchikanti (2008) Dashfield (2005) Bush (1991)	Mathews (1987) Hesla (1979) Breivik (1976)	Level I evidence for short- and long-term relief of chronic pain secondary to disc herniation or radiculitis and discogenic pain without disc herniation or radiculitis. Level II-1 or II-2 for caudal epidural injections in managing chronic pain of post lumbar laminectomy syndrome and spinal stenosis. This systematic review provides information that caudal epidural injections are effective ***and there may not be any significant difference with the addition of steroids.***
	Post surgery syndrome	Caudal	Manchikanti (2008) Revel (1996) Helsa (1979)		
	Spinal stenosis	Caudal	Manchikanti (2008)		
	Discogenic pain without herniation or radiculitis	Caudal	Manchikanti (2008) Manchikanti (2001)		

Disc herniation and radiculitis

Six RCTs provided evidence for analysis, five of these were judged to be positive for short-term relief and four reported positive results with long-term follow-up of more than 6 months. The results in two *studies utilizing fluoroscopy were superior to blind epidural injections.*

Post surgery syndrome

Three RCTs provided the evidence for analysis. All of them were shown to be positive for short and long-term relief.

Spinal stenosis

There was one randomized trial evaluating the role of caudal epidural. Two observational studies also met the inclusion criteria. The one randomized trial evaluating spinal stenosis with or without steroids with local anaesthetic showed positive results for short- and long-term relief. Observational studies also showed positive short-term and long-term improvement.

Discogenic pain (predominant low back pain without disc herniation)

One randomized trial and two observational studies met inclusion criteria. All three had the same leading author. The RCT reported positive results for both short- and long-term pain relief, the

observational studies both reported positive results for short term relief. In the one observational study where long-term results were available they were positive.

Authors comments and conclusions

In this review Conn et al (2009) posed a different question to the other reviews. The authors were interested in the effect of caudal epidural injections *per se* in modulating a number of painful spinal conditions. The authors concluded that the evidence, which was based on RCTs and observational studies, was variable but positive for the four conditions that were evaluated and that;

"This systematic review provides information that caudal epidural injections are effective and there may not be any significant difference with the addition of steroids."

Conn et al (2009) noted that results of their systematic review were similar to some previous reviews and guideline syntheses, but were in contradiction to other reviews. Thus while some previous reviews evaluated the evidence based on the route of administration others combed multiple conditions and multiple techniques into one category, according to Conn et al (2009) "invariably leading to wrong conclusions".

Conn et al (2009) also observed that those systematic reviews of the same evidence, evaluated by different authors, had provided different results. Factors including poor quality evidence assessment, inappropriate evidence synthesis and conflicts of interest were cited as possible factors in the discrepancies.

Summary: systematic reviews

Between them these systematic reviews appeared to present positive evidence of effectiveness for virtually *all of the routes of delivery and major pain conditions reviewed,* Table 4.10.

Table 4.11. Summary of evidence assessments relating to the effectiveness of local steroid injections for various lumbar and cervical conditions

Indication	Transforaminal	Interlaminar	Caudal
Lumbarsacral radiculopathy	• Strong for short-term, moderate for long term (Abdi et al., 2007) • Fair evidence that they are superior to placebo (Roberts 2009) • Good evidence that they are surgery sparing (Roberts 2009). • Good evidence that they are superior to interlaminar and caudal injections for radicular pain (Roberts 2009) • Good evidence that a single injection of steroid has similar efficacy to that of aesthetic or saline (Roberts 2009).	• Strong for short-term and limited for long-term relief (Abdi et al., 2007).	• Strong for short-term and moderate for long-term (Abdi et al., 2007). • Level I evidence for short- and long-term relief of chronic pain secondary to disc herniation or radiculitis and discogenic pain without disc herniation or radiculitis (Conn et al 2009).
Cervical nerve root pain	• Moderate for short-term and long-term (Abdi 2007)	• Moderate for short-term and long-term relief for cervical radiculopathy (Abdi 2007)	
Post-lumbar laminectomy syndrome	• Limited (Abdi 2007)		• Strong for short-term relief and moderate for long-term relief (Abdi 2007). • Level II-1 or II-2 for caudal epidural injections in managing chronic pain of post lumbar laminectomy syndrome and spinal stenosis (Conn et al 2009)
Axial low back pain, axial neck pain, lumbar disc extrusions	• Indeterminate (Abdi 2007) • Significant effect in relieving chronic pain of lumbar disc herniation and radiculitis (Buenaventura 2009)	• Indeterminate (Abdi 2007) • Significant effect in relieving chronic intractable cervical pain and provide long-term relief (Benyamin 2009)	• Moderate for chronic low back pain for short and long-term improvement (Abdi 2007)

A number of points are worth highlighting.

- When a true placebo was employed as a control, the evidence of effectiveness was weaker (though still positive) than when *active controls* were employed (S. T. Roberts et al., 2009).
- A surgery sparing role for transforaminal lumbar steroid injections was supported for some patient populations (S. T. Roberts et al., 2009).
- For some types of pain (e.g. disc herniation pain and radiculopathy) a transforaminal approach appeared to be superior to other approaches.

- Ongoing controversy and conflicting evidence relating to the effectiveness of local steroid injections for painful spinal conditions has prompted the most recent reviews to focus on the effectiveness of epidural injections *per se. Two reviews* (Conn et al., 2009; S. T. Roberts et al., 2009) *presented evidence supporting the thesis that lumbar and caudal epidural injections with or without steroids gave effective or similar pain relief.*

Comparison with the 2005 IPM review of effectiveness

Compared with the assessment of the evidence made in 2005 (New Zealand Accident Compensation Corporation, 2005, 2006), the more recent evidence presented in reviews published between 2005 and 2011, appeared to support, strengthen and in some instance extended the evidence of effectiveness of local steroid injections for painful spinal conditions. In particular, the additional evidence appeared to suggest that these injections may provide longer relief than previously reported (Abdi et al., 2007), although the time periods varied from study to study. There was some support for the use of these injections for chronic low back pain (Abdi et al., 2007). Support for the use of local epidural steroid injection for cervical pain was also reported (Abdi et al., 2007) and evidence for effectiveness of the different delivery routes (e.g. interlaminar and caudal routes) was advanced (Abdi et al., 2007; Benyamin et al., 2009; Conn et al., 2009).

Limitations

A meaningful comparative assessment of these results was hindered by a number of difficulties. The evidence reviewed in the various studies was evaluated using *different quality assessment and recommendation grading tools* and the reported strength of the evidence in favour of local steroid injections varied between reviews. Moreover, a number of confusing or conflicting statements relating to the evidence were apparent, and it was not always clear that the assessment tools used were being correctly applied or that the authors had specific training in their use and application.

In some reviews, trials in which epidural injections were carried out "blind" were included in assessments with studies using the more accurate fluoroscopically guided delivery method. In some reviews studies reporting on different routes of injection were combined and in all virtually all of the studies reviewed the treated patient populations were heterogeneous.

There was also variation in what was considered to be a "positive" result for a given intervention; in one review criteria for a positive result were not reported. Studies with varying amounts of injectate and number of injections were also combined and/or compared.

There were other methodological weaknesses. These reviews focussed almost exclusively on RCTs in "best evidence" reviews. Whilst on the surface this would appear to be laudable, the controls used in the RCTs assessed in each review were heterogeneous. For example, Abdi et al (2007) summarised evidence for transforaminal lumbar epidural steroid injections for lumbar nerve root pain from RCTs with controls including both different types of injectants and different types of injections. Moreover, many of the RCTs were considered to be of poor quality due to (unavoidable) lack of blinding.

One of the main difficulties of this review of epidural steroid injections was the lack of consensus relating to what constituted a suitable control against which the effectiveness of epidural steroid

injections could be assessed. Roberts et al (2009) argued that while logistically difficult, a randomised placebo-controlled blinded study where the placebo comprised a sham injection (rather than epidural saline injection) was the ideal test.

Another difficulty was the limitations imposed by the brief. This together with time and resource restrictions made it impracticable to independently examine and evaluate all of the eligible primary research studies to achieve a single uniform synthesis and grading of the evidence to answer specific questions.

In the evidence reviewed here, the answer to the question, "Does local epidural injection of steroid moderate the effect of discogenic and related pain?" remains unclear and appears to depend on what is considered to be sound or appropriate evidence of effectiveness for injection therapies. Moreover, recent reviews suggest that the key question may be "Do epidural injections *per se* moderate discogenic and related pain? The answer may then relate to the size and clinical significance of the effect obtained from different injectants their relative safety, convenience and cost.

Additional guidelines for the use of epidural steroid injections (2005 to 2011).

Two American guidelines were identified that published recommendations for the use of epidural steroid injections (Armon et al., 2007; ICSI, 2010), however, it should be noted that the search of the grey literature for relevant guidelines was not exhaustive (see methods section).

American Academy of Neurology (Armon et al., 2007)

In an assessment of use of epidural steroid injections to treat radicular lumbosacral pain for the American Academy of Neurology (AAN) Armon et al (2007) assessed the use of epidural steroid injections to treat radicular lumbosacral pain.

Following a systematic search of the literature for *placebo-controlled, double-blind RCTs*[174]*,* four eligible studies were identified. These four studies and the two highest quality studies from a review by the Technology Assessment Committee of the Institute of Clinical systems Improvement (ICSI, 2004) which focused on fluoroscopically guided, transforaminal epidural steroid injections in radicular lumbar pain were compared and assessed.

The *four placebo-controlled, double-blind* RCTs identified by the study search strategy were published between 1985 and 2000 and were considered in the 2005 IPM review. The two additional RCTs (from the ICSI 2004 review) were included in four systematic reviews described above (Abdi et al., 2007; Buenaventura et al., 2009; DePalma & Bhargava, 2006; S. T. Roberts et al., 2009).

Thus this guideline (Armon et al., 2007) contributed no new evidence or information, and it has not been considered in detail further. However, its recommendations are worth noting since they are at variance with other reviews and guidelines and stimulated lively debate.

"Epidural steroid injections may result in some improvement in radicular lumbosacral pain when determined between 2 and 6 weeks following the injection, compared to control treatment (Level C, Class

[174] The methods process of the AAN process is described in detail on the website (http://www.aan.com/go/practice/guidelines) and does not include expert opinion or consensus.

I–III evidence). The average magnitude of effect is small, and the generalizability of the observation is limited by the small number of studies, limited to highly selected patient populations, the few techniques and doses studied, and variable comparison treatments. In general, epidural steroid injections for radicular lumbosacral pain have shown no impact on average impairment of function, on need for surgery, or on long-term pain relief beyond 3 months. Their routine use for these indications is not recommended (Level B, Class I–III evidence)."

A criticism of the Armon (2007) publication is also worth noting. Manchikanti (CEO American Society of Interventional Pain Physicians) et al (2007)[175] in the context of selection bias commented that:

"Armon et al only included four studies considered to have met the predetermined inclusion criteria, although previous studies have included larger numbers of randomized trials in systematic evaluations including the Cochrane review[176] *and European guidelines177. For these reasons, the report by Armon et al may negatively affect the successful conduct of interventional pain management."*

These statements serve to illustrate some of the differences of opinion and interpretation of the evidence that abounds in this area. It should be noted that in response to the ongoing confusion and debate many authors have called for higher quality randomised controlled trials and in particular placebo controlled blinded trials in the hope of establishing stronger, more concrete evidence of effectiveness.

Based on the available evidence, the American Academy of Neurology guideline reported by Armon et al (2007) made the following statements:

- Epidural steroid injections may result in some improvement in radicular lumbosacral pain.
- When assessed between two and 6 weeks following the injection, compared to control
- treatments (Level C, Class I-III evidence). Their routine use for these indications is not recommended (Level B, Class I-III evidence).
- There is insufficient evidence to make any recommendation for the use of epidural
- steroid injections to treat radicular cervical pain (Level U).

Recommendations relating to different types of epidural steroid injection were not included.

The Institute for Clinical Systems Improvement (ICSI) 2010[178]

In November 2010 the ICSI published the 14th edition of its Adult Low Back Pain Guideline (ICSI, 2010). The guideline made the following key points:

- Successful epidural steroid injections may allow patients to advance in a conservative
- treatment program.

[175] Manchikanti L,Boswell M, Giordano J, Kaplan E. Use of epidural steroid injections to treat radicular lumbosacral pain. Neurology 15th July 2007.
[176] Nelemans PJ, Debie RA, DeVet HC, Sturmans F. Injection therapy for subacute and chronic benign low back pain. Spine 2001; 26:501-515.
[177] Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F., et al. Chapter 4: European guidelines for the management of chronic nonspecific low back pain. Eur Spine J 2006; 15:S192-S300.
[178] http://www.icsi.org/low_back_pain/adult_low_back_pain__8.html

- That epidural steroid injections should be performed under fluoroscopy or CT.
- Epidural steroid injections should only be considered after an initial appropriate conservative treatment program has failed.

The guideline noted that the goal of epidural steroid injections in patients with back and leg pain and symptomatic lumbar spinal stenosis or a herniated disc was pain control and functional improvement. It advised that injections should be performed under fluoroscopy and with contrast in order to deliver cortisone close to the disc herniation, area of stenosis, or nerve root impingement as determined by MRI or CT, and with as little morbidity as possible.

In the case of stenosis it considered that an adjacent segment or an alternative approach (interlaminar versus transforaminal) may be needed to deliver medication to the appropriate level. The guideline also noted that failure of treatment may result from a failure to deliver medications to the treatment field *or* clinical unresponsiveness to catabolic steroid preparations.

It was further noted that *no study had shown a clear advantage* for;

- one approach (interlaminar, caudal or transforaminal)
- one type of cortisone
- a particular volume of injectate.

However, this statement appeared to be made on the basis of two narrative reviews (Cannon & Aprill, 2000; McLain, Kapural, & Mekhail, 2005).

Evidence was quoted from several studies including a meta-analysis (Wilson-MacDonald, Burt, Griffin, & Glynn, 2005) and an RCT (Karppinen et al., 2001), that *a single* epidural injection could afford short-term pain relief. Limited evidence was found in two RCTs (Buttermann, 2004; Riew et al., 2000) to support *one or more* epidural injections to control pain and advance appropriate conservative therapy in an attempt to avoid or decrease the incidence of surgical intervention.

The guidelines concluded that;

"Based on limited data, the results appear promising. However, at this time there is insufficient evidence for the efficacy of epidural steroid injections. Only consider epidural steroid injections after initial appropriate conservative treatment program has failed. Successful epidural steroid injections may allow patients to advance in a conservative treatment program. Patients should be made aware of the general risks of short-term and long-term use of steroids."

Comment

The recommendations made by these guidelines published in 2010 are generally more negative and/or conservative than those made by the authors of the systematic reviews reported above. In some instances they appear to contradict the findings of one or more of these systematic reviews. However, it should be noted the search for pain guidelines was not exhaustive and guidelines produced by other groups may differ in their recommendations

Summary and conclusions: Pain generation

In *pain medicine*, diagnostic procedures are used to either identify the source of pain or to determine the cause of pain; some diagnostic interventions are used to determine the mechanism of the pain.

In *interventional pain management (IPM)*, many of these diagnostic interventions are used to provide long-term pain relief by increasing the amount or type of material injected. Such interventions include, for example, epidural steroid injections, facet joint injections, single nerve root blocks and peripheral nerve injections. The most frequently used substance injected for temporary relief of pain due to swelling and inflammation is the anti-inflammatory steroid hormone cortisone.

Over the past decade there has been an increasing use of IPM procedures. In 2005 the ACC published its own evidence-based guidance on over 50 separate interventions; more than half of these were potentially of therapeutic utility in the treatment of painful conditions of the spine. However, only epidural steroid injections into the lumbar and caudal sacral spine were recommended for *general use* in the treatment of lumbosacral radiculopathy, sciatica, failed back surgery syndrome, herniated nucleus pulposus and lumbar radicular pain.

A number of procedures were recommended for use *only in a research setting* (i.e. under very controlled conditions). This included lumbar medial branch block for chronic low back pain and medial branch block for facet joint pain.

For two interventions where evidence of a positive effect had been found, but was not strong enough for a general recommendation and circumstances existed where conventional treatment had failed, it was recommended that they could be considered/purchased for use on a case-by-case basis. These interventions were botulinum toxin injection for low back pain and botulinum toxin injection for neck pain.

Whilst the recommendations arising from the 2005 IPM review were positive for caudal/sacral, lumber and transforaminal steroid injections the evidence was not strong and use of cervical epidural steroid injections was not supported. Since 2005 debate has continued in the medical literature as to the value of epidural steroid injections in managing spinal pain with the pros and cons argued in the literature and further systematic reviews incorporating and assessing new evidence carried out. To complement and update the findings in relation to the effectiveness of local steroid injections for spinal pain additional evidence of effectiveness published between 2005 and 2011 was examined.

Five additional systematic reviews and two guidelines published in this later period were identified. The systematic reviews examined the evidence of effectiveness of epidural steroid injections given by a number of different delivery routes for short and long-term pain relief for a wide variety of spinal conditions. Between them, these reviews appeared to present positive evidence of effectiveness for virtually *all of the routes of delivery and major pain conditions reviewed.*

Compared with the assessment of the evidence made in 2005 new evidence presented in these later reviews appeared to support, strengthen and in some instance extended the evidence of effectiveness of epidural steroid injections for painful spinal conditions. In particular, additional evidence appeared to suggest that these injections may provide longer relief than previously reported, and there was some

support for the use of these injections for chronic low back pain. Support for the use of local epidural steroid injection for cervical pain was also reported in these additional publications and evidence for effectiveness of the different delivery routes (e.g. interlaminar and caudal routes) was advanced.

Amongst the new key findings arising from these more recent systematic reviews were;

- a potential surgery sparing role for transforaminal lumbar steroid injections for some patient populations and for some types of pain (e.g. disc herniation pain and radiculopathy)
- the superior effectiveness of the transforaminal approach
- a weaker (though still positive) effect when a true placebo was employed as a control than when active controls such as saline or anaesthetic alone were employed.
- that epidural injections *with or without steroids* gave effective lumbar pain relief.

However, despite a large volume of new literature published between 2005 and 2011 and the publication of a number of new systematic reviews of this literature, controversy over the use of epidural steroid injections for painful conditions of the spine remains. This has been attributed to (a) a lack of true placebo controlled trials, (b) the extreme heterogeneity of published primary studies, and (c) heterogeneity in the methods and standards used to assess these studies in systematic reviews. The most common criticism of the reviews themselves is that they combine evidence from very different studies using different methods, patient populations, routes of delivery and injectants in their syntheses.

Two recent American guidelines were identified that published recommendations for the use of epidural steroid injections. However, it should be noted that the search of the grey literature for relevant guidelines was not exhaustive and guidelines produced by other groups may differ in their recommendations.

The recommendations made by the reviewed guidelines were generally more negative and/or conservative than those made by the authors of the systematic reviews reported above; in some instances they appeared to contradict the findings of one or more of these systematic reviews. One of the guidelines *did not recommend* epidural steroid injections for radicular lumbosacral pain and considered there was *not enough evidence* to make a recommendation for cervical radicular pain. The other guideline considered that epidural steroid injections for back pain should only be considered after initial appropriate conservative treatment program had failed and that successful epidural steroid injections may allow patients to advance in a conservative treatment program.

In addition to IPM procedures, a variety of more invasive surgical interventions targeting specific pain generating structures may be advised to modulate discogenic and related pain. These procedures were briefly described.

The most commonly performed procedures include laminectomy (surgical removal of the lamina of the vertebra) discectomy (surgical removal of herniated disc material intervertebral), intervertebral fusion (removal of disc and fusion of adjacent vertebral bodies), disc replacement (removal of problematic disc and replacement with a prosthetic disc). These procedures may be carried out alone, or in conjunction with each other, or together with other related procedures (e.g. facetectomy).

Intervertebral fusion with or without instrumentation has become an increasingly popular surgical intervention for discogenic and related pain. The effectiveness of this intervention compared to that of discectomy, laminectomy and disc replacement is reviewed in another report.

Appendix I : Treatment procedures video links

Treatment videos from “Spine Health” http://www.spine-health.com/information/treatment-videosTo access via hyperlink press “control” place cursor over the link title and “click”

- ALIF Video: ALIF Surgery with the Endoskeleton TA Interbody Fusion Device from Titan Spine (Sponsored)
- ALIF: Anterior Lumbar Interbody Fusion Video
- Anterior Cervical Corpectomy Video
- Anterior Cervical Discectomy Video
- Anti-Inflammatory Medications for Back Pain Relief Video
- Back Surgery Video: How Spinal Fusion Stops Back Pain
- Cervical Epidural Steroid Injection Video
- Cervical Facet Radiofrequency Neurotomy Video
- Cervical Posterior Foraminotomy Video
- Cervical Selective Nerve Root Block Video
- Cervical Transforaminal Epidural Steroid Injections Video
- Chiropractic Adjustment of the Cervical Spine (Neck) Video
- Chiropractic Adjustment of the Lumbar Spine (Low Back) Video
- Chiropractic Adjustment of the Sacroiliac Joint Video
- Chiropractic Adjustment of the Thoracic Spine (Upper Back) Video
- Costovertebral Block Video
- Discography Video: Non-Surgical Back Pain Diagnostic Procedure
- Epidural Steroid Injections for Back Pain and Leg Pain Video
- Facet Joint Injections for Back Pain Relief Video
- Hamstring Exercises for Low Back Pain Relief Video
- IDET Interactive Video
- Interbody Spine Fusion Surgery Video
- Interspinous Process Spacers - A New Development in Spinal Stenosis Treatment Video

- Intrathecal Pump Implant Video
- Kyphoplasty: Osteoporosis Fracture Treatment Video
- Laminaplasty Back Surgery Video
- Laminectomy Back Surgery for Spinal Stenosis Video
- Lateral Lumbar Interbody Fusion (XLIF) Video
- Lumbar Corpectomy Surgery Video
- Lumbar Micro Endoscopic Discectomy Video
- Lumbar Radiofrequency Neurotomy Video
- Lumbar Sympathetic Block Video
- Medial Branch Block Video
- Microdiscectomy Surgery Video: A Spine Surgeon Explains the Procedure
- Microdiscectomy: Lumbar Microdecompression Spine Surgery Video
- Motion Preservation Procedures Video
- Multi-level Spinal Fusion Video
- Osteoarthritis Video: Inflammation, Pain and Treatment Options
- Posterior Lumbar Interbody Fusion (PLIF) Video
- RACZ Caudal Neurolysis Video
- Sacroiliac Joint Steroid Injection Video
- Spinal Cord Stimulator Implant Video
- Spine Fusion Surgery Video
- Spondylolisthesis Symptoms and Causes Video
- Total Disc Replacement Back Surgery Video
- Transforaminal Lumbar Interbody Fusion (TLIF) Video
- Treatment for Back Pain Flare-Ups Video
- Trigger Point Injections Video
- Vertebroplasty Interactive Video
- Video: Am I a Candidate for Back Surgery?

- Watch Your Back Video - Tips for Good Back Health in Office Chairs
- X-STOP Interactive Video
- Your First Chiropractic Adjustment: What To Expect Video

Complete list of Video Topics from “Spine Health”

- Back Pain Video Center
- Anatomy Videos
- Arthritis Videos
- Disc Disease Videos
- Herniated Disc Videos
- Osteoporosis Videos
- Sciatica Videos
- Spinal Stenosis Videos
- Spondylolisthesis Videos
- Lower Back Pain Videos
- Upper Back Pain Videos
- Treatment Videos
- Back Exercise Videos
- Chiropractic Videos
- Injection Videos
- Surgery Videos

Section 5: Spinal conditions – causation and natural history

A description, using the terms set out in the descriptive dictionary (see item 1. above), of the likely *causation* and *natural history* of:

a) Spondylolysis and Spondylolytic Spondylolisthesis
b) Degenerative spondylolisthesis
c) Synovial cysts/facet joint effusion
d) Annulus fissure
e) Spinal stenosis syndromes
f) Sacralised L5
g) Disc bar, disc/osteophyte complex and longitudinal ligament.

Methods

For a comprehensive description of the searches carried out for this review and the reporting methods see the General Methods section at the beginning of the document. Briefly, a systematic search of the literature for high evidence level studies and overviews (systematic reviews, meta-analyses and clinical guidelines) relating to the conditions of interest was carried out.

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews.

Search results

The search strategy developed for the review of the likely causation and natural history of selected spinal conditions identified 607 potentially relevant publications. Upon review, *no* systematic reviews or guidelines were identified that focussed on the conditions of interest. Twelve systematic reviews of the *treatment* of one or more of the conditions were identified and these were examined for evidence relating to aetiology and natural history. A large number (239) of *non-systematic* reviews of the literature relating to these conditions was identified.

Non-systematic reviews pose a number of problems in the context of evidence based medicine. Firstly, the selection of material for review is likely to be biased by the author's personal and conscious/unconscious agenda and possibly limited by his or her range of knowledge and experience. A lack of a formal data extraction process is likely to obscure between-study heterogeneity increasing the chance of spurious comparisons. In addition, the scientific quality of non-systematic reviews is generally lower than that of systematic reviews. Selected studies are generally treated as equally credible or valid as they do not undergo critical evaluation or quality assessments. With no limitations put on the type of evidence reviewed inferences drawn from such reviews may at best be suspect and at worst misleading.

Bearing in mind these limitations, and in the absence of relevant systematic reviews on the topic, the following appraisal of the current knowledge of the aetiology and natural history of the conditions of interest is taken, for the most part, from recent non-systematic reviews of experimental studies. Where no relevant narrative reviews were identified primary studies themselves are the information source.

References

Citations for primary studies quoted in eligible reviews are included in *footnotes* rather than the report bibliography to distinguish them from those identified independently for the current report by the systematic search procedure.

Background

Anatomy of the spine

The spine comprises 31 separate bones or vertebrae, 7 cervical or neck vertebrae (C1-C7), 12 thoracic vertebrae (Th1-Th12), 5 lumbar vertebrae (L1-L5), 5 fused vertebrae which from the sacrum (Os sacrum) and 2 coccygeal vertebrae (coccyx), Figure 5.1 . The bony vertebrae are stacked on top of each other with a fibrous intervertebral disc between each one. Each vertebra is held to the others by groups of ligaments while associated tendons that fasten muscles to the vertebrae.

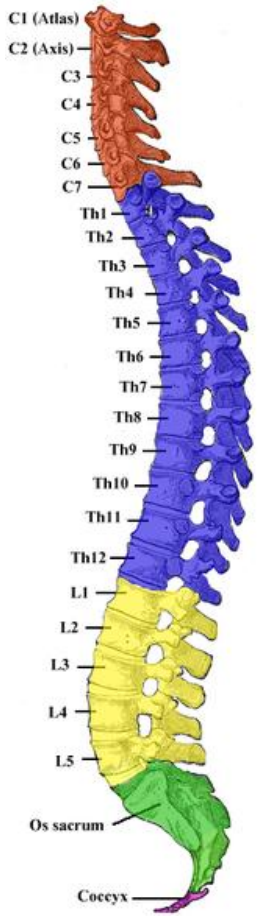


Figure 5.1. The vertebrae of the spine

Together, the vertebral bodies act as a support column to hold up the spine. The weight borne by the spinal column and the size of the intervertebral discs increases progressively from the cervical to the sacral regions. Overall, the spinal column supports about half of the weight of the body, with the other half supported by the muscles.

The vertebral column is divided up into sections by **form and function**. The cervical vertebrae support the head and neck, the thoracic vertebrae serve as attachments for the ribs and the robust lumbar vertebrae serve as attachments for the large back and pelvic muscles. Below the lumbar

vertebrae are the sacral vertebrae which are fused to form the sacrum, and the caudal vertebrae which are fused to form the coccyx.

With the exception of the first and second cervical vertebrae, each vertebra has the same basic structure which comprises a vertebral body anteriorly and a neural arch posteriorly, Figure 5.2. The neural arch encloses an opening called the vertebral foramen which protects the spinal cord.

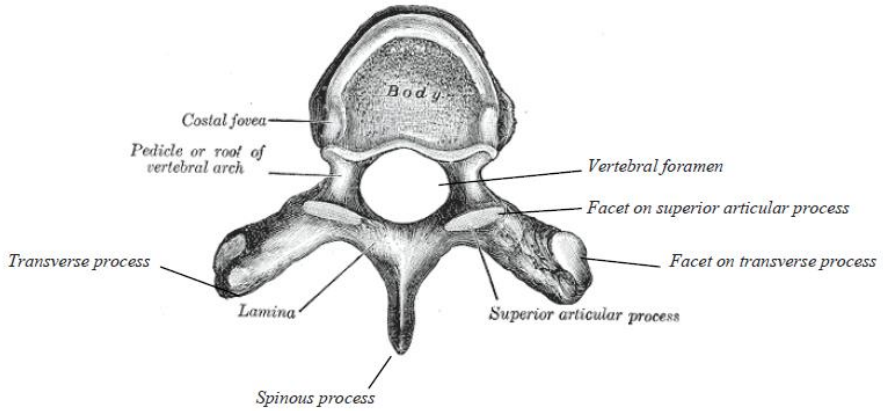


Figure 5.2. A "typical" vertebra taken from the middle of the thoracic region. View from above. Adapted from Gray's Anatomy
http://education.yahoo.com/reference/gray/illustrations/figure?id=82

Protruding from the posterior extreme of each neural arch is a **spinous process** and extending from the lateral edges of each arch are *transverse processes*. In the lumbar spine these bony elements serve as sites of attachment of back muscles. The neural arch of each vertebra is divided into component parts by these processes. The parts of the neural arch between the spinous and transverse processes are known as the **laminae** and the parts of the arch between the transverse processes and the body are know a as the *pedicles*. At the point where the laminae and pedicles meet, each vertebra contains two *superior articular facets* and two *inferior articular facets*. The former pair of facets forms articulations, which are synovial joints, with the two inferior articular facets of the vertebra immediately above (or the skull, in the case of the first cervical vertebra). The pedicle of each vertebra is notched at its superior and inferior edges. Together the notches from two contiguous vertebrae form an opening, the *intervertebral foramen*, through which spinal nerves pass

Although each of the vertebrae conforms to this basic plan, vertebrae in each area of the spine vary in form and function and how they are attached to adjacent structures.

Cervical vertebrae

The cervical spine is much *more mobile* than the other spinal regions allowing for rotation of the skull. Although the cervical spine is very flexible, it is also at risk for injury from strong, sudden movements, such as whiplash-type movements. This high risk of harm is due to (a) the limited muscle support that exists in the cervical area, and (b) the weight of the head. Sudden, strong head movement can cause damage to the cervical spine.

Typically, the cervical vertebrae have large spinal canals, oval shaped vertebral bodies, and articular facets oriented obliquely, Figure 5.3. Their most characteristic features are their bifid spinous

processes and a foramen in their transverse processes. These *foramina transversaria* contain the vertebral artery and vein.

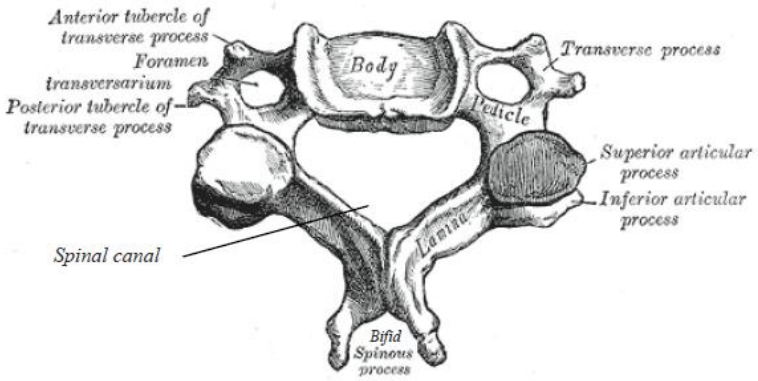


Figure 5.3. A cervical vertebra (http://education.yahoo.com/reference/gray/illustrations/figure?id=84)

The first and second cervical vertebrae are however, are atypical. The first cervical vertebra or *atlas* has no vertebral body and contains an anterior tubercle instead. Its superior articular facets articulate with the occipital condyles of the skull and are oriented in a roughly parasagittal plane. The head thus moves forward and backwards on this vertebra, Figure 5.4.

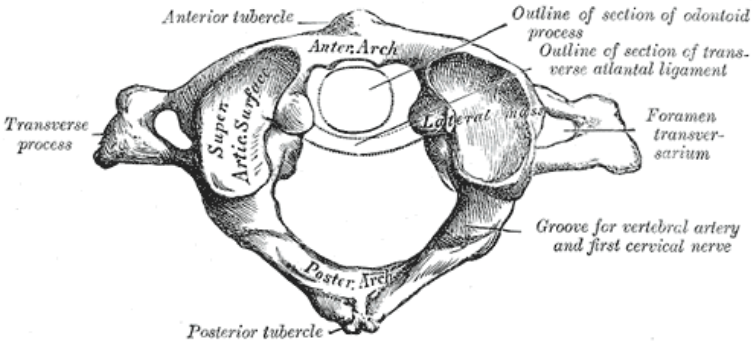


Figure 5.4. Atlas or first cervical vertebra. http://education.yahoo.com/reference/gray/illustrations/figure?id=86

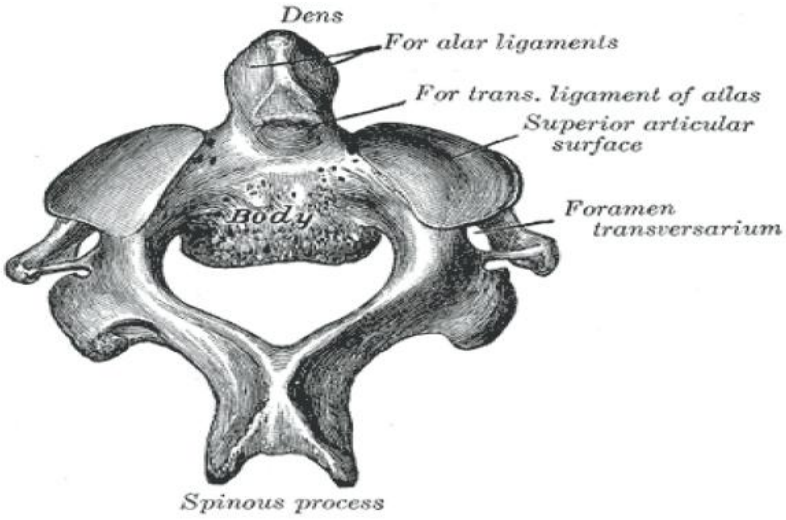


Figure 5.5. Axis or second cervical vertebra. http://education.yahoo.com/reference/gray/illustrations/figure?id=87

The second cervical vertebra or axis contains a prominent odontoid process, or dens, which projects superiorly from its body. It articulates with the anterior tubercle of the atlas, forming a pivotal joint. Side to side movements of the head take place about this joint, Figure 5.5.

Thoracic vertebrae

The thoracic vertebrae connect to the ribs and form part of the back wall of the thorax. This part of the spine has very narrow, thin intervertebral discs, and there is much less movement allowed between vertebrae than in the lumbar or cervical parts of the spine. There is also less space in the spinal canal for the spinal nerves to pass through.

The thoracic vertebrae uniquely include articular facets (costal demifacets) for the ribs. Each vertebra contains two pairs of **costal demifacets** on its body and one on each transverse process Figure 5.6 and Figure 5.7. Typical ribs articulate with the inferior demifacet and transverse process of a thoracic vertebra and the superior demifacet of the vertebra below it.

Each vertebra contains two pairs of these *costal demifacets* on its body and one on each transverse process (fig. 5.6). Typical ribs articulate with the inferior demifacet and transverse process of a thoracic vertebra and the superior demifacet of the vertebra below it

The 11th and 12th thoracic vertebrae are sometimes considered atypical because they lack a superior costal facet. The 11th and 12th ribs thus articulate only with the 11th and 12th thoracic vertebrae, respectively are articular facets for the ribs.

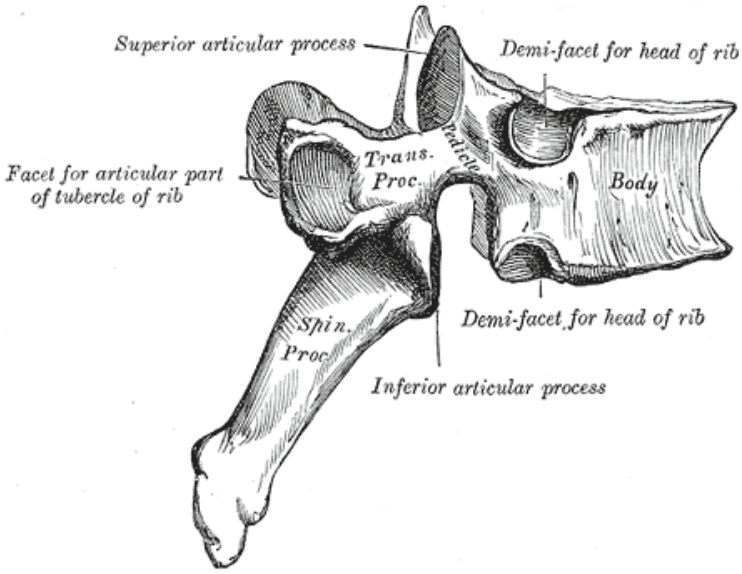


Figure 5.6. Thoracic vertebra viewed from the side.
http://education.yahoo.com/reference/gray/illustrations/figure?id=90

The *first, ninth, tenth, eleventh,* and *twelfth* thoracic vertebra present certain peculiarities, and require special consideration, Figure 5.7.

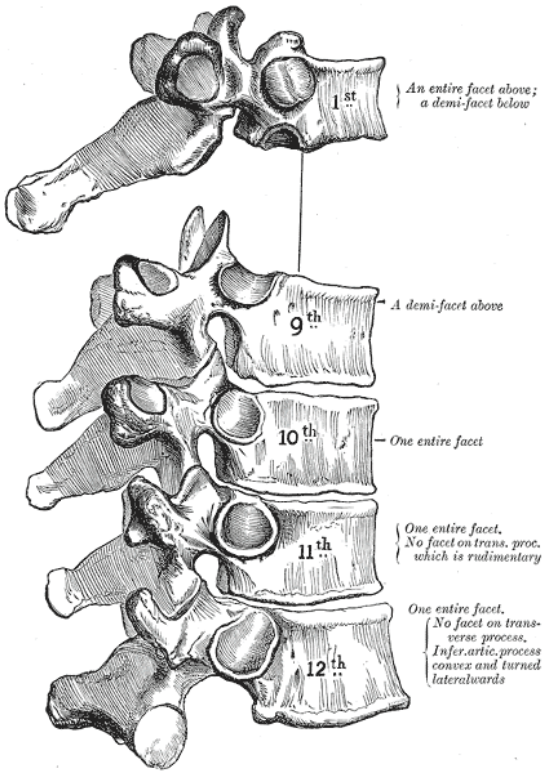


Figure 5.7. Variant thoracic vertebrae.
http://education.yahoo.com/reference/gray/illustrations/figure?id=91

The first thoracic vertebra has, on either side of the vertebral body, an entire articular facet for the head of the first rib, and a demi-facet for the upper half of the head of the second rib. The ninth thoracic vertebra may have no demi-facets below[179]. The articular facets for the heads of the ribs are of large size, and placed chiefly on the pedicles, which are thicker and stronger in this and the next vertebra than in any other part of the thoracic region.

Lumbar vertebrae

The lumbar spine carried the most weight and experiences the most motion compared to other parts of the spine.

Lumbar vertebrae are characterized by large bodies and robust spinous and transverse processes. Their articular facets are oriented somewhat parasagittally, which is thought to contribute the large range of anteroposterior bending possible between lumbar vertebrae. Lumbar vertebrae also contain small mammillary and accessory processes on their bodies. These bony protuberances are sites of attachment of deep back muscles, Figure 5.8.

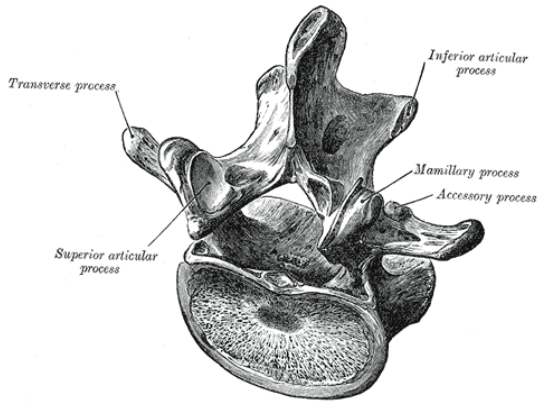


Figure 5.8. A lumbar vertebra from above and behind.
http://education.yahoo.com/reference/gray/illustrations/figure?id=93

Sacrum and coccyx

Below the lumbar spine, up to nine vertebrae (depending on the individual and the observer) grow together. Five form the triangular bone called the sacrum, which is held between the iliac bones of the pelvis on either side and serves to transfer the weight of the upper body to the legs, Figure 5.9.

[179] In some subjects however, it has two demi-facets on either side; when this occurs the tenth has only demi-facets at the upper part. The tenth thoracic vertebra has (except in the cases just mentioned) an entire articular facet on either side, which is placed partly on the lateral surface of the pedicle. In the eleventh thoracic vertebra the body approaches in its form and size to that of a lumbar vertebra.

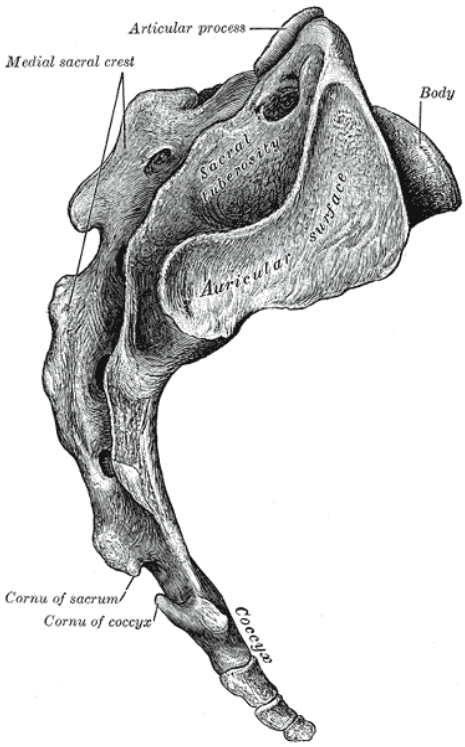


Figure 5.9. Lateral surfaces of sacrum and coccyx[180]. http://education.yahoo.com/reference/gray/illustrations/figure?id=97

The lowest vertebrae (2-4 depending on the individual and the observer) form the tailbone or coccyx, which is the terminal point at the base of the spine.

The facet joints

Facet joints are more properly called zygapophyseal or apophyseal joints; they link the vertebrae together. Each vertebra has two sets of facet joints, a superior articular facet and an inferior articular facet.

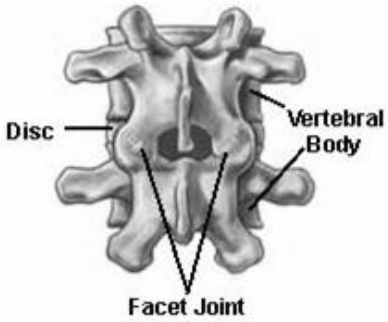


Figure 5.10. Facet joints of a posterior spinal segment http://www.spineuniverse.com/anatomy/facet-joints-spine-anatomy

[180] The coccyx is usually considered to be made up of 4 bones which may be fused.

Facet joints are synovial joints, each joint is surrounded by a capsule of connective tissue and produces a fluid to nourish and lubricate the joint. The joint surfaces are coated with cartilage allowing the joints to move or glide smoothly (articulate) against each other. These joints allow flexion, extension, and twisting motions. Certain types of movement are restricted and the spine is made more stable due to the interlocking nature to adjacent vertebrae.

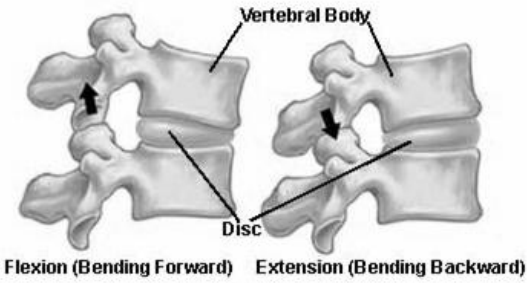


Figure 5.11. Facet joints in motion. http://www.spineuniverse.com/anatomy/facet-joints-spine-anatomy

The intervertebral articulations connecting adjacent vertebrae are extensively reinforced by ligaments. These ligaments connect the tips of the spinous processes (supraspinous ligaments), the base of the spinous processes (interspinous ligaments), and the transverse processes (intertransverse ligaments). In addition the laminae of adjacent vertebrae are bound together by a ligamentum flavum, Figure 12.

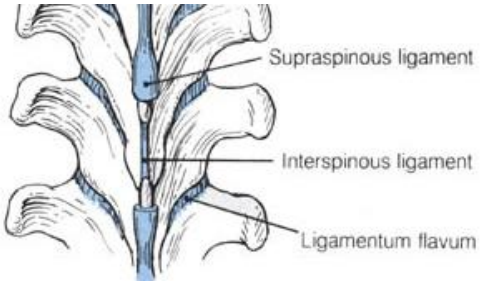


Figure 5.12. Ligament reinforcing intervertebral articulations. http://www.emory.edu/ANATOMY/AnatomyManual/back.html

5.1 Spondylolysis

Spondylolysis[181] is a spinal condition in which the there is a unilateral or bilateral defect or break in the *pars interarticularis or isthmus*[182] which is the portion of the neural arch that connects the lamina with the pedicle, facet joints and transverse processes of a vertebra. The defect in the pars may be developmental or traumatic. The pars interarticularis is a key component in segmental integrity (Ganju & Ganju, 2002).

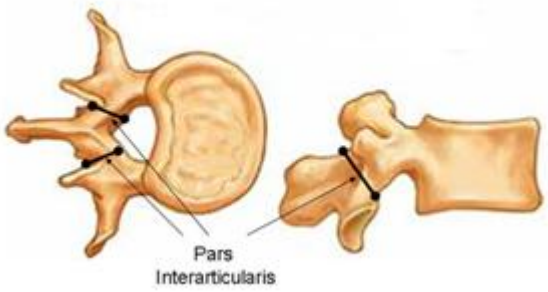


Figure 5.1.1. Lumbar vertebrae showing the position of the pars interarticularis. From http://www.globalspine.net/spondylolysis_spondylolisthesis.html

The nature of the spondylolytic defect in a group of surgical patients who had failed conservative treatment was investigated by Shipley and Beukes (1998). The spondylolytic defect was found in most cases to be a synovial pseudoarthrosis that communicated with the facet joint above and (less frequently) with the facet joint below. Failure to heal was suggested to be due to the presence of synovial fluid leaked from the nearby facet joint (Shipley & Beukes, 1998)

Epidemiology

Spondylolysis is reported to occur in between 6% and 11.5%[183] of adult Caucasians (Kalichman et al., 2009) with a male-to-female ratio for the condition of 2:1 (Beutler et al., 2003) and progression to spondylolisthesis more likely in female patients (Meyerding, 1941). There is great ethnic variation, with a prevalence of up to 54% reported in adult Inuit and 2% in the African American population[184]. The prevalence of the condition is reported to increase in children and adolescents who are active in sports particularly those involving repetitive hyperextension of the trunk[185]. The reported incidence of spondylolysis varies from 11% in young gymnasts to 30% in wrestlers and 43% in divers[186].

[181] The term is derived from the Greek words spondylos, meaning vertebra, and lysis, meaning break or defect.
[182] Latin for "bridge between two joints"
[183] Based on CT imaging of an unselected community-based population, the prevalence of lumbar spondylolysis was reported by Kalichmen et al (2009) to be 11.5%, nearly twice the prevalence of previous plain radiograph-based studies
[184] Simper LB. Spondylolysis in Eskimo skeletons. Acta Orthop Scand 1986;57:78-80. Fredrickson BE, Baker D, McHolick WJ, Yuan HA, Lubicky JP. The natural history of spondylolysis and spondylolisthesis. J Bone Joint Surg [Am] 1984;66-A:699-707.
[185] Soler T, Calderón C. The prevalence of spondylolysis in the Spanish elite athlete. Am J Sports Med 2000;28:57-62. Rossi F, Dragoni S. Lumbar spondylolysis: occurrence in competitive athletes: updated achievements in a series of 390 cases. J Sports Med Phys Fitness 1990;30:450-2
[186] Rossi F, Dragoni S. Lumbar spondylolysis: occurrence in competitive athletes: updated achievements in a series of 390 cases. J Sports Med Phys Fitness 1990;30:450-2. Teitz CC. Sports medicine concerns in dance and gymnastics. Clin Sports Med 1983;2:571-93. Jackson DW, Wiltse LL, Cirincoine RJ. Spondylolysis in the female gymnast. Clin Orthop 1976;117:68-73.

Spondylolysis is reported to be exceptionally rare in the newborn child (Robertson & Nicholson, 2000)[187] but appears after walking begins, with incidence reported to increase from 4.4% in children aged six to 6% at the age of 18 years; incidence is reported to remain stable at that rate throughout adulthood (Kalichman et al., 2009). Spondylolysis developing after the end of spinal growth and in adult life is reported to be uncommon[188] (Tsirikos & Garrido, 2010).

Aetiology

Tsirikos and Garrido (2010) reported that **mechanical and anatomical** factors probably acting in conjunction led to the development of a spondylolysis. They noted that, in the great majority of cases (90%), the defect in the pars interarticularis (spondylolysis) occurred at the junction of the relatively stable sacrum and the mobile lumbar spine. During spinal flexion/extension the load on the posterior bony arch in a normal spine increases considerably from L1 to L5; the highest mechanical stress is concentrated at the pars interarticularis of L5. Spondylolysis may also occur in other lumbar vertebrae, as well as in the thoracic vertebrae (Tsirikos and Garrido 2010). Hu et al (2008), reporting on the mechanism of failure of the pars interarticularis, noted that when the lumbar spine extends, the inferior articular process of the cranial (uppermost) vertebra impacts the pars interarticularis of the caudal (lower) vertebra. It was suggested that repetitive impacts produce a stress or fatigue fracture of the pars interarticularis. The fact that lumbar hyperextension activities, such as gymnastics and lumbar hyperextension secondary to spinal deformity have been associated with spondylolysis were cited to support a traumatic mechanism. This direct compression by means of a ''nutcracker'' mechanism was also reported to be consistent with the observation that spondylolysis had not been reported in individuals who could not walk and the fact that up to 40% of athletes with spondylolysis recalled a specific back injury . However, Hu et al (2008) also cited recent studies from Montreal that suggested that the pars interarticularis fails in tension through a traction mechanism (Hu, Tribus et al. 2008).

An **inherited predisposition** to spondylolysis has been proposed (Tsirikos & Garrido, 2010), with an increased familial incidence and a parallel occurrence of spondylolysis and spina bifida occulta (Newman & Stone, 1963). Wiltse (1957) believed that congenital weakness had a role to play;

"……the lesion in the pars interarticularis results from dissolution of continuity of the bone due to a congenital weakness at this point'

Fredrickson et al (1984) in a prospective study of children (and their families) with spondylolysis and spondylolisthesis also concluded that **inheritance** was an important factor in the development of a pars interarticularis defect, probably based on either genetic heterogeneity with multiple mendelian forms or on multifactorial inheritance, with some family members having a higher liability to the lesion than others (Fredrickson, Baker, McHolick, Yuan, & Lubicky, 1984); they also noted that, at that time, most authors favoured this theory. Haun et al (2005) reported that there was some degree of genetic predisposition to the condition citing the fact that in the study by Fredrickson et al (1984), there was an increased prevalence of spondylolysis within the families of school age children with the condition; fathers were affected 32% of the time, mothers 17%, and male siblings 34% (Haun, Kettner, Haun, & Kettner, 2005).

[187] Borkow SE, Kleiger B. Spondylolisthesis in the newborn. A case report. Clin Orthop 1971; 81: 73-6.
[188] Roche MB, Rowe GG. The incidence of separate neural arch and coincident bone variations: a survey of 4,200 skeletons. *Anat Rec* 1951;109:233-52.

Lifestyle is also reported to play a part. Engaging in vigorous activities when the posterior arch is not completely ossified and the intervertebral disc is very elastic makes the pars susceptible to fatigue failure. A study of the biomechanical loading in the lumbar spine showed that the point of highest stress within a vertebral segment is found within the pars interarticularis (Newman & Stone, 1963) which correlates well with the concept of spondylolysis as a fatigue or stress fracture. While an acute fracture of the pars is possible and has been reported (A. S. Hilibrand, Urquhart, Graziano, & Hensinger, 1995), most individuals with spondylolysis are unable to identify any particular traumatic incident that could have caused the fracture. Also, in consideration of the higher incidence of spondylolysis in persons playing particular sports, a repetitive stress fracture aetiology seems most likely(Haun et al., 2005). Exaggeration of lumbar lordosis during sporting activities involving repetitive hyperextension of the trunk is believed to cause increased stress in the pars interarticularis, resulting in a fatigue fracture[189] (Tsirikos & Garrido, 2010).

Natural history

The natural history of spondylolysis (and spondylolisthesis) was determined in a landmark study of 500 unselected children 5-18 years of age (Fredrickson et al., 1984). Twenty seven children with a known pars interarticularis defect at L5 were closely followed for 25 years with follow-up extended to 45 years in a second study (Beutler et al., 2003).

Spondylolysis was found to be very rare in children younger than 5 years. Patients who developed pars defects during the period of observation did not develop symptoms during the time that the defects developed. Low back pain was found to have developed in only four subjects during the first 25 years of follow-up. Approximately 15% of radiographically detected spondylolysis was accompanied by spondylolisthesis. Healing of the pars defect was only demonstrated in one patient (a six year old girl); the defect was still evident at the age of 10 and 12 years but had healed at the final follow-up when the patient was 28 years old.

Slipping (spondylolisthesis), when it occurred, was demonstrable at about the same time that the pars interarticularis defect was first detected roentgenographically. Fredrickson also reported that slipping increased up to the age of sixteen, but did so rarely and that development of the pars interarticulans defect, with or without spondylolisthesis, did not cause pain in most patients. Spina bifida occulta occurred more frequently in patients with a pars interarticularis defect than in patients without a defect (Fredrickson et al., 1984).

In a 45-year follow-up study of the same group of patients, those with bilateral pars defects followed a clinical course similar to that of the general population (Beutler et al., 2003) . Subjects with unilateral pars defects never developed a slip over the course of the study. Of those 25 subjects with bilateral defects, 16 initially had no slip. The remaining nine had both pars defects and spondylolisthesis on the initial radiographs in 1955. Of the 16 with no slip initially, 10 went on to develop spondylolisthesis, five never slipped, and one was lost to follow–up in the later years of the study. Of the ten that developed spondylolisthesis after initially not having a slip, eight developed the slip as a teenager, and the remaining two between age 20 and 40.[190]

[189] Failure of a structure as a result of cyclic stresses whose intensity is within the elastic domain but far less than the ultimate tensile or compressive strength of that structure cf pathological fracture.
[190] http://www.spineuniverse.com/professional/research/srs/2002/natural-history-spondylolysis-spondylolisthesis-45

Haun et al (2005) also reported that the majority of affected individuals appeared to be asymptomatic displaying clinically inactive spondylolysis; in a study of inheritance and spondylolysis, only 4% of relatives of people with spondylolysis admitted to having any symptoms, but 19% were found to have a defect[191](Haun et al., 2005). These authors suggested that the individuals most likely to have a symptomatic spondylolysis were adolescents that were developing a defect and that patients with unstable spondylolysis may be more prone to low back pain (Haun et al., 2005).

Ohmori et al (1995) studied the progression of 22 adult patients with spondylolysis. When comparing the initial presentation with follow-up approximately 12 years later, they found that of 18 patients without a listhesis initially, 13 still had no slip, and five had progressed to an average of 16.6% slip. There was an average of 6% increase in slip among those patients who had anterolisthesis initially (Ohmori, Ishida, Takatsu, Inoue, & Suzuki, 1995).

[191] Wynne-Davies R, Scott JH. Inheritance and spondylolisthesis: a radiographic family survey. J Bone Joint Surg Br 1979;61-B:301–5.

5.2 Spondylolisthesis

Spondylolisthesis[192] is a condition in which there is anterior or posterior displacement of a vertebra or the vertebral column in relation to the vertebrae below. Most commonly the slip involves the L5 vertebra slipping forward (anterolisthesis) over the S1 vertebra (Wang, 2010). Spondylolisthesis and spondylolysis are often (but not always) seen together, Figure 5.14.

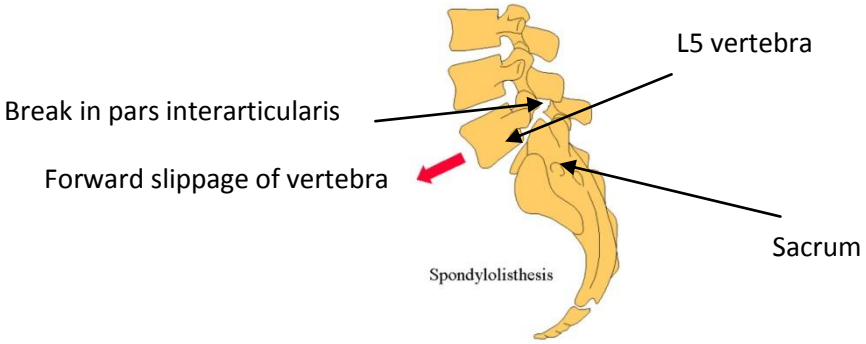


Figure 5.2.1. Spondylolysis with forward slippage (Spondylothisthesis).

Spondylolisthesis has been linked in a number of publications to bipedalism as it is reportedly not been recognized in any other species except man and typically the condition is not observed in newborns or non-ambulatory individuals. Thus it is believed by some that the development of spondylolisthesis may be related to man's ability to maintain an erect posture and the development of lumbar lordosis, the latter being unique to humans (Ganju & Ganju, 2002). However, more recently Carl et al (2007)[193] reported a case of an isolated isthmic spondylolisthesis in a 17 year-old patient who has never ambulated and suggested that bipedal posture was not an absolute requirement for the development of this lesion.

Classification

A number of different types of spondylolisthesis have been recognised and at least five different classifications have been published (Herman, Pizzutillo, Herman, & Pizzutillo, 2005; Inoue et al., 2002; Mac-Thiong & Labelle, 2006a; Marchetti & Bartolozzi, 1997; Wiltse, Newman, & Macnab, 1976). A variety of causal mechanisms and anatomical factors that have been reported to contribute to the development of spondylothisthesis have been used to form the basis of these classification systems, which are, for the most part, discordant.

The most commonly used classification system (Newman & Stone, 1963; Wiltse et al., 1976)[194] is reproduced and illustrated below (Table 5.2.1 and Table 5.2.2) to provide a context for the current description of the likely causation and natural history of spondylolytic (or isthmic) spondylolisthesis and degenerative spondylolisthesis two spinal conditions which are of particular interest to ACC. This classification classifies spondylolisthesis into five types **and** uses reported causal mechanisms and anatomical factors to group cases. It is the only classification to distinguish both spondylolytic (isthmic) and degenerative spondylolisthesis which are the focus of the current report.

[192] From the Greek "spondylo" meaning vertebra and "olisthesis" meaning to slip down an incline.
[193] Isthmic spondylolisthesis in a nonambulatory patient: a case report. Carl RL. Noonan KJ. Nemeth BA. Spine. 32(24):E723-4, 2007.
[194] Wiltse et al (1976, 1981) is reported to have refined the classification originally proposed by Newman and Stone (1963).

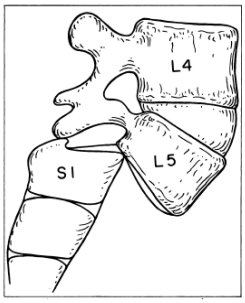
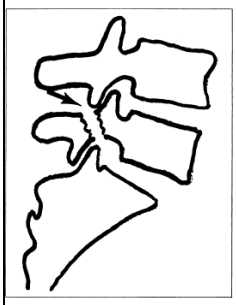
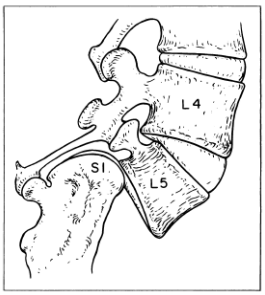
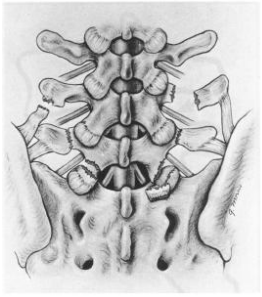
Table 5.2.1. Spondylolisthesis Classifications of Wiltse et al (1976) and Wiltse (1981)[195]

Type/ subtype	Nomenclature	Comments/description (from Wiltse (1981))
I	Dysplastic (congenital)	"There is congenital dysplasia of the upper sacrum or the neural arch of L5. Because of this dysplasia, there is insufficient strength to withstand the forward thrust of the superincumbent body weight, and the last free lumbar vertebra gradually slips forward. The pars interarticularis may remain unchanged. If it remains unchanged and the ring is intact, the slip cannot exceed more than about 35 percent before there will be pressure on the cauda equina. There is a strong hereditary element in this type.[196]"
II	Isthmic	"The basic lesion is in the pars interarticularis. Secondary changes (e.g., alteration in the shape of the body of L5) may occur but are not fundamental to its etiology."
II A.	Lytic-fatigue fracture of the pars	"This is due to separation of the pars resulting from a fatigue fracture[197]. It is the common type below age 50. Statistically, it is seldom seen in patients below age 5, but it does occur even in infancy. At the end of the first year of school, the incidence is 4.4 percent. By the age of 18, the incidence increases to 6 percent.1 Boys have the condition about twice as frequently as girls. Flexion, extension and twisting motions are all probably important in producing the stress fractures, but extension is most important.[198]"
II B.	Elongated but intact pars.	"This is fundamentally the same disease as Subtype A. Repeated micro-fractures in the pars allow it to heal in an elongated position as the body of L5 slides forward. The author knows of five families in which the pro-bands had an elongated but intact pars while several other members of their immediate families had typical spondylolysis or spondylolisthesis with the classic pars defect seen in Subtype A."
II C.	Acute fracture of pars †	"These are an acute fracture of the pars secondary to severe trauma and are extremely rare."
III	Degenerative	"This lesion is due to longstanding intersegmental instability. Remodelling of the articular processes at the level of involvement results. Farfan[199] believes that in addition to degeneration of the disc there are multiple small stress compression fractures of the inferior articular processes of the olisthetic vertebra. As the slip progresses, the articular processes change directions and become more horizontal. One side nearly always rotates more than the other. This is an integral characteristic of this disease. Farfan believes that the typical hour-glass deformity seen on the myelogram is due to rotation of the upper vertebra with displacement of the pedicle.In patients with clinical symptoms, degenerative spondylolisthesis occurs six times more frequently in females than in males[200]; six to nine times more frequently at the L4 interspace than at adjoining levels; and four times more frequently when the 5th lumbar vertebra is sacralized. When the lesion is at L4, the L5 vertebra is more stable and in less lordosis than average. The author has not seen this lesion in any patient under age 40."
IV	Post Traumatic	"This lesion is secondary to a severe injury which fractures some part of the supporting bone other than the pars. This allows forward slip of the vertebra above on the one below. Unlike the acute isthmic fracture, an isolated pars fracture is not present. The slip occurs gradually. It is not an acute fracture dislocation."
V	Pathologic	"Because of local or general bone disease, the bony hook mechanism (consisting of the pedicle, the pars, the superior and inferior articular processes) fails to support the forward thrust of the superincumbent body weight and forward slip of a vertebra on the one below occurs."

†Not to be confused with "traumatic" [see IV]. = Types of spondylolisthesis described in the current report.

[195] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2328707/pdf/iowaorthj00033-0056.pdf
[196] Wynne-Davies, R., Scott, H.S.: Inheritance and spondylolisthesis: a radiographic family survey. J. Bone and Joint Surg., 61-B:301, 1979.
[197] Wiltse, L.L., Widell, E.H. Jr., Jackson, D.: Fatigue fracture: the basic lesion in isthmic spondylolisthesis. J. Bone and Joint Surg., Vol. 57-A, No. 1, 17-22, 1975.
[198] Farfan, H.F.: The radiological anatomy of degenerative spondylolisthesis. Spine 5, no. 5:412-418, 1980. Wynne-Davies, R., Scott, H.S.: Inheritance and spondylolisthesis: a radiographic family survey. J. Bone andJoint Surg., 61-B:301, 1979.
[199] Farfan, H.F.: Mechanical disorders of the low back. Lea & Febiger, Philadelphia, 1973.
[200] Rosenberg, N.: Degenerative spondylolisthesis, predisposing factors. J. Bone and Joint Surg., 57-A:467, 1975.

Table 5.2.2 Drawing to illustrate Wiltse (1981) classification of spondylolisthesis (note drawing for Type III and Type V were not presented).

Type I. Dysplastic (congenital) spondylolisthesis	Type IIa. Lytic spondylolisthesis	Type II b, Elongation of the pars without separation	Type IV. Post traumatic.
			
Drawing of congenital or dysplastic spondylolisthesis. Note superior articular processes of S1 are underdeveloped	Lateral drawing of isthmic spondylolisthesis, Type II-a.	Lateral drawing of elongated but intact pars, Type II-b.	Drawing of an actual case of traumatic spondyspondylolisthesis. lolisthesis.

S1= scacral 1 ,L4= lumbar 4, L5= lumbar 5

Although spondylolisthesis has been commonly described in the literature using the classification by Wiltse et al. (1976,1981), a later classification by Marchetti and Bartolozzi (1997) which distinguished developmental from acquired spondylolisthesis and further divided developmental spondylolisthesis into low- and high-dysplastic types has also gained popularity. This has caused some difficulties as isthmic or spondylolytic spondylolisthesis may be considered to be both developmental and acquired and as Hammerberg (2005) noted;

"Unfortunately, developmental and spondylolytic, or "isthmic," spondylolisthesis in adolescents and young adults have been grouped and discussed together. As a consequence, the natural histories of these processes have been obscured....,(Hammerberg, 2005)"

Both classification have been criticised and neither take sagittal sacro-pelvic balance into account, which recent studies have suggested its important (Mac-Thiong et al., 2008). Moreover detractors have produced another classification which is claimed to clarify the concept of low and high-dysplasia introduced by Marchetti and Bartolozzi and incorporates recent knowledge in the study of sagittal sacro-pelvic balance and morphology (Mac-Thiong & Labelle, 2006b; Mac-Thiong et al., 2008).

Thus at least three different classifications of spondylolisthesis were encountered in the literature identified for this report, since these classifications are mostly disparate it is possible that information/data relating to spondylolytic and degenerative spondylolisthesis has been reported but was not retrievable as it was subsumed within another reported group.

The most common grading system for the *degree of slippage* of the L5 vertebra relative to S1 is the Meyerding classification, Figure 5.2.2 (Meyerding, 1932).

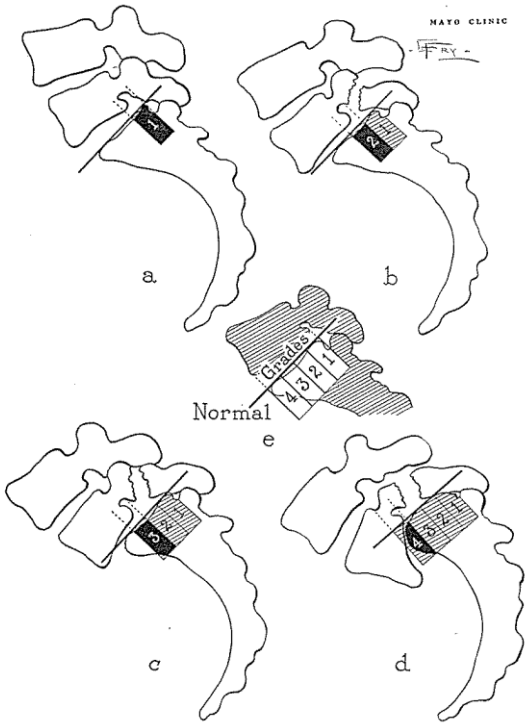


Figure 5.2.2. Gradation of degrees of spondylolisthesis. From Meyerding (1932)

This grading[201] is commonly reported as the percentage of translation of the upper vertebra over the lower one:

Grade I is defined as <25%
Grade II is defined as 25-50%
Grade III is defined as 50-75%
Grade IV is defined as 75-100%
Grade V is defined as 100% or greater (known as spondyloptosis).

Depending upon the severity or grade of the slip compression of nerve roots may occur.

Aetiology

Spondylolisthesis has many aetiologies, all of which ultimately lead to a loss of the stability offered by the locking mechanism of the articular processes of the vertebrae that allow the superior vertebrae to slide forward (or backwards) over the inferior vertebrae (Kalichman & Hunter, 2008a). Hammerberg (2005) commented that;

"It should now be understood that each type of spondylolisthesis is the similar radiographic end result of different and distinct disease processes. These disparate pathologic conditions produce spondylolisthesis because of the common morphology and biomechanical forces applied to the lumbosacral junction."(Hammerberg, 2005)

Nevertheless, over the two centuries since the condition was first described, there has been ongoing debate over aspects its aetiology.

[201] The exact boundaries of which vary between publications.

There does appear to be general agreement that a **number of different processes** play a part in the development of the condition and much of the debate appear to be about which process forms the *primary or underlying cause* of slippage[202]. This debate has been complicated by the fact that a large number of different types of spondylolisthesis have been described in the literature and it is not always clear if the debate relates to spondylolisthesis *per se* or one of the many different types of spondylolisthesis that have been described. Thus the account below describes a range of proposed mechanisms which have been reported to contribute to or cause slippage *per se*, followed by a description of the aetiology of two types of spondylolistheses of specific interest to ACC (spondylolytic or isthmic spondylolisthesis and degenerative spondylolisthesis). These accounts draw on some of the classic or landmark clinical studies of the past and the most recent narrative reviews.

Many slips involve the L5 vertebra which is supported on the upper sloping surface of the sacrum (S1). The normal slope of the sacrum is slight and any tendency of the vertebra above to "slide" counteracted by one or more restraining mechanisms. A defects or failure of one or more of the restraining mechanisms has traditionally been viewed as being causally related to vertebral slip. Newman and Stone (1963) noted that;

" The tendency to forward slipping is constant and is counteracted by: 1) adequacy of facets; 2) intact pedicles and neural arches ; 3) normal bone structure . The mechanism as a whole is consolidated by integrity of the soft tissue. A deficiency in any one of these three is liable to allow forward slipping, especially if the soft tissues binding the affected vertebrae are faulty."(Newman & Stone, 1963)

The role of vertebral restraint failure in the aetiology of spondylolisthesis has however been a matter of some debate and in particular whether or not failure of vertebral restraint mechanisms is the primary cause of spondylolisthesis or a consequent of the stresses/forces associated with slippage.

The intervertebral disc is important in retaining the vertebra in place. Abnormal shearing forces on the disc may affect this function through shrinkage of the disc and loss of height. However, the vertebra may only slide forward as far as the capsules will allow (normally about 8-10mm) as is commonly observed in both developmental and spondylotic spondylolisthesis.

Fracture of the pars interarticularis[203] , which may be due to repetitive stress (i.e. a stress fracture) and/or a genetic weakness at the site, has been closely associated with some types of spondylolisthesis. Deformities or growth distortions of the facet joints have also been causally associated with spondylolisthesis. Newman and Wiltse [i] originally suggested that primary "congenital" dysplasia of the facet joints was a cause in the paediatric age group, but Fredericksen (1984) in his three decade follow up, showed that these abnormalities were the result of the slipping, not the cause (Fredrickson et al., 1984).

In the normal spine, the large ilio-lumbar ligaments also restrain the L5 vertebra from sliding by joining strongly between the transverse process of L5 and the iliac crest. However, inadequate or unusually small ilio-lumbar ligaments and/or small transverse processes may hinder this.

More recently a number of radiological postural/morphological measurements have been shown to have an abnormal relationship in spondylolisthesis (Wang, 2010; Wang et al., 2008). Duval-Beaupère

[202] This is reflected in the fact that a number of different classifications based on one or more of the proposed underlying causes of the condition are in use.
[203] part of vertebra located between the inferior and superior articular processes of the facet joint

et al. (1998) described pelvic incidence (PI)[204] as a fundamental parameter of the geometric configuration of the pelvis . The pelvic incidence (or pelvis/sacral angle) is the sum of sacral inclination and pelvic tilting and is defined as the angle between a line perpendicular to the sacral plate at its midpoint and a line connecting the same point to the centre of the bicoxofemoral axis, Figure 5.2.3. The slope of the sacrum (or "pelvic incidence") is reported to be specific and constant for each individual; forward rotation of the sacrum (or "pelvic tilt") increases the pelvic incidence (PI) and the sliding force of the vertebra above.

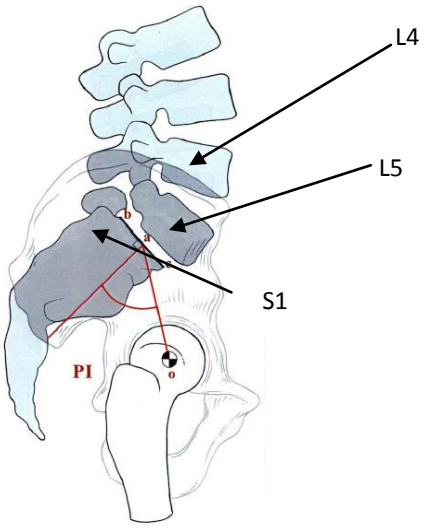


Figure 5.2.3. Pelvic incidence: defined as the angle subtended by a line drawn from the centre of the femoral head (o) to the midpoint of the sacral endplate (oa) and a line perpendicular to the centre of the sacral endplate (a). The scacral endplate is defined by the line segment bc constructed between the posterior superior corner of the sacrum and the anterior tip of the S1 endplate at the sacral promontory. From Wang (2010) Influence de la morphologie sacro-pelvienne dans l'évolution du spondylolisthesis L5-S1 développemental. Mémoire présenté à la Faculté des études supérieures en vue de l'obtention du grade de Maître ès sciences (M.Sc.) https://papyrus.bib.umontreal.ca/jspui/handle/1866/4964?locale=en

The forward angulation of the sacrum is an essential part of the normal curvature of the spine, referred to as "lumbar lordosis"[205] . However, in individuals who have an exaggerated curve and the sacrum extends backwards, to balance the trunk the lumbar spine is pushed forward increasing the slope of the top surface of the sacrum and thus the forces tending to slide L5 off the top of S1. An association between PI and spondylolisthesis has been reported in a number of studies [206]4-7.

[204] Pelvic incidence (or pelvis/sacral angle) is the sum of sacral inclination and pelvic tilting and is defined as the angle between a line perpendicular to the sacral plate at its midpoint and a line connecting the same point to the center of the bicoxofemoral axis.
[205] Lordosis is the term used to describe the inward curvature of a portion of the lumbar and cervical vertebral column.
[206] 4.Duval-Beaupère G, Schmidt C, Cosson P: A Barycentremetrix study of the sagittal shape of spine and pelvis: the conditions required for

However, PI has been shown to increase with age (in the studies of Mac-Thiong et al and Hanson et al.) and the increase attributed to age related adaptive changes which may suggest that PI may not be etiologic in spondylolisthesis (Wang et al., 2008)

The sagittal configuration of the sacrum has also been reported to be an important parameter in the occurrence and progression of spondylolisthesis[207]. Wang et al (2008) suggested that sacral morphology, as measured by the sacral table angle (STA), Figure 5.2.4, could be a more constant measure than the pelvic morphology, as measured by PI. The authors noted that a longitudinal study with age correlation will be needed to confirm this hypothesis.

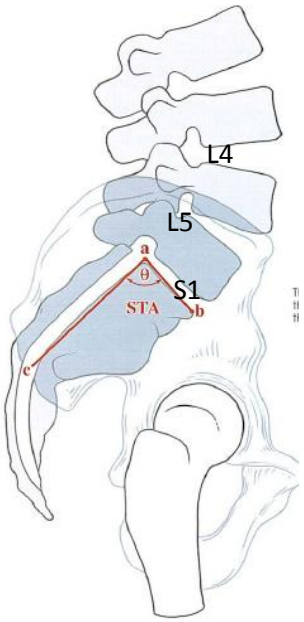


Figure 5.2.4. The sacral table angle (STA) which is the angle subtended by the sacral endplate line (ab) and a line drawn along the posterior aspect of the S1 vertebral body (ac). From Wang (2010) Influence de la morphologie sacro-pelvienne dans l'évolution du spondylolisthesis L5-S1 développemental. Mémoire présenté à la Faculté des études supérieures en vue de l'obtention du grade de Maître ès sciences (M.Sc.) https://papyrus.bib.umontreal.ca/jspui/handle/1866/4964?locale=en

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an ergonomic standing position. Ann Biomed Eng 1992,20:451-462. Labelle H, Roussouly P, Berthonnaud E, et al. Spondylolisthesis, pelvic incidence and sagittal spino-pelvic balance: a correlation study. Spine 2004, 29:2049-54. Huang RP, Bohlman HH, Thompson GH, et al. Predictive value of pelvic incidence in spondylolisthesis. Spine 2003,28:2381-5. Rajnics P, Templier A, Skalli W, et al. The association of sagittal spinal and pelvic parameters in asymptomatic persons and patients with isthmic spondylolisthesis. J Spinal Disord 2002, 15:24–30

[207] Marty C, Boisaubert B, Deschamps H, et al. The sagittal anatomy of the sacrum among young adults, infants, and spondylolisthesis patients. Eur Spine J 2002,11:119-25. Inoue H, Ohmori K, Miyasaka K. Radiographic classification of L5 isthmic spondylolisthesis as adolescent or adult vertebral slip. Spine 2002,27:831-838. Whitesides T.E., Horton W.C., Hutton W.C., et al. Spondylolytic spondylolisthesis: A study of pelvic and lumbosacral parameters of possible etiologic effect in two genetically and geographically distinct groups with high occurrence. Spine 2005,30:S12-S21.

Reviews of surgical and radiographic findings in patients with high-grade spondylolisthesisas well as biomechanical studies have suggested that abnormalities of the sacral growth plate may be a cause of high-grade slippage. Yue et al. [208]found that the only constant abnormal anatomic feature in twenty-seven patients treated for spondyloptosis was rounding of the proximal sacral end plate. Hu et al (2008) suggested that these studies have raised the question of which of these abnormalities, the pars interarticularis defect or the sacral growth plate, is the primary cause of spondylolysis and related spondylolisthesis.

[208] Yue WM, Brodner W, Gaines RW. Abnormal spinal anatomy in 27 cases of surgically corrected spondyloptosis: proximal sacral endplate damage as a possible cause of spondyloptosis. Spine. 2005;30(6 Suppl):S22-6.

5.3 Spondylolytic spondylolisthesis (also commonly known as isthmic spondylolisthesis[209])

There are reported to be two peaks in the temporal presentation of isthmic[210] spondylolisthesis one occurring between the ages of 5 and 7 years and a second occurring in the teenage years (Fredrickson et al., 1984). The development of the condition after the end of spinal growth and in adulthood is uncommon (Tsirikos & Garrido, 2010). Spondylolysis/spondylolisthesis has been frequently associated with various conditions with musculoskeletal abnormalities [211] as part of their overall presentation.

Although typically considered to be a paediatric condition, isthmic spondylolisthesis is reported to be more commonly **symptomatic** in adults. Although few studies have addressed the subject of adult isthmic spondylolisthesis [212] (Agabegi, Fischgrund, Agabegi, & Fischgrund, 2010) radicular pain and varying degrees of nerve root dysfunction are reported to present in adult isthmic spondylolisthesis patients and can be the result of compression of the L5 root within its foramen.

Classification

Three sub-types of spondylolytic spondylolisthesis are described in the Wiltse classification of spondylolisthesis (Wiltse, 1981), all involve defects (fractures) in the pars interarticularis. In the "classic" type a stress/fatigue fracture causes separation of the pars (lytic type, IIa), in another sub-type the stress/fatigue fracture heals (repeatedly) resulting in an elongated pars (elongated type, IIb), in the third (and rarest) sub-type there is an acute fracture of the pars.

Following a radiographic and morphologic study to investigate low-grade spondylolisthesis in cases with pre-existing L5 isthmic spondylolysis, Inoue et al (2002) concluded that slips with deformities of the sacral table were most likely to have developed in adolescence, while slips without this deformity were most likely to have developed during adulthood. On the basis of these findings they suggested that adult and adolescent low-grade spondylolytic spondylolisthesis could be distinguished (Inoue et al., 2002).

Isthmic spondylolisthesis has also been classified as low- or high-grade. Low-grade spondylolisthesis refers to slippage less than 50% (using the Meyerding classification) and high grade refers to slippage of greater than 50%. This distinction is considered to reflect differing reported natural histories in patients with low and high grade listhesis. In general, the higher-grade slippages are reported to have the highest risk of progressive deformity (Agabegi et al., 2010).

Unfortunately, the various different types of spondylolytic/isthmic spondylolisthes have often been grouped or discussed together blurring distinctions between them and as a consequence their aetiologies and natural histories.

[209] Hammerberg (2005) has suggested that the term "isthmic" should be avoided because it is a nonspecific anatomic reference and does not differentiate between developmental and acquired forms of spondylolisthesis. However, a large proportion of the literature in this area uses the term isthmic spondylolisthesis without making a distinction between developmental and acquired forms as defined in the classification of Marchetti and Bartolozzi (1997) and the term is retained in this report where it has been used in the literature.
[210] Wiltse LL, Rothman SLG: Spondylolisthesis: classification, diagnosis, and natural history. Semin Spine Surg 1:78–94, 1989
[211] Congenital anomalies, such as spina bifida occulta have been found to be associated with isthmic spondylolisthesis
[212] Peek RD, Wiltze LL, Reynolds JB, et al. In situ arthrodesis without decompression for Grade III and IV isthmic spondylolisthesis in adults who have severe sciatica. J Bone Joint Surg Am 1989;71: 62–8. DeWald CJ, Vartabedian JE, Rodts MF, et al. Evaluation and management of high-grade spondylolisthesis in adults. Spine 2005; 30(6 Suppl):S49–59.

Epidemiology

Spondylolysis (and presumably therefore spondylolytic spondylothisthesis) is reported never to have been present at birth (Woolfson, 2008). It is the common type of spondylolisthesis in people below 50 years and is the most common type of spondylolisthesis presenting in young people (Wiltse, 1981). Isthmic spondylolisthesis is reported to occur twice as often in males as females, however, the latter are fourfold more likely to suffer progression of the slippage. The prevalence of the condition increases in children and adolescents who are active in sports such as gymnastics, weight-lifting, swimming, wrestling and rowing. The incidence of spondylolysis varies from 11% in young gymnasts to 30% in wrestlers and as high as 43% in divers (Tsirikos & Garrido, 2010).

Aetiology

Isthmic or spondylolytic spondylolisthesis almost always occurs at the lower end of the spine. The most common site of presentation is at the L5–S1 level as the result of an L-5 *pars interarticularis defect*. It has been estimated that this pars abnormality is at L-5 in 90% of cases, L-4 in 5%, and other areas in the remaining cases[213](Ganju & Ganju, 2002).

Classic spondylolytic spondylolisthesis is reported to result from a bilateral defect in the pars interarticularis (bilateral spondylolysis). The posterior aspect of the vertebral body separates from the anterior body which is free to slip forward. A radiographic image of spondylolytic spondylolisthesis in Figure 19 shows a L5 vertebral body forward slip on the S1 vertebral body.

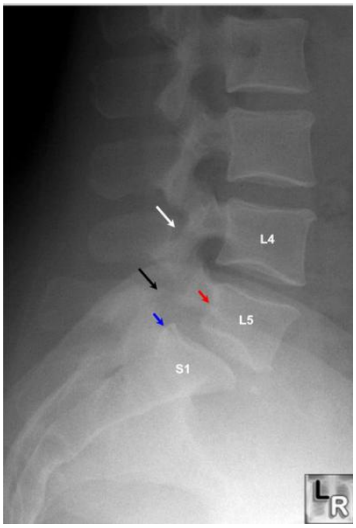

Figure 5.3.1. Grade 2 spondylolytic spondylolisthesis: lateral view of the lumbar spine demonstrates a bilateral break in the pars interarticularis (translucency shown by black arrow) that allows the L5 vertebral body (red arrow) to slip forward on the S1 vertebral body (blue arrow). The normal pars interarticularis is shown by the white arrow.

[213] Wiltse LL, Winter RB: Terminology and measurement of spondylolisthesis. J Bone Joint Surg Am 65:768–772, 1983

When the lumbar spine extends, the inferior articular process of the cranial vertebra impacts the pars interarticularis of the caudal vertebra. These repetitive impacts are postulated to produce a stress or fatigue fracture of the pars interarticularis. Lumbar extension is thought to concentrate shear stresses on a thin pars A number of findings are reported to support this mechanism (a) lumbar hyperextension activities, such as those undertaken in gymnastics and American football are associated with spondylolysis and (b) spondylolysis has never been reported in individuals that cannot walk[214] (Hu, Tribus, Diab, & Ghanayem, 2008).

However, more recently it has also been proposed that the pars interarticularis fails in tension through a *traction mechanism*[215]. Which of these two mechanisms is more likely to be present in a given individual is thought to be determined by the lordosis of the spine and the lumbosacral relationship (Hu et al., 2008).

While the incidence of isthmic spondylolisthesis is reported to be between 4-8% in the general population this incidence rises to 25-30% in near relatives of individuals with isthmic spondylolisthesis suggesting that **genetic factors** contribute to the condition. Ganju and Ganju (2002) considered that a congenital predisposition to spondylolysis in the setting of repeated microtrauma to the pars was the most likely cause of isthmic spondylolisthesis (Ganju & Ganju, 2002).

Whitesides et al (2005) in a study of two genetically and geographically distinct groups found that there was a genetically determined difference in the upper sacral tilt as described by the sacral table angle (STA), Figure 5.3.2

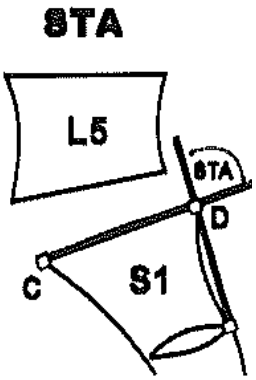

Figure 5.3.2. The sacral table angle. Adapted from Whitesides et al (2005)

They also determined that the radiographic parameter most strongly associated with the pars defect was also STA. Genetically homogeneous groups with a lower mean STA in the normals of that group (i.e. steeper sacral table tilt) were reported to have an increased occurrence rate of spondylolysis. The authors suggested that a genetic group with a higher STA in the normal population might be protected from a pars defect and thus from secondary slippage and deformities when compared

[214] Ferguson RJ, McMaster JH, Stanitski CL. Low back pain in college football linemen. J Sports Med. 1974;2:63-9. Jackson DW, Wiltse LL, Cirincoine RJ. Spondylolysis in the female gymnast. Clin Orthop Relat Res. 1976;117:68-73. Ogilvie JW, Sherman J. Spondylolysis in Scheuermann's disease. Spine. 1987;12:251-3.

[215] Labelle H, Roussouly P, Berthonnaud E, Dimnet J, O'Brien M. The importance of spino-pelvic balance in L5-S1 developmental spondylolisthesis: a review of pertinent radiologic measurements. Spine. 2005;30(6 Suppl):S27-34. Labelle H, Roussouly P, Berthonnaud E, Transfeldt E, O'Brien M, Chopin D, Hresko T, Dimnet J. Spondylolisthesis, pelvic incidence, and spinopelvic balance: a correlation study. Spine. 2004;29:2049-54.

with other populations where the STA is lower. Mechanistically, in a normal subject standing erect, the greater the slope of the sacral table, the greater the shear stress on the disc and bending stress on the pars. It would therefore be protective from pars failure to have a high STA (Whitesides, Horton, Hutton, & Hodges, 2005).

Aetiology summary

Isthmic or spondylolytic spondylolisthesis results from a bilateral defect in the pars interarticularis. The causal factors are believed to be (a) a stress or fatigue fracture of the pars articularis and/or (b) a failure in tension through a traction mechanism related to postural changes and (c) a genetic pre-disposition.

Natural history

Low-grade isthmic spondylolisthesis has a *benign clinical course* in most patients, regardless of age (Agabegi et al., 2010). Progression is uncommon in the presence of <30% slippage and rarely occurs after adolescence (Tsirikos & Garrido, 2010). However, while skeletally mature individuals with low-grade spondylolisthesis are generally asymptomatic they may become symptomatic in adulthood and seek treatment. The higher the grade of slip the more likely it is to progress. (Agabegi et al., 2010).

Symptomatic high-grade isthmic spondylolisthesis in children and adolescents is reported to have an unfavorable natural history with a high risk of progression. However, adults with high-grade slips Adults with high-grade slips have often reached a stable position and typically do not experience progression (Agabegi et al., 2010).

Frederickson et al (1984) in a longitudinal study of 500 children, reported that approximately 15% of individuals with a pars interarticularis lesion progressed to spondylolisthesis and that the slip was seen predominantly during the growth spurt with minimal change after the age of 16 years (Fredrickson et al., 1984). Individuals with the pars lesion were followed for over 40 years (Beutler et al., 2003). In this population;

- no slip was >40% and only five subjects developed a slip of 25% or more
- slip progression appeared to slow with each decade with slip progression greatest early in life; progression for all subjects in the second decade was 7.5%., in the third and fourth decades the slip progressed 2% and 5%, respectively, in the fifth decade slip progression was an average of 1%.
- of 10 patients that developed spondylolisthesis after initially not having a slip, eight developed the slip as a teenager, and the remaining two between age 20 and 40 years
- disc height of the involved segment (as a ratio of the disc above to the involved level) decreased over the 40 years
- marked disc degeneration at the level of the slip was seen in only 3 subjects (two with listhesis and one without)
- the progression of the slip was associated with further disc degeneration
- at the onset of the sixth decade of the 19 subjects with spondylolisthesis only five had progressed to grade II spondylolisthesis.

5.4 Degenerative Spondylolisthesis

In a recent evidence based review of the diagnosis and treatment of degenerative spondylolisthesis the North American Spine Society (NASS) workgroup published a consensus working definition of degenerative lumbar spondylolisthesis which was given as;

"An acquired anterior displacement of one vertebra over the subjacent vertebra, associated with degenerative changes, without an associated disruption or defect in the vertebral ring." (Watters et al., 2009)

Degenerative spondylolisthesis is essentially a forward slippage[216] of a lower lumbar vertebra, nearly always at the fourth lumbar level (Newman & Stone, 1963). It is generally reported to develop as a result of degeneration of the lumbar spine (Bolesta & Bohlman, 1989; Newman, 1976) and is associated with changes in the *articular facets* rather than the pars interarticularis. The condition *typically* occurs at one of two levels of the lumbar spine:

- The L4-L5 level of the lower spine (most common location)
- The L3-L4 level.

It is relatively rare at other levels of the spine, but may occur at two levels or even three levels simultaneously. While not as common as lumbar spondylolisthesis, cervical spondylolisthesis can occur. Jiang et al (2011) noted that degenerative cervical spondylolisthesis had generally received little attention and that the condition may be more common than previously thought. It was reported to be most common in C3/4 and C4/5, reportedly because of the relative hypermobility and the different pattern of movement in this area of the spine in association with the relaxation of surrounding ligaments and degenerative articular changes (Jiang et al., 2011).

Degnerative spondylolisthesis is usually asymptomatic but may progress to spinal stenosis (Jacobsen et al., 2007). It has traditionally been considered as one of the *major* causes of low back pain among the elderly and a major cause of spinal stenosis related to low back pain and leg pain (Kalichman & Hunter, 2008a). The condition is found in classifications of spondylolisthesis, spinal stenosis and segmental instability indicating a varied clinical presentation (Kalichman & Hunter, 2008b). Watters et al (2008) noted that degenerative spondylolisthesis was an anatomic finding and that clinical symptoms varied; patients may be asymptomatic but they may also present with present with axial back pain, or with neurogenic claudication and/ or radicular pain, with or without axial back pain (Watters et al., 2008). Slippage is reported to be generally mild (Grade I) because it is limited by an intact neural arch (Woolfson, 2008) and rarely exceeds 30% of the width of the subjacent vertebra.

The lesion in degenerative spondylolisthesis was reported by Wiltse (1981) to be due to longstanding instability with subsequent remodelling of the articular processes and changes in the direction of these processes with one side almost always rotating more than the other [217] (Farfan, Osteria, & Lamy, 1976; Wiltse, 1981). The typical "hour glass" deformity shown on myelograms was believed by Farfan to be due to rotation of the upper vertebra with displacement of the pedicel, Figure 5.4.1.

[216] It should be noted that there can be a posterior displacement (retrolisthesis). Personal communication, Graham Martin, reviewer.
[217] Farfan, H.F.: Mechanical disorders of the low back. Lea & Febiger, Philadelphia, 1973.

Figure 5.4.1. AP myelogram of a typical case of degenerative spondylolisthesis. From Wiltse 1981.

Epidemiology

Degenerative spondylolisthesis is generally reported to be more common in people over the age of 50 years, rarely seen in individuals under 40 years and far more common in individuals older than 65. It is also more common in females than males by a 3-6:1 margin depending on the study and the presence of symptoms in the study population[218] (Wiltse, 1981). In patients presenting with degenerative **cervical** spondylolitsdheis the difference in the incidence between men and women was reported as not statistically significant (Jiang et al., 2011) .

Overall the epidemiology of degenerative spondylolisthesis is not well reported. Pathogenetic studies of degenerative spondylolisthesis are reported to have gained prominence compared to epidemiological studies and the relatively few epidemiological studies published have been criticised for involving selected groups recruited at spine centres and thus being of risk for biased conclusions (Jacobsen et al., 2007).

To remedy this Jacobsen et al (2007) carried out a comprehensive cross-sectional epidemiological survey of lumbar degenerative spondylolisthesis in an **unselected** cohort of 4151 study subjects from *22 to 93 years* of age[219]. This study confirmed prevalence estimates of approximately 6% of L4 degenerative spondylolisthesis in white women with L4 slips about five times more frequent than L5 slips; L4 slips in men were only two times more frequent than L5 slips.

The overall male to female ratio of lumbar degenerative spondylolisthesis was 1:5. An increase of BMI observed during 17 years and BMI assessments at the time of radiographic recording (1993) were significantly associated with L4 and L5 degenerative spondylolisthesis in women. Increased angle of lumbar lordosis also constituted a significant risk factor of slip development in women. However, mean differences were marginal, and odds ratios were quite slim regarding both longitudinal assessment of BMI development and relative lordosis. In men only increased age was reported to be associated with L4 degenerative spondylolisthesis (Jacobsen et al., 2007).

[218] Rosenberg, N.: Degenerative spondylolisthesis, predisposing factors. J. Bone and Joint Surg., 57-A:467, 1975.
[219] This was the Copenhagen Osteoarthritis Study, a sub study of the Copenhagen City Heart Study. The Copenhagen City Heart Study is a longitudinal survey of an adult, white cohort selected from the county of Osterbro in Copenhagen.

In a similar community-based study cross-sectional study and ancillary project to the Framingham Heart Study, Kalichman et al (2010) reported on the age specific prevalence of degenerative spondylolisthesis in this unselected population, Table 5.4.1. This confirmed the fact that the condition was rare in those under 50 years but thereafter increased with age (Kalichman & Kim, 2010).

Table 5.4.1. Age specific prevalence of degenerative spondylolisthesis.

Degenerative condition	<40years	40-49 Y	50-59 y	60+ y
Age specific prevalence of degenerative spondylolisthesis n (%)	0(0)	1 (2.1)	7 (10.8)	17(35.4%)

A number of **significant associations** were demonstrated. In univariate regression, **facet joint osteoarthritis** was significantly associated with other spinal degenerative features, such as

- disc narrowing
- spondylolysis
- degenerative spondylolisthesis
- low density of multifidus and erector spinae (muscle).

Disc narrowing also showed significant association with degenerative spondylolisthesis. Degenerative spondylolisthesis showed significant association with density of multifidus and erector spinae.

In a multiple logistic regression analyses, facet joint osteoarthritis showed significant association with low density of multifidus and erector spinae and close to significant association with spondylolysis and degenerative spondylolisthesis. Degenerative spondylolisthesis showed close to significant association with disc narrowing and low density of multifidus. While these results in an unselected population are of interest, the cross-sectional design of this study *does not permit the establishment of causal relationships* (Kalichman & Kim, 2010).

Aetiology

Degenerative lumbar spondylolisthesis

Martin et al (2007) in a systematic review of the surgical management of degenerative lumbar spondylolisthesis stated that it was;

"a pathologic state where the combination of arthritic and degenerative changes in disc and facet joints results in vertebral displacement and ensuing spinal stenosis." (C. R. Martin et al., 2007)

While this general statement of causation is echoed in most of the reviewed literature there is ongoing debate as to the precise mechanisms involved and the nature of the primary underlying cause(s).

In 1963 Newman and Stone reported that slippage in 80 cases with an intact neural arch was due to an *acquired deficiency in the facet joints* (Newman & Stone, 1963). Marked *osteoarthritic changes* were invariable present in the *facet joints* and there was involvement of the nerve tissue, either the 5th lumbar root or less commonly the cauda equina.

Measurement of slippage for up to 15 years showed an average slip of 2 millimetres every four years during the progressive period of the slip which was never reported to go further than a quarter of the diameter of the vertebral body. At operation in all cases, it was found that the *inferior articular facets* of the slipping vertebra, exhibiting severe *degenerative change*, had ground their way between the superior facets of the vertebra below in a forward direction. Owing to the anterior hook of the superior facets , the degree of slipping was halted before it became severe (Newman & Stone, 1963). Stone, reporting further on the aetiology of degenerative spondylolisthesis noted that at operation;

" The neural arch of the slipping vertebra is not loose as in another type of spondylolisthesis. On either side lateral to the lamina is found a mound of osteophytic bone without evidence of the joint line between the two facets. When the dome of this mound has been removed it is seen that the inferior articular facet of the fourth lumbar vertebra has sunk in and become covered over by the osteophytic outgrowths from the superior articular facet of the vertebra below. After removal of the lamina it is often found that the dura is compressed from either side by osteophytic outgrowths from these joints, presenting an hour-glass constriction. These combined with the osteophytic ridge of the back of the superior angle of the body of the fifth lumbar vertebra give a marked constriction of the spinal canal (Fig. 23). Not until a partial facetectomy has been performed are the fifth lumbar roots found. These are seen to be compressed beneath the anterior edge of the superior articular facets."

The relative height of the inter-crestal line, relative strength of the iliolumbar ligaments, degree of pelvic inclination/ reclination, degree of adjacent disc degeneration, and L1–S1 angle (relative lordosis) are other possible causative factors that have been investigated in cadaver, skeletal, or radiologic studies (Fitzgerald & Newman, 1976).

More recently, Jabcobsen et al (2007) noted that a1:5 male-female ratio of degenerative spondylolisthesis had long been recognized but inconclusively explained. A postmenopausal decrease in estrogen production was reported to play a role in the pathogenesis of osteoarthritis in women in a number of studies[220] . Jacobsen et al (2007) further noted that the rise of L4 degenerative spondylolisthesis incidence occurred in middle age, for women about the normal age for menopause (Jacobsen et al., 2007).

Jacobson et al (2007) also noted that some authors had observed increased sagittalisation of the facet joints in patients with degenerative spondylolisthesis compared to normal individuals and suggested that that mal-orientation of the facet joints was at the pathogenetic core of the slip; others were reported to have argued that have argued that loss of *soft tissue resistance* precedes

[220] Schnohr P, Jensen G, Lange P, et al. The Copenhagen city heart study- O¨sterbroundersøgelsen - tables with data from the third examination 1991– 1994. Eur Heart J 2001;3:1–83. Jacobsen S, Sonne-Holm S, Soballe K, et al. Factors influencing hip joint space in asymptomatic subjects. A survey of 4151 subjects of the Copenhagen City Heart Study: The Osteoarthritis Substudy. Osteoarthritis Cartilage 2004;12:698–703.

facet joint failure, while other researchers hypothesized that mal-orientation of the facet joints is the *result* of degenerative remodelling, not the cause of it [221] (Jacobsen et al., 2007).

Facet joint orientation in relation to degenerative spondylolisthesis was further explored a case-control study published two years later (Toyone et al., 2009). The authors considered that while facet joint orientation, facet joint osteoarthritis, synovial cysts and facet joint effusion had all been linked with degenerative spondylolisthesis, the precise aetiology of the condition remained uncertain; greater sagittal orientation of the fact joints at L4-L5 in patients with degenerative spondylolisthesis had been considered as both a cause and an effect. Toyone et al (2009) found that the cephalad part of the facet joints were significantly more sagittaly orientated and that the caudal parts of the facet joints were more coronally orientated in patients with degeneratative spondylolisthesis than those without any evidence of the condition. These findings were observed at the uninvolved L3-L4 level as well as at the involved L4-L5 level. The authors concluded that these results supported the view that such spatial differences in the facet joints were part of the pre-existing morphology and not solely a secondary result of spondylolisthesis (Toyone et al., 2009).

In a review of neuroimaging of spinal diseases Kasdan and Howard (2008) declared that degenerative spondylolisthesis was due **to degenerative disc disease and facet arthropathy** at L4–5 and that degenerative spondylolisthesis occurred with narrowing of the spinal

canal (R. B. Kasdan & J. L. Howard, 2008). The authors went on to state that that in patients with degenerative spinal diseases the facet joints and discs tended to degenerate together with disc degeneration preceding facet degeneration[222]. However, in the same year Hu et al (2008) suggested that degenerative spondylolisthesis was secondary to osteoarthritis *leading* to facet incompetence and **disc degeneration** (Hu et al., 2008)

Following reports that the incidence of L5 sacralization was higher in patients with degenerative spondylolisthesis at L4-L5 than in the general population[223] Kong et al (2008) examined the relationship between the two conditions (Kong et al., 2008). In a review of the literature, the authors noted that an association between L5 sacralisation and the development of degenerative disc disease and degenerative spondylolisthesis in the lumbar spine had been proposed in a number of studies[224]. In an accompanying radiological study, Kong et al (2008) also found that the incidence of L5 sacralisation was higher (69%) in patients with degenerative spondylolisthesis at L4-L5. However, there were no significant differences between patients with and without sacralisation of L5 in four key radiographic parameters;

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[221] Grobler L, Robertson P, Novotny J. Etiology of spondylolisthesis. Assessment of the role played by of lumbar facet joint morphology. *Spine* 1993;18:80–91. Love T, Fagan A, Fraser R. Degenerative spondylolisthesis. Developmental or acquired? *J Bone Joint Surg Br* 1999;81:670–4. Matsunaga S, Sakou TMY. Natural history of degenerative spondylolisthesis. Pathogenesis and natural course of the slippage. *Spine* 1990;15:1204–10. McAfee P, Yuan H. Computed tomography in spondylolisthesis. *Clin Orthop Relat Res* 1982;166:62–71. Nagaosa Y, Kikuchi S, Hasue M. Pathoanatomic mechanisms of degenerative spondylolisthesis. *Spine* 1998;23:1447–51.

[222] Kirkaldy-Willis WH, Farfan HE. Instability of the lumbar spine. Clin Orthop Relat Res 1982;165:110–123 16. Butler D, Trafimow JH, Andersson GBJ, McNeill TW, Huckman MS. Discs degenerate before facets. Spine 1990; 15:111–113

[223] Cinotti G, Postacchini F, Fassari F, Urso S: Predisposing factors in degenerative spondylolisthesis. A radiographic and CT study. Int Orthop 1997; 21: 337-342. Lee CK, Langrana NA: Lumbosacral spinal fusion. A biomechanical study. Spine 1984; 9: 574-581. Tini PG, Wieser C, Zinn WM: The transitional vertebra of the lumbosacral spine: its radiological classification, incidence, prevalence, and clinical significance. Rheumatol Rehabil 1977; 16: 180-185.

[224] Berlemann U, Jeszenszky DJ, Buhler DW, Harms J: The role of lumbar lordosis, vertebral end-plate inclination, disc height, and facet orientation in degenerative spondylolisthesis.J Spinal Disord 1999; 12: 68-73. Castellvi AE, Goldstein LA, Chan DP: Lumbosacral transitional vertebrae and their relationship with lumbar extradural defects. Spine 1984; 9: 493-495. Elster AD: Bertolotti's syndrome revisited. Transitional vertebrae of the lumbar spine. Spine 1989; 14: 1373-1377. Magora A, Schwartz A: Relation between the low back pain syndrome and x-ray findings. 2 Transitional vertebra (mainly sacralization). Scand J Rehabil Med 1978; 10: 135- 145. Otani K, Konno S, Kikuchi S: Lumbosacral transitional vertebrae and nerve-root symptoms. J Bone Joint Surg Br 2001; 83: 1137-1140. Wigh RE, Anthony HF Jr: Transitional lumbosacral discs. Probability of herniation. Spine 1981; 6: 168-171.

- anterior slippage of L4 on L5
- facet orientation of L4-L5
- facet osteoarthritis of L4-L5,
- disc degeneration of L4-L5.

These findings suggested that degenerative changes in the facet joints and intervertebral disc were already far advanced in degenerative spondylolisthesis itself and that the presence of sacralisation did not have a significant additional effect on radiographic changes in degenerative spondylolisthesis. The authors concluded that the influence of sacralisation of L5 (on radiological findings) in degenerative spondylolisthesis at L4-L5 *may be less significant than previously suggested.*

Kalichman and Hunter (2008) conducted a narrative review of the anatomy, biomechanics and risk factors for degenerative spondylolisthesis. Following an examination of the roles of a number potential causal (e.g. postural changes, disc degeneration, orientation of the facet joints and muscular factors) and associated factors (including age, sex, pregnancy, genetic predisposition and body composition, osteoporosis, diabetes, physical activity and occupation) the authors concluded that degenerative spondylolisthesis was a complex multifactorial problem and that a combination of *lumbar facet joint degeneration with segmental hypermobility* could potentially lead to degenerative spondylolisthesis (Kalichman & Hunter, 2008a). The authors summarised their findings in a scheme to indicate the relative contributions of potential predictors (Kalichman & Hunter, 2008a).

In a review of the current knowledge of facet joints Varlotta et al (2011) reported that Macnab (1950)[225] implicated degenerative changes in the *posterior ligamentous structures* as well as in the facet joints and that Chaput et al. (2007) in a case control study found that patients with degenerative spondylolisthesis were more likely to have a *higher grade of facet joint osteoarthritis*[226](Chaput et al., 2007; Varlotta et al., 2011). Varlottal et al (2011) also reported on a growing support in the medical literature for the idea that **sagittal orientation** *of the facet joints* was an important factor in the development of degenerative spondylolisthesis[227] and noted that **facet joint tropism** (asymmetry between right and left facet joint angles) was being increasingly studied with respect to the condition.

Degenerative cervical spondylolisthesis

Degenerative *cervical* spondylolisthesis is much less reported in the literature than degenerative lumbar spondylolisthesis. Jiang et al (2011) in a systematic review of eight published studies of degenerative cervical spondylolisthesis stated that:

"Disc degeneration and facet hypertrophy were the main causes of this clinical entity."(Jiang et al., 2011)

[225] Macnab I. Spondylolisthesis with an intact neural arch—the socalled pseudospondylolisthesis. J Bone Jt Surg Br. 1950;32:325–33.
[226] They were also more likely to have had synovial cysts and larger effusion sizes
[227] Grobler LJ, Robertson PA, Novotny JE, Pope MH. Etiology of spondylolisthesis. Assessment of the role played by lumbar facet joint morphology. Spine. 1993;18(1):80–91.Berlemann U, Jeszensky DJ, Buhler DW, et al. Facet joint remodeling in degenerative spondylolisthesis: an investigation of joint orientation and tropism. Eur Spine J. 1998;7:376–80. Cinotti G, Postacchini F, Fassari F, Urso S. Predisposing factors in degenerative spondylolisthesis. A radiographic and CT study. Int Orthop. 1997;21(5):337–42. Kim NH, Lee JW. The relationship between isthmic and degenerative spondylolisthesis and the configuration of the lamina and facet joints. Eur Spine J. 1995;4(3):139–44. Nagaosa Y, Kikuchi S, Hasue M, Sato S. Pathoanatomic mechanisms of degenerative spondylolisthesis. A radiographic study. Spine. 1998;23(13):1447–51. Sato K, Wakamatsu E, Yoshizumi A, Watanabe N, Irei O. The configuration of the laminas and facet joints in degenerative spondylolisthesis. A clinicoradiologic study. Spine. 1989;14 (11):1265–71. Dai LY. Orientation and tropism of lumbar facet joints in degenerative spondylolisthesis. Int Orthop. 2001;25:40–2.

These authors hypothesised that rigidity or ankylosis could diminish cervical spine mobility increasing stress on the adjacent discs and facets and *stretching the disc and ligaments*, allowing slippage to occur. They also reported that that thinning of the facets and narrowing of the joint space was also hypothesised to be the primary cause of degenerative cervical spondylolisthesis rather than the disc involvement[228]. Restabilisation of degenerative spine conditions was postulated to prevent progression of the disease and lead to various forms of deformity.

It was reported to be difficult to correlate the symptoms to severity of spondylolisthesis (Jiang et al., 2011).

Aetiology summary

Degenerative spondylolisthesis has been described as a complex multifactorial problem. It is interlinked with other pathologies, such as disk degeneration, facet joint osteoarthritis and spinal stenosis. Its aetiology and the pathomechanics of vertebral slipping remain unclear. While it is almost universally reported to be an acquired condition of the elderly in which degenerative changes in the disc and arthritic changes in the facet joints are causally implicated, debate continues as to the primary underlying cause. Recently, there has been particular interest in the role of a number of potential contributors to the development of the condition. These include postural deviations, the orientation of the facet joints, sacralisation of L5, hormone changes (in females with degenerative spondylolisthesis), and degenerative changes in the posterior ligamentous and muscle structures.

Natural history of degenerative lumbar spondylolisthesis

One of the questions posed by the North American Spine Society Evidence-Based Clinical Guidelines for the Diagnosis and Treatment of Degenerative Lumbar Spondylolisthesis (Watters et al., 2008) related to the natural history of the condition;

"What happens to patients with degenerative lumbar spondylolisthesis who do not receive treatment?"

The guideline identified and reviewed four studies reporting on the natural history of degenerative spondylolisthesis published between 1990 and 1998 (Kauppila, Eustace, Kiel, Felson, & Wright, 1998; Matsunaga, Ijiri, & Hayashi, 2000; Matsunaga, Sakou, Morizono, Masuda, & Demirtas, 1990; Vogt et al., 1998). These studies were reported to provide level II and III evidence in relation to the natural history of degenerative lumbar spondylolisthesis.

Matsunga et al (1990) retrospectively reviewed 40 patients with a follow-up period that averaged eight years. Progression of slippage[229] was observed in 30% of patients which were defined as the "progressive group". These patients did not show any difference in age at presentation, duration of illness or duration of follow-up when compared with the larger "nonprogressive group". Further, whereas the lumbosacral angle, lamina angle and facet inclination angle were greater than normal in both groups, there were no significant differences between the progressive and nonprogressive groups. Progression of the slip did not correlate with clinical symptoms. No progression of slippage was noted in patients who showed narrowing of the intervertebral disk, spur formation,

[228] Lee C, Woodring JH, Rogers LF, Kim KS (1986) The radiographic distinction of degenerative slippage (spondylolisthesis and retrolisthesis) from traumatic slippage of the cervical spine. Skeletal Radiol 15:439–443

[229] Where progression was defined as a slippage rate of 5% or more during the observation period

subcartilaginous sclerosis, or ossification of ligaments and it was suggested that mechanisms of spinal restabilization prevent progression of the disease. Slip was reported to be more likely to progress in labourers whose jobs required repetitive anterior flexion of the spine (Matsunaga et al., 1990)[230].

Matsunga et al (2000) carried out a further prospective study of 145 nonsurgically managed patients (36 men and 109 women) with more than more than 10 years (range 10-18 years) of follow-up (Matsunaga et al., 2000) . This study was performed to determine (a) the progression of spondylolisthesis, (b) changes in clinical symptoms, and (c) patients' final functional abilities. With progression of slippage defined as a slippage rate of 5% or more during the observation period, progression was found in 49 cases (34%). The final percentage of slippage averaged 15.6% (7–29%). A percentage of slippage of 25% or more was found in 10 cases.

The patients in whom a decreased intervertebral space size was demonstrated exhibited no subsequent progression of slippage. In contrast, 49 (96%) of 51 patients in whom no decrease in intervertebral space size was demonstrated, exhibited progression of slippage. The degree of decrease in the size of the intervertebral space was reported to be significantly larger in the group of 23 patients in whom slippage did not progress as compared with the group in whom it did. Instability [231]was demonstrated in 76 patients at the first visit; however, this instability decreased steadily over the follow-up period. Interestingly 85 (90%) of 94 patients in whom a *decrease* in intervertebral space size was demonstrated over the period experienced *improvement* of low-back pain (Matsunaga et al., 2000).

The authors suggested that restabilization occurred over the natural course of degenerative spondylolisthesis and that an observed decrease in the range of motion of the slipped segment supported this suggestion. In this study, many patients who had no neurological deficits at initial examination remained free of neurological deficits after 10 years follow-up study, however, most patients who had neurological symptoms at the initial examination and refused surgery suffered deterioration of these symptoms (Matsunaga et al., 2000).

Vogt et al (1998)[232] conducted a cross-sectional study of white Pennsylvanian women over 65 years. Anterolisthesis was found in 29% of the study population, was most likely to occur at a single level and did not necessarily correlate with back pain.

Kauppila et al (1998) retrospectively studied a cohort 217 men and 400 women in who radiographs were taken at a mean age of 54 years and again at 79 years. Twelve percent of the men and 25% of the women developed degenerative spondylolisthesis (defined as > 3mm forward or backward slip). Only one third of patients were symptomatic. The authors concluded that degenerative spondylolisthesis could be acquired in an asymptomatic population with a higher incidence in females (4:1).

These studies reported a number of characteristics of untreated degenerative spondylolisthesis, which included;

[230] Woolfson (2008), reported in a synopsis of causation of spondylolisthesis for the UK Ministry of Defense that there was no evidence that any particular activities such as heavy manual work were associated with degenerative spondylolisthesis.
[231] With the assumption that an angular displacement of 9° or more constitutes instability.
[232] Vogt MT, Rubin D, Valentin RS, et al. Lumbar olisthesis and lower back symptoms in elderly white women. The Study of Osteoporotic Fractures. *Spine.*1998;23(23):2640-2647.

- a higher incidence in females than males
- single level slips
- no association with the presence of back symptoms
- progression of slip estimated to occur in 30-34% of patients not deemed to need surgery, with 77% of these patients experienced improvement during follow-up
- progression not associated with age at presentation, duration of illness or duration of follow-up
- in patients who refused surgery, 83% had worsened neurologic deficit on examination, which was noted **not to correlate** with the progression of slippage.

5.5 Synovial cysts

Synovial cysts are ovoid masses that are intraspinal and extradural (Ustuner, Tanju, Dusunceli, Deda, & Erden, 2007). They are defined in the National Library of Medicine Medical Subject Headings (MeSH 2012)[233] as:

"Non-neoplastic tumor-like lesions at joints, developed from the SYNOVIAL MEMBRANE of a joint through the JOINT CAPSULE into the periarticular tissues. They are filled with SYNOVIAL FLUID with a smooth and translucent appearance."

Spinal synovial cysts have been identified as a cause of back pain, radicular symptoms, and neurogenic claudication. The cysts mostly originate from the facet joints and while they may occur in the cervical and thoracic spine, they are most commonly found in the lumbar region (Gupta & Lutz, 2010). The first description of a *spinal* synovial cyst, is *credited to* Von Gruker in 1880, who initially discovered this lesion while performing an autopsy (Gelabert-Gonzalez, Prieto-Gonzalez, Santin-Amo, Serramito-Garcia, & Garcia-Allut, 2009). The first report of *symptoms attributed to spinal cysts* was made by Vosschulte and Borger in 1950 who described spinal nerve root compression by synovial cysts. Kao et al confirmed this report in 1968 (C. C. Kao, Uihlein, Bickel, & Soule, 1968). Since then a large amount of clinical literature has accumulated on spinal cysts of various types.

Although synovial cysts are an uncommon cause of radicular pain, improvements in neurological imaging techniques, such as computed tomography and magnetic resonance imaging, have resulted in increased reports of synovial cysts being identified as causative agents of radicular pain. The reported location and frequency of synovial cysts varies. They are reported to occur most frequently in the lumbar spine (88% to 99% depending on the series), followed by the thoracic spine (up to 8%) , and the cervical spine (1% to 4%), and are more common reported in patients over 60 years (Gelabert-Gonzalez et al., 2009).

Nomenclature, definition and classification

The peer reviewed literature relating to synovial spinal cysts presented a number of problems. Wide variations in the nomenclature used to describe these cysts posed difficulties in relation to the literature search[234] and variation in the definition of synovial cysts caused problems in the determination of eligibility. The relevance of this problem in the current context is that some eligible studies may have been missed because of idiosyncratic nomenclature and some of the reviewed studies purporting to report on synovial cysts may not be reporting homogeneous populations in relation to cyst type.

Multiple forms of spinal cysts have been reported in the literature. These include;facet cyst, zygapophyseal joint or z-joint cyst, synovial cyst, juxtafacet cyst, extradural juxtaarticular cyst, ganglion cyst, degenerate articular cyst, discal cyst, intraspinal cyst, ligamentum flavum cyst, transverse ligament synovial cyst and intraspinal degenerative cyst.

Depending upon its location, origin, and histological features a spinal cyst may be classified as;

[233] http://www.nlm.nih.gov/cgi/mesh/2012/MB_cgi
[234] This affected both the sensitivity and specificity of the search.

- synovial cyst (SC)
- ganglion cyst (GS)
- ligamentum flavum cyst (LFC)
- posterior longitudinal ligament cyst (PLLC

In a recent clinical study, Ayberk et al (2008) reported on each of the four types of spinal cyst describing their histology, location and diagnostic characteristics (Ayberk et al., 2008), Figure 5.5.1.

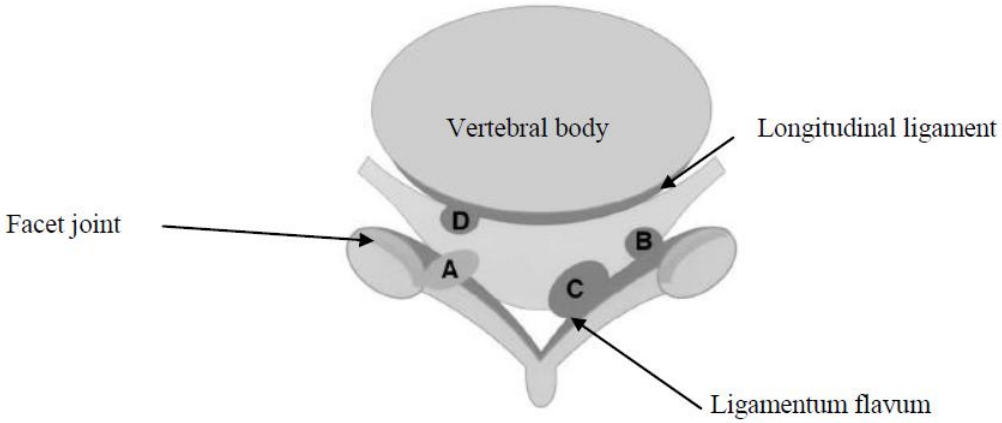

Figure 5.5.1. **Schematic drawing of different types of lumbar spinal cyst. A Synovial cyst located posterolateral to the lumbar spinal canal; B=Ganglion cyst located posterolateral to the lumbar spinal canal; C= Ligamentum flavum cyst located posterior to the lumbar spinal canal; D= posterior longitudinal ligament cyst located anterolateral to the lumbar spinal canal. Adapted from Ayberk (Ayberk et al., 2008).**

Synovial cysts are generally distinguished by their lining of epithelial tissue and continuity with the facet joint. *Ganglion cysts* may be distinguished by their periarticular location, *lack of* epithelial cell lining and lack of continuity with the synovial cavity of the facet joint; *ligamentum flavum cysts* may be distinguished by their location (embedded in the inner surface of the ligamentum flavum) and lack of epithelial lining and no continuity with facet joint synovium; *posterior longitudinal ligament cysts* may be distinguished by their location in the PLL and lack of epithelial lining and no continuity with facet joint synovium.

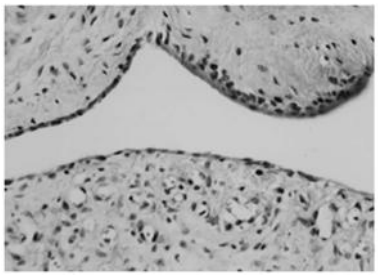

Figure 5.5.2. Photomicrograph of a synovial cysts lined with a compressed single layer of epithelial cells. From (Ayberk et al., 2008).

However, despite the existence of, what would appear to be, a relatively straightforward classification system, there appears to be considerable confusion in the reporting of these entities in clinical literature, and in particular between synovial and ganglion cysts. Indeed, Ayberk et al (2008) at times referred to all four types of spinal cysts as "synovial cysts".

Many other examples of inconsistencies in the nomenclature used to describe spinal cysts were found. For example, the term juxtafacet or epidural cyst was used synonymously for both synovial and ganglion cysts and to describe all cysts located adjacent to the facet joints or arising from or extending into the ligmentum flavum (Christophis, Asamoto, Kuchelmeister, & Schachenmayr, 2007; Freidberg, Fellows, Thomas, & Mancall, 1994; Gupta & Lutz, 2010).

Wilby et al (2009) also acknowledged this problem citing at least six different terminologies for these cysts;

- synovial cysts
- ganglion cysts
- pseudocysts
- lumbar intraspinal facet cysts
- fibrous cysts
- cystic formations of mobile spine

They are also referred to simply as "*facet cysts*" in a number of studies.

The confusion was added to in 2004 in a paper describing *synovial excrescences* which were described as *hyperplastic irritated synovium* of the spine, voluminous with the reactive part overshadowing the cystic portion of the lesion in most instance (Sze et al., 2004).

Wilby et al (2009) also drew attention to anomalous interpretations of cyst pathology and the assertion by some that *synovial* and *ganglion* cysts were the same entity (C. C. Kao, Winkler, & Turner, 1974). It was suggested that contradictions in the terminology applied to lumbar juxtafacet cysts arose from the frequent scarcity of synovial lining cells, which has led to synovial cysts often

being called "ganglion cysts" despite lacking confirmatory pathology (Wilby, Fraser, Vernon-Roberts, & Moore, 2009).

It has also been argued that there is no clinical relevance to a differentiation between ganglion and synovial cysts, as their presentations, treatments, and prognoses are identical (Howington, Connolly, & Voorhies, 1999; Amir M. Khan, Synnot, Cammisa, & Girardi, 2005; Onofrio & Mih, 1988; Sabo, Tracey, & Weinger, 1996). Another popular argument for not distinguishing between ganglion and synovial cysts is that they are part of a continuum with continuity with the facet synovia becoming lost.

In the current report, *spinal synovial cysts* are defined as cystic lesions located in the posterolateral side of the spinal canal, which *remain in continuation with the facet joints usually have a watery or xanthochromic content and are lined by cuboid epithelium-like synovial cells*. They may be distinguished from ganglion cysts which do not have an epithelial lining or continuation with the synovial cavity and from cysts arising in the ligamentum flavum or the posterior ligament by location (Bydon et al., 2010; Khalatbari & Ansari, 2008).

Imaging characteristics

Imaging plays an important role in the identification, diagnosis and classification of spinal cysts and the majority of degenerative changes in the facet joint are easily recognised with standard MRI. However, some changes are not easily imaged and may remain occult ; D'Aprile et al (2007) advocated the use of T2 fat-weighted images to visualize degenerative-inflammatory changes in the lumbar spine (D'Aprile, Tarantino, Jinkins, & Brindicci, 2007).

Based on MRI features, a synovial cyst appears as a smooth, extradural, well-circumscribed, cystic mass arising adjacent to the facet joint Figure 5.5.3.

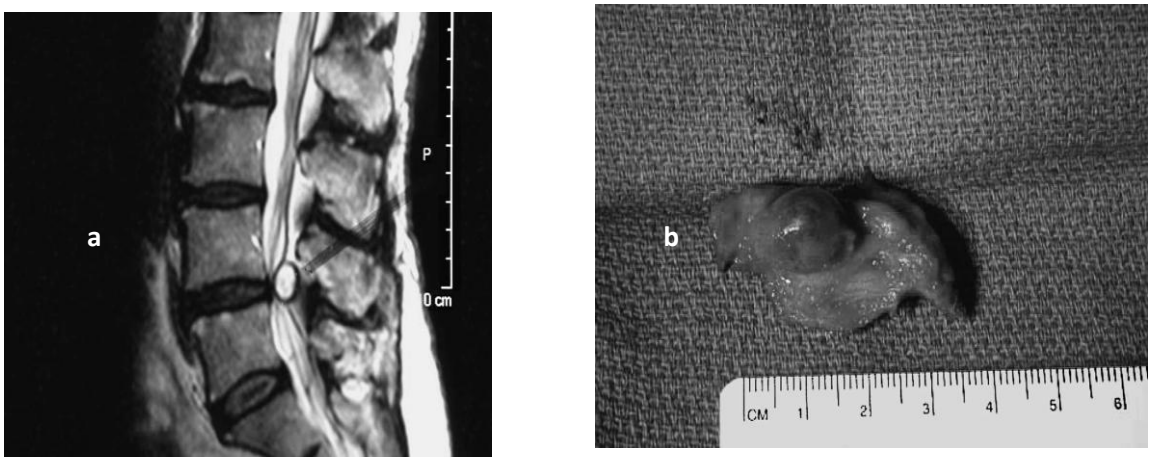

Figure 5.5.3. a. A pre-operative sagittal MRI of the spine demonstrating a right synovial cyst at L4-5 level, b. A synovial lumbar cyst retrieved from surgery. (Amir M. Khan et al., 2005)

Synovial cysts without haemorrhage appear isointense (same intensity), or slightly hyperintense (more bright), relative to the cerebrospinal fluid on T1- weighted images. In some cases,

haemorrhage into the cyst occurs. The low signal intensity at the rim of the haemorrhagic cyst on T2-weighted MR images has been reported to be due to the presence of a fibrous capsule with haemosiderin (iron-storage complex) deposits noted pathologically (Maezawa et al., 2000).

However, it has been noted that while the sensitivity of MRI scans to detect spinal cysts is 90%, the rate of visualisation of the *connection to the facet joint can be low* (Alicioglu & Sut, 2009; Chaput et al., 2007), thus without surgical/histological confirmation it may not be possible to distinguish between ganglion and synovial cysts with certainty using MRI.

Methods

Search results

A MEDLINE search of the literature for studies reporting on synovial cysts of the spine using MeSH terms and associated keywords identified 325 citations; 133 were published between 1972 and 1999 with the remaining 192 published between 2000 and 2011. Two hundred and thirty one citations specifically mentioned synovial cysts, 135 were published between 2000 and 2011 these were scanned for eligibility and/or relevance.

Three quarters (75%) of these publications reported single cases (47%) or small case series (28%), 12 were reviews of one sort or another (8%); there was one duplicate publication and the remainder (16%) were not relevant to the current review. Thirty-five publications were considered to be potentially eligible or of interest and these were assessed/examined further for inclusion. Two of these studies reported on cervical cysts (Costa, Menghetti, Cardia, Fornari, & Ortolina, 2010; Shima, Rothman, Yasura, & Takahashi, 2002) and two reported on thoracic cysts (Almefty, Arnautovic, & Webber, 2008; Merkle, Psaras, Tatagiba, Danz, & Schmidt, 2009), where specified, the remainder reported on lumbar spinal cysts.

There were no systematic or narrative reviews that focused on etiology and or natural history of spinal synovial cysts. There were a number of narrative reviews (some embedded in clinical studies) that included literature reviews to elucidate aetiology, pathogenesis and/or natural history of these lesions.

Given the low number of reviews/overview identified and the lack of systematic reviews, an examination of pre- 2000 citations was carried out. The pattern of these publications did not differ from that of the more recent publications (case reports with literature reviews or case series) and no earlier systematic or narrative reviews were identified.

Aetiology

It is widely reported in the clinical literature that the aetiology of spinal synovial cyst is “unclear” or “unknown” (Alicioglu & Sut, 2009) and “the cause of some debate” (Boviatsis et al., 2008). Most clinical studies report that the aetiology of spinal synovial cysts is degenerative and includes arthritic disruption of the facet joint and spondylolisthesis. In a number of studies, acute or repeated micro trauma is implicated in their origin. Boviatsis et al (2008) suggested that repetitive minor injuries may go unnoticed/unreported and not come up in the patient’s history (Boviatsis et al., 2008).

No literature reviews were identified that focussed on the aetiology of spinal cysts and no clinical studies were identified that examined the question of aetiology in depth. Most clinical studies proffered some causal explanation, few supported their claims with high quality evidence or evidence based on large clinical studies.

The full text of thirteen reviews or clinical studies containing literature reviews was assessed. Four reported very little information/data of relevance to cyst aetiology (Arnold, 2009; Epstein, 2004; Richard B. Kasdan & Jaime L. Howard, 2008; Mathis & Ortiz, 2010) and are not reported further. Of the nine remaining publications, one was a systematic review of treatment outcomes that reported briefly on causation (Bydon et al., 2010), and one was a review/commentary of this systematic review (Gupta & Lutz, 2010). Seven publications included narrative literature reviews of varying depth and quality (Almefty et al., 2008; Apostolaki, Davies, Evans, & Cassar-Pullicino, 2000; Costa et al., 2010; A. M. Khan & Girardi, 2006; Moquin, 2006; Sze et al., 2004; Xu et al., 2011); four of these publications also included clinical reports (Almefty et al., 2008; Apostolaki et al., 2000; Costa et al., 2010; Xu et al., 2011) . Relevant evidence and/or information reported in these studies is presented below.

Systematic reviews

In a systematic review of postoperative outcomes in patients with spinal synovial cysts Bydon et al (2010) reviewed 83 studies. The authors reported briefly on the characteristics of a symptomatic patient population and on hypotheses relating to the possible causes of synovial cysts (Bydon et al., 2010). The evidence reported in the review was derived from a total population of 966 treated patients with a mean age of 64.7 years (±12.3 years); 49% of patients were male. The presenting symptoms included radicular pain (70%), back pain (48%) and neurological claudication (28%); 1% presented with recent trauma.

Most patients presented with lumbar synovial cysts at the L4-L5 level (68%), 14% presented with cysts at the L3-L4 level, 12% at the L5-S1 level, 2% at the L2-L3 level and less than 1% at the L1-L2 level. Synovial cysts in other areas of the spine were much less common with 2.6% located in the cervical spine and 1.2% in the thoracic spine.

Segmental instability and hypermobility were reported to play a pathoetiological role in synovial cyst formation, and it was noted that Knox and Fon (1991) demonstrated that over 85% of spinal synovial cysts were associated with degenerative changes in the facet joint beyond those associated with normal aging (Knox & Fon, 1991). In support of the role of hypermobility in the pathogenesis of spinal synovial cysts Bydon et al (2010) cited a number of retrospective case series (Bydon et al., 2010; Amir M. Khan et al., 2005) that reported better outcomes with segment fusion (stabilisation) than decompression or laminectomy.

In a review of Bydon's (2010) study, Gupta & Lutz (2010) argued that there was extensive controversy regarding the definition, prevalence, pathogenesis and risk factors of spinal synovial cysts and that there had been no prospective studies that compared the natural history to outcome after treatment. Three possible origins were suggested for the cysts - trauma, degenerative spondylosis and segmental instability. Quoting two recent case series (Ayberk et al., 2008; Bydon et al., 2010) Gutpa & Lutz (2010) theorized that the intraligamentous synovial cysts developed in the following sequence(Gupta & Lutz, 2010);

Osteoarthritis in the facet joint liberates fragments of debris off the joint surface

↓

The fragments act as free-floating bodies

↓

They eventually enter pre-existing bursal channels and become lodged

↓

The response is a granulomatous reaction leading to scar tissue

↓

Over time, blocking the bursa eventually leads to cystic dilatation

The greatest risk of synovial cyst development was reported to be at the L4–L5 level i.e. at the most mobile lumbar segment. It was argued that this level was subjected to most arthritic changes, has the greatest propensity for segmental instability, and has the largest and longest bursa[235] and was therefore most prone to developing synovial cysts. Blockage of the bursa was noted to occur up to 1 cm from the joint capsule. Gupta & Lutz (2010) also noted that the incidence of lumbar synovial cyst has increased with improvements in diagnostic imaging and reported recent statistics given by Ayberk et al (2008) which suggested an overall incidence between 0.65 to 2.3% (depending on the diagnostic method), and an overall prevalence of anterior and posterior facet joint cysts of 2.3% and 7.3% respectively. Back pain was noted to be the main symptom of posterior cysts with the ligamentum flavum acting as a barrier to the formation of anterior cysts (Ayberk et al., 2008).

Narrative reviews

Cervical spine

Costa et al (2010), in a short review of selected literature relating to *cervical synovial cysts* [236], reported on a possible mechanism of development of synovial cysts (Costa et al., 2010). They suggested that mechanically stressed joints induced up-regulation and release of *inflammatory factors* resulting in the creation of a cyst or extrusion of synovium through the joint capsule (possibly secondary to a trauma or instability)[237].

Thoracic spine

Almefty et al (2008) described four cases and reviewed the literature relating to 20 other reported cases. The scarcity of thoracic synovial cysts was believed to be due to the relative immobility of the thoracic spine (Almefty et al., 2008). Thus Almefty et al (2008) rejected the theory that increased facet joint movement and micro-trauma, proposed by some authors to be cause of lumbar synovial cysts, was the most likely cause of synovial cysts in the thoracic spine. The majority of thoracic cysts appeared to be located in the T10-T12 interspaces. For these cysts, stress due to differences in mobility in the lumbar and thoracic spine which accelerated degenerative changes was implicated in

[235] A synovial bursa is a closed fibrous sac lined with a smooth membrane, producing a viscous lubricant known as synovial fluid. Synovial joints ease movement through the use of this lubricating liquid, which is supplied by the synovial membrane that lines movable joints.
[236] These cysts are more rarely reported than lumbar cysts and at the date of publication the authors had only uncovered reports of 28 cysts.
[237] Another publication was reported on cervical ganglion and synovial cysts (Shima et al., 2002)

their aetiology. For the four cases reviewed by Almefty et al (2008), capsular inflammatory processes arising in the facet joint were hypothesised to initiate a series of processes (e.g. neovascularisation and calcification) leading to cyst development (Almefty et al., 2008).

Lumbar spine

Apostolaki et al (2000), in a literature review and clinical report of the MRI features of 40 patients with spinal synovial cysts, summarised the findings of over 100 clinical studies reporting on lumbar facet joint synovial cysts. Less than half of the patients in the clinical series had a diagnosis of lumbar facet synovial cyst confirmed by surgery or CT facet joint arthrograms. Data obtained from the literature review are reported below, Table 5.5.1.

Table 5.5.1. Features of synovial cysts reported in over 100 clinical studies reporting on lumbar facet joint synovial cysts. (Apostolaki et al., 2000)

Reported feature	Results	Number of clinical studies
Mean age	57 years (range 16-81 years)	15
% female	Female preponderance (53%)	15
Presenting features	Most presented with chronic low back pain, 84% with radicular symptoms[238], neurogenic claudication may be the presenting symptom. Cauda equine syndrome simulating an acute disc prolapse can be caused by spontaneous or post-traumatic haemorrhage into a cyst. Lumbar facet synovial cysts were also reported in patients with inflammatory arthopathies and gout, and following trauma or previous surgery. In one series most patients were asymptomatic at the time of diagnosis.	19
Cyst location	In 137 cases culled from the literature; L4-L5 level = 68% L5-S1 level = 15% L3-L4 level = 12% More proximal level = 5% Few reports specifically mentioned the side of the cyst; at least 6 cases of bilateral cysts were reported. The majority of cysts were reported to arise on the medial aspect of the facet joints within the posterolateral aspect of the spinal canal	20
Facet joint condition	Facet joint degeneration is an almost universal finding in the literature. In one series of 50 cases only 7 (14%) showed no signs of facet degeneration. In three further series, comprising 19, 6 and 5 cases, respectively, facet joint degeneration was found in all cases on MR imaging or CT. The incidence of a degenerative spondylolisthesis varied between 42 and 65%.	9
Cyst size	Studies indicated a lumbar facet synovial cyst size range of 5-25 mm.	6
Thecal sac compression	Thecal or lateral recess stenosis was reported to be a frequent finding	9
Bone erosion	A number of studies reported pressure effects on adjacent bones causing expansion of the lateral recess, lysis of the pars interarticularis and inferior articular process and focal scalloping of the posterior rim of the vertebral body.	9
Cyst wall	The wall of the cyst (rim) may become calcified, the surrounding tissue may be inflammatory. Showing marked image enhancement	4

In the ensuing discussion of the findings of the literature review and the clinical series, the authors argued that synovial and ganglion cysts had similar imaging characteristics and that the histopathology may be indeterminate where there is extensive scarring and the synovial lining is indistinct. In addition, they argued that both synovial and ganglion cysts appeared to arise in

[238] In one series 45 patients were asymptomatic at the time of diagnosis .

association with degenerative lumbar pathology and cause similar symptom complexes (Apostolaki et al., 2000). Thus in the review, the authors did not distinguish between synovial and ganglion cysts and used the term lumbar facet synovial cyst (LFSC) to include ganglion cysts. Using this broadened definition the authors then reported that the aetiology of "LFSC"s remained "poorly understood" and that a number of different theories had been put forward. The most favoured theory being the "protrusion of synovial tissue through a capsular defect secondary to stress" (Eyster & Scott, 1989; Kaufmann, Halliday, West, Fewer, & Ross, 1996; Onofrio & Mih, 1988). It should be noted that most of these studies reported in this review were published over 20 years ago, moreover, this review was not systematic, the inclusion criteria for the selection of studies for reporting were not given and thus the reporting biases are unknown.

Khan et al (2006) reviewed a number of studies reporting on the development of lumbar cysts (A. M. Khan & Girardi, 2006). The reviewed studies reported associations between lumbar cysts and degenerative spondylosis, spinal instability and trauma. However, only just over half of the studies reported on synovial cysts (the remainder reported on juxtafacet cysts), and in the former it is not clear if the cysts were "true" synovial cysts[239].

Moquin (2006) in a review focussing on the clinical presentation and treatment of spinal synovial cysts, also briefly reviewed the literature on their pathophysiology (Moquin, 2006). The mechanism of origin of these cysts was reported to be controversial, although it was reported to be "well accepted" that the precipitating factor was osteoarthritis of the facet joint (Liu, Williams, Drayer, Spetzler, & Sonntag, 1989; Onofrio & Mih, 1988). Moquin (2006) suggested that increased motion at the facet joint could lead to herniation of the synovium through a defective joint capsule with resultant cyst formation. He argued (as have many others), that this theory was supported by the observation that the most common spinal level of synovial cyst formation is at L4-5, which is also the level of greatest spinal mobility. Moquin (2006) also noted that synovial cysts were most frequently found in the presence of spondylolisthesis, facet joint hypermobility, and scoliosis (Freidberg et al., 1994; Hsu, Zucherman, Shea, & Jeffrey, 1995; Lyons et al., 2000; Trummer, Flaschka, Tillich, & al, 2001; Yarde et al., 1995). Other postulated mechanisms of formation were reported that included;

- proliferation of pluripotential mesenchymal cells,
- degeneration of periarticular fibrous tissue after trauma,
- latent growth of the rest of synovial tissue,
- tissue metaplasia,
- synovial fluid extrusion from the joint (Onofrio & Mih, 1988; Yarde et al., 1995)

A possible aetiological link between synovial and ganglion cysts was also reported (Yarde et al., 1995) with the proposal that degenerating synovial cysts could lose their communication with the joint space. It was also noted that histological evaluations of synovial and ganglion cysts exhibited a continuum of findings and that there was no difference in the clinical presentation of these spinal cysts (Moquin, 2006).

Sze et al (2004) reported on the relevant literature and reviewed all pathology reports of tissues submitted as either spinal "synovial cysts" or "excrescences" submitted at their institution over a

[239] It was beyond the brief of this report to carry out a systematic review of primary research studies i.e. to re-review the individual studies.

period of five years. Synovial cysts were described as arising within the synovium, having a thick wall containing granulation tissue, numerous histiocytes and giant cells. These hyperplastic irritated synovia of the spine were termed "synovial excrescences" and reported to be voluminous and overshadowing the cystic portion of the lesion in most instances. The authors attempted to distinguish synovial cysts and excrescences both intraoperatively and at the time of histological review, noting that the distinction was less clear in pre-operative neuroimaging studies. The authors claimed that cysts and excrescences could occur as separate, singular entities but could occur together suggesting that they may represent part of a spectrum of synovial damage with a common aetiological cause. A wide range of histological features were found in diseased synovial material removed from the spine and it was suggested that this histological heterogeneity may contribute to the panoply of names for spinal cystic/diseased synovial tissue (Sze et al., 2004).

Summary: reveiws

No reviews were identified that *focussed* on the aetiology of spinal synovial cysts. Most clinical studies reporting on synovial cysts proffered some causal explanation, few supported their claims with high quality evidence or evidence based on large clinical studies. Eight reviews were identified that included references to, or discussion of, causation. Most reviews acknowledged that the aetiology of synovial cysts was an area of debate and controversy. A number of possible aetiologies were put forward and each review appeared to focus on, or favour, a different/particular hypothesis whilst quoting a number of other less favoured hypotheses.

Several studies suggested that *osteoarthritis* of the facet joint was the *initiating event* (Gupta & Lutz, 2010; Moquin, 2006). Other studies highlighted the role of segmental instability and hypermobility (Bydon et al., 2010; Costa et al., 2010; A. M. Khan & Girardi, 2006). An association between the occurrence of synovial cysts and degenerative spondylosis and spondylolisthesis was reported in several reviews (Gupta & Lutz, 2010; Moquin, 2006). While the co-occurrence in some instances of cysts and "excrescences" led to the hypothesis in one review that they may both represent part of a spectrum of synovial damage with a common aetiological cause (Sze et al., 2004). Trauma was causally related to synovial cysts in a number of reviews (Apostolaki et al., 2000; Costa et al., 2010; A. M. Khan & Girardi, 2006).

Gupta and Lutz (2010) proposed a sequence of cyst development which started with osteoarthritis of the facet joint and shedding of fragments of arthritic debris and ended with the blockage of bursal channels and development of a cyst.

Primary research: clinical studies

With the increased use of MRI imaging the number of reported cases of synovial cysts has been increasing and a number of sizeable clinical studies were identified. Given the lack of focus and consistency in the literature reviews reported above, and in order to try to get a clear idea of causation, a number of primary studies were also reviewed[240].

Large clinical series

Lyons et al (2000) reported a retrospective analysis of 194 patients surgically treated at Mayo clinics in the USA. The authors acknowledged the ongoing debate regarding the cause of synovial cysts, with *trauma* (Franck, King, Petro, & Kanzer, 1987; Gorey et al., 1992; Kornberg, 1995; Liu et al., 1989; Pendleton, Carl, & Pollay, 1983; Tatter & Cosgrove, 1994) and *segmental instability* (Azzam, 1988;

[240] This was outside ACC's the original brief for this review.

Cameron & Hanscom, 1992; Onofrio & Mih, 1988; Sabo et al., 1996; Silbergleit, Gebarski, Brunberg, McGillicudy, & Blaivas, 1990) being the most often reported.

In the Mayo clinics' surgical patients, 48% of patients were female and the average age was 66 years (range 28-94 years).The most common presenting symptoms were reported to be radiculopathy (85%), or neurogenic claudication (44%), with associated sensory loss (43%) and motor weakness (27%). *Acute onset occurred in 10% of patients*. The most common level for cyst development was reported to be L4-L5 (64%). In 46% of patients a previous diagnosis of degenerative disc disease had been made, *12 % had a history of traumatic injury*, 50% of patients assessed preoperatively had spondylolisthesis with most (98%) having Meyerding Grade I disease. The level of spondylolisthesis correlated well with the level of the synovial cyst. The correct preoperative diagnosis of lumbar synovial cyst was made radoiologically in 56% of patients. Histological evidence of *intracyst haemorrhage* was present in 18 of 161 cysts (11%) and there was a non-significant trend for this to be associated with *acute symptom onset* (Lyons et al., 2000).

Xu et al (2010) reviewed 167 consecutive patients undergoing surgery for symptomatic synovial cysts at the Johns Hopkins hospital over a period of 19 years. In this series of patients 97.5% presented with radiculopathy, 82.5% with mechanical back pain, 20% with neurogenic claudication and 3% with bladder dysfunction. In a discussion of the aetiology of synovial cysts Xu et al (2010) reported that in their clinical series the cysts were most commonly associated with spondylolisthesis (32.9%), commonly Grade I, followed by degenerative disc disease (13%) and that cysts most commonly occurred (57%) at the L4-L5 level. The authors favoured the thesis that facet joint instability was a significant aetiological factor in the development of these cysts. Xu et al (2010) postulated a potential pathogenic cycle where the microtrauma of daily activities causes spinal degeneration, prompting synovial membrane proliferation and destabilisation of the facet joint, which then stimulates the synovial membrane to proliferate further exacerbating and perpetuating spinal segmental instability (Bydon et al., 2010)

Metellus et al (2006) confirmed that the most frequently accepted hypothesis about the pathogenesis of synovial cysts was the appearance of defects of the joint capsule, secondary to *microtrauma* and degenerative phenomena, through which a hernia of the synovial membrane develops. It was hypothesised that this new paraarticular cavity filled with synovial fluid thus forming a synovial cyst which, at least initially, communicates with the joint. It was further suggested that the synovial cyst could degenerate and lose its connection with the adjacent joint; *segmental spinal instability* and *spinal trauma* was suggested as being involved in these lesions. In a retrospective study of 77 patients presenting with lumbar synovial cysts the role of *trauma* was reported to play a role in 1 of 77 (1%) of patients. *Segmental hypermobility* was reported to play an important role in the development of these lesions with spinal synovial cysts described at all of the mobile levels of the vertebral column as reported in the literature. The association with spondylolisthesis in 48% of the patient groups was cited in support of a major role for segmental *instability.* Osteoarthritis was associated with synovial cysts in *all patients* in this study and degenerative disc disease was also a frequent finding. Sagittal orientation of the lumbar facet was found in 76.6% of cases and the authors noted that a strong relationship had been reported between segmental *instability and sagittal orientation of at least one facet joint*. The authors concluded that their clinical findings were consistent with the literature and strengthened the argument for major role played by *segmental spinal instability in the genesis of lumbar synovial cysts* (Metellus et al., 2006).

Doyle et al (2004) carried out a retrospective review of 303 MRI scans of the lumbar spine to determine the prevalence of lumbar facet joint synovial cysts arising from the joints anteriorly and posteriorly. Seven anterior cysts (prevalence = 2.3%) were identified, only two of which did not clearly cause nerve root compression. Twenty-three posterior cysts in 22 patients (prevalence = 7.3%) were identified. Statistically significant associations with increased frequency and severity of facet joint osteoarthritis and with spondylolisthesis were demonstrated compared to patients without cysts. The authors concluded that both anterior and posterior lumbar facet joint synovial cysts were rare, that posterior cysts were more common than anterior cysts and that both types of cysts were related *to facet joint osteoarthritis* but not to disc disease.

Trauma

Physical trauma or injury was cited as the causal factor for a synovial cyst in five clinical studies (Alyas, Turner, & Connell, 2007; Kaneko & Inoue, 2000; Maezawa et al., 2000; Prescod, Bedaysie, Mahadeo, & Capildeo, 2002; Xu et al., 2011)[241].

In an MRI study of 33 asymptomatic young *elite tennis players* Alyas et al (2007) reported that synovial cysts[242] were present in 10 of 33 subjects (*30.3%*; 95% CI, 15.6% to 48.7%); These subjects had a total of 15 cysts, measuring between 2 and 4 mm. Eight of the 15 cysts involved left sided joints and seven involved right sided joints. *All were related to facet joint arthropathy*, with eight of the 15 joints showing moderate arthropathy. None extruded into the exit foramina. The authors noted that synovial cysts in their small sample of subjects occurred more often than in the asymptomatic population (30.3% vs 0.6%). They also noted that only two of the 15 cysts identified were in the epidural space and that neither of these was causing significant compression of the cauda equina. Most cysts occurred in the paravertebral space where theoretically pain could be caused by capsular distension. The authors suggested that since the capsule of the facet joint was reported to be stronger in the usual direction of stretch (i.e. flexion) than in the direction perpendicular to normal stretch (i.e. axial rotation).Repetitive twisting and flexion from play may increase tension on these fibres and predispose to the formation of facet joint cysts. This study had a number of methodological factors that could affect the validity of the results and conclusions (Alyas et al., 2007).

Maezawa et al (2000) reported on a 15-yearold boy who played football every day for 2 years previously, and had sprained his back playing football 2 months prior to his referral. An X-ray of the lumbar spine showed no osteoarthritic changes in the facet joints or spondylolytic and spondylolisthetic changes. MRI showed a juxta-articular synovial cysts from the L4-L5 facet joint. Spontaneous remission of the cysts occurred following conservative treatment. The authors noted that the case was unusually young and, based on other (earlier) reports describing the mechanism of excess stress such as motion and direct trauma (Awwad et al., 1989; Franck et al., 1987; Sypert et al., 1973). They concluded that in their young male sport- (football-) related overactivity possibly caused partial distraction and injury of the left L4–5 facet joint, herniation of the synovial lining into the adjacent ligamentum flavum and gradual proliferation and expansion of the cystic element by

[241]A further six studies were published prior to 2000 (Awwad, Sundaram, & Bucholz, 1989; Cartwright, Nehls, Carrion, & Spetzler, 1985; Farrokh, 1998; Franck et al., 1987; Jabre, Shahbabian, & Keller, 1987; Sypert, Leech, & Harris, 1973)

[242] Synovial cysts were defined as rounded, fluid containing lesions related to the facet joint and located in the epidural, foraminal, or paravertebral (adjacent to paravertebral muscles) positions.

accumulation of viscous synovial fluid with *acute haemorrhage*, resulting in neurological symptoms (Maezawa et al., 2000).

Prescod et al (2002) reported a case of a 60 year old male who developed a lumbar synovial cyst following an episode of trauma (a fall) together with a review of the literature. The authors noted that cysts were usually located adjacent to an abnormal facet joint and that facet arthrosis led to chronic irritation of the synovium leading to a proliferation of articular tissue. The relationship between trauma and cysts development was not reported.

Kaneko et al (2000) described a case of a 55-year-old man with acute radiculopathy resulting from *haemorrhage* involving a synovial cyst at a lumbar facet joint. Three days before admission, he fell and subsequently had pain radiating into his left leg from his buttock to the posterolateral aspect of the calf. Traumatic factors were thought to have *caused bleeding* around or into the synovial cyst.

Xu et (2011) reported a case of a 68 year-old man with a spinal cyst following a fall on ice and reviewed the literature for *haemorrhagic synovial cyst* (Xu et al., 2011). The authors reported that of more than 500 reports of juxafactet cysts in the literature less than 10% were associated with intracystal haemorrhage. Following a comprehensive review of the literature Xu et al (2011) identified 31 published cases of haemorrhagic synovial or ganglion cysts; 3 ganglion , 26 synovial cysts and 2 cases where the cyst type was not reported. They found that 7 of 26 (8%) haemorrhagic synovial cysts and their associated symptoms occurred almost immediately after *an inciting trauma*. In the remaining 19 *antigoagulation* was cited as risk factor in two cases, with risk factors for the remaining 17 not reported. Xu et al (2011) suggested that because the synovium was richly vascularised it was at increased risk of haemorrhage that could be caused by *direct physical trauma or microtrauma associated with daily movement secondary to physical trauma or an unstable lumbar spine.*

Note: Ducker (Department of neurosurgery Johns Hopkins, USA) quoted in [243] reported his experience of treating runners and joggers and hypothesised that chronic and repeated low grade trauma may have contributed to their cyst formation.

Summary: primary clinical studies

Clinical studies more consistently implicate osteoarthritis of the facet joint and spinal instability and its resulting microtrauma as the major causes of spinal synovial cysts with inciting physical trauma/injury a factor in 1-12% of cases. In particular populations, e.g. elite tennis players and footballers, the reported incidence of synovial cysts was reported to be higher. Haemorrhage into synovial cysts was reported to be associated with physical trauma and acute onset of symptoms in a number of cases; microtrauma associated with daily movement of the lumbar spine was also considered to possibly initiate haemorrhage into a cyst.

Natural history

Generally, the natural history of a synovial cyst was reported to be unpredictable; some patients experience *improvement or stabilization* of their symptoms while in others *traumatic events*

[243] See (Ayberk et al., 2008)

appeared to cause cyst enlargement due to haemorrhaging into the cavity of the cysts, resulting in epidural compression of the medulla or spinal roots (Costa et al., 2010).

Xu et al (2009) described the natural history of *haemorrhagic synovial cysts*. Trauma was thought to initiate an acute episode of haemorrhage into a developing intraspinal cyst causing subacute onset of back pain, radicular symptoms and leg weakness. Further *subclinical microtrauma* of the lumbar spine was reported to be a possible cause of additional haemorrhages and further exacerbation of neurological deficits (Xu et al., 2011).

Spinal synovial cysts may be asymptomatic and found incidentally (Hemminghytt, Daniels, Williams, & Haughton, 1982; Yarde et al., 1995). Costa et al (2010) suggested that cysts were *usually* asymptomatic and generally assumed to be slow growing *with symptoms gradually increasing over a period of months or years.* Mathis et al (2010) suggested that cysts were asymptomatic while small but compressed the thecal sac as they enlarged (Mathis & Ortiz, 2010). Progressive symptoms have been reported in association with increasing cyst size has been reported by a number of other authors (Mercader, Munoz Gomez, & Cardenal, 1985; Silbergleit et al., 1990). Shah et al (2003) suggested that symptoms only arose when the cyst invaded the spinal canal, usually the lateral recess, and compressed the spinal nerve (R. V. Shah & Lutz, 2003). Chronicity of lumbar facet cysts, identifiable by the presence of expansion of the affected lateral recess, was reported in 20% of cases by Apostolaki (Apostolaki et al., 2000).

Prescod et al (2002) reporting on the pathogenesis of synovial cysts described changes in the cyst with age. Secondary changes, due to mechanical pressure, inflammation or haemorrhage were thought to accrue as the cyst aged resulting in the disappearance of the synovial lining. With advanced degeneration the cyst wall was reported to become transformed into scar tissue with moderate to severe calcification (Prescod et al., 2002).

Difficulty in distinguishing between synovial and ganglion cysts in some patients has been linked to the possibility that the natural history of lumbar cysts may involve changes in which the definitive connection of the synovial cysts with the facet joint synovium is lost. Alicioglus et al (2009) suggested that as the degenerative process progresses from the phase of instability to the phase of restabilization the connection disappears (Alicioglu & Sut, 2009). When a cyst loses its connection with the facet joint, it reportedly can migrate cranially or caudally from its original place. To support this theory Alicioglu et al (2009) reported that none of the cases with grade 3 facet joint osteoarthritis had visible communication between synovial cysts and the facet joints. Similarly, Ayberk et al (2008) also suggested that, as part of their natural history, synovial cysts may degenerate and loose continuity with the facet joint and the synovial lining (Ayberk et al., 2008).

Spontaneous remission of synovial cysts was considered unlikely by Shah et al (2003), however, the spontaneous resolution of a an intraspinal cyst associated with spondylolysis causing radiculopathy in a young football player was recently reported by (Friedrich & Standaert, 2010). Houten et al (2003) described three cases of spontaneous cyst remission (Houten, Sanderson, & Cooper, 2003). Another case was reported by Swartz et al (2003) (Swartz & Murtagh, 2003). Cyst rupture was reported to be the reason for spontaneous resolution of these cysts by a number of authors (Eyster & Scott, 1989; Hemminghytt et al., 1982; D. E. Jackson, Jr., Atlas, Mani, & Norman, 1989; Reust et al., 1988). Houten et al (2003) suggested intermittent seepage of synovial fluid from the cysts may

cause regression or that alteration of the local forces driving the cyst formation could diminish and cause cyst shrinkage (Houten et al., 2003).

Ayberk et al (2008) noted that while lumbar synovial cysts may show spontaneous resolution, if left untreated they may progress to lysis in the bone and hemaorrage. Bydon et al (2010) reported same site synovial cysts recurrence could occur following removal (Bydon et al., 2010).

5.6 Facet joint effusion

The literature relating to facet joint effusion was sparse – the search did not identify any *reviews or overviews* relating to the condition and only identified seven clinical studies reporting on facet joint effusion (Alicioglu & Sut, 2009; Chaput et al., 2007; D'Aprile et al., 2007; Fujishiro et al., 2002; Lakadamyali, Tarhan, Ergun, Cakir, & Agildere, 2008; Lattig et al., 2012; Oishi, Murase, Hayashi, Ogawa, & Hamawaki, 2010). One of these studies was a case report of pseudogout the remainder reported effusions primarily in the context of degenerative spinal pathology and patients with low back pain.

Facet joint effusion is a facet joint pathology. It manifests as an accumulation of excess fluid in the facet joint and are commonly seen on MRI scans. The presence or absence of fluid in the facet joints can be recorded on T2-W fast spin echo transverse scans. When the measured thickness of the visible fluid layer within the joint was more than 1 mm, it may be considered as a synovial effusion (Alicioglu & Sut, 2009). However, some changes are not easily imaged and may remain occult and D'Aprile et al (2007) advocated the use of T2 fat-weighted images (D'Aprile et al., 2007)

Case control study

Lakadamyali et al (2008) examined the lumbar MRI findings in 372 patients with non-radicular lower back pain and degenerative changes in the posterior stabilizing elements and compared them with healthy controls (Lakadamyali et al., 2008). All patients were given the diagnosis of pathologic change in at least one of the posterior elements stabilizing the vertebral column; facet joint effusions were the most common abnormality (85.5%). In the control group facet joint effusions were identified in 45.8% (p=0.0001). Neocyst formation and synovial cysts were reported mainly in the 15- to 30- year (69.8%) and 31- to 40-year (69.4%) age groups in patient with symptoms (cases) Figure 5.6.1.

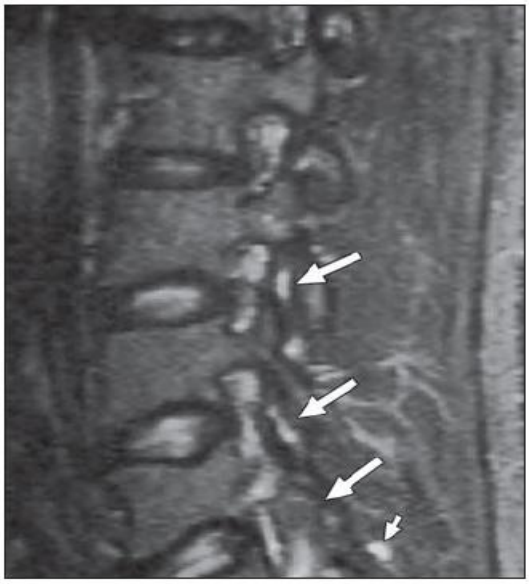

Fig. 3—21-year-old man with lower back pain. Sagittal STIR MR image shows high-signal-intensity facet joint effusion (*long arrows*) at L3–L4, L4–L5, and L5–S1 and small neocyst formation (*short arrow*) next to L5–S1 facet joint.

Figure 5.6.1. STIR [244]MRI image showing high- signal-intensity facet joint effusions (long arrows) at L3-L4, L4-L5 and L5-S1 and a small neocyst formation (short arrow) next to the L5-S1 facet joint. The patient was a 21 year old man with low back pain. From (Lakadamyali et al., 2008).

In the subjects without symptoms (controls), these findings were made mostly in the 71-year and older group (22.2%). In the age-group comparison, these findings were more frequent in the case than in the control group. In most of the cases of symptomatic facet joint cysts (95%), there was concomitant effusion in the neighbouring facet joint; effusion was present in only 69% of the subjects without symptoms.

The authors suggested that degenerative changes in the facet joint and an increased amount of intraarticular fluid were amongst the important overlooked causes of low back pain (Lakadamyali et al., 2008).

Clinical series and case reports

Alicioglu et al (2009) in an examination of the relationship between lumbar synovial cysts and degenerative spondylolisthesis on MRI, compared patients with degenerative spondylolisthesis with and without synovial cyst in terms a number of characteristics including facet joint effusion. Logistic regression showed that the presence of facet joint effusion was 8.706 fold higher in cases with synovial cysts (Alicioglu & Sut, 2009).

Chaput et al (2007), in an examination of increased fluid signal on MRI found that large (> 1.5mm) facet effusions were highly predictive of degenerative spondylolisthesis at L4-L5 and associated

[244] Short inversion time inversion recovery (STIR) sequencing.

(p=0.0008) with synovial cysts (Chaput et al., 2007). Facet joint effusions were also found to be significantly larger in patients with Grade 2 or less osteoarthritis than in patients with Grade 3 osteoarthritis. Alicioglu (2009) suggested that this could be explained by the theory that as the degenerative process progresses from a phase of instability to a phase of restabilization, there should be a corresponding decrease in facet joint effusion (Alicioglu & Sut, 2009).

D'Aprile et al (2007) reported on the value of fat saturation sequences and contrast medium administration in MRIs of degenerative disease of the posterior/perispinal elements of the lumbosacral spine. The authors argued that such techniques could provide better visualisation of a number of degenerative alterations that are occasionally not seen with standard imaging sequences. Joint effusions were included in the list of degenerative alterations that may be better visualised with such techniques, Figure 5.6.2.

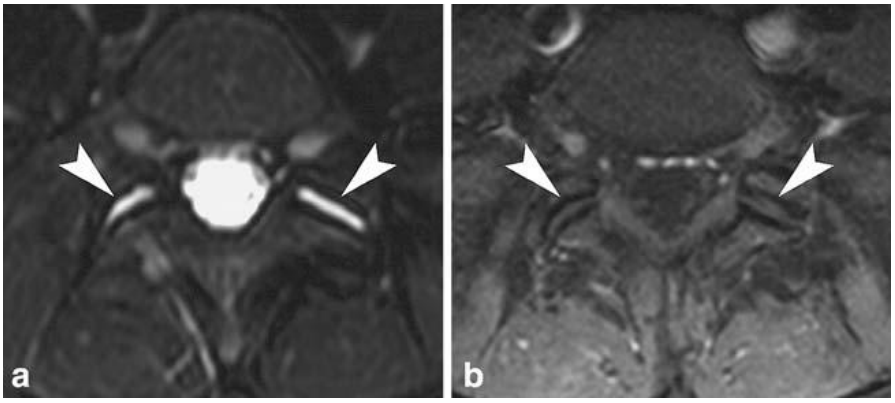

Figure 5.6.2. Patient with low back pain during prolonged erect position. a) Axial T2-weighted image with fat saturation; b) axial T1-weightedimage with fat saturation following intravenous contrast medium administration. The posterior spinal facet joint space demonstrates high signal on T2-weighted imaging (a: arrowhead), but noenhancement after the administration of intravenous contrast medium (b:arrowhead). These findings indicate a noninflamed facet joint effusion(D'Aprile et al., 2007)

D'Aprile et al (2007) linked facet joint effusions and facet joint synovial cysts in the following statement:

"The pathogenesis of synovial cysts is linked to degenerative joint disease likely associated with joint effusion and elevation of intra-articular pressure; combined with kinetic-weight-bearing maneuvers, the joint fluid theoretically creates a sudden or chronic-progressive expansion of the synovial surface into the form of an aneurismal sac."

No evidence was offered for this statement and no reference was given.

Fujishiro et al (2002) reported a case of acute low back pain caused by pseudogout attack of the lumbar facet joint (Fujishiro et al., 2002). The patient had a facet joint effusion at the L4-L5 level; aspiration and examination of the effusion yielded white blood cells and calcium pyrophosphate crystals.

A very recently published study by Lattig et al (2012) explored the link between facet joint effusion and segmental instability in degenerative spondylolisthesis (DS) using standard standing x-rays and supine MRIs[245] of 160 patients (Lattig et al., 2012). Over two thirds (67.5%) of patients showed a difference in slip on supine MRI and standing x-ray of more than 3%. There was a significant correlation between the extent of effusion of the facet joints on MRI and the difference in the degree of slippage between the standing and lying positions in patients with DS. It was suggested that if facet joint effusion is present on supine MRI , it could be anticipated that a mild central and/or lateral spinal stenosis could develop into a severe stenosis in the standing position, or that a small

[245] Chaput et al. (2007) highlighted the possibility that degenerative spondylolisthesis (DS) could be completely overlooked in the MRI, if this was the only imaging used for evaluation, because of spontaneous segmental repositioning of the DS in the supine position short inversion time inversion recovery. (Chaput et al., 2007)

facet joint cyst could develop into a larger one that compresses the nerve root. Follow-on studies were planned which would assess whether analysis of facet joint effusion on routine MRI can help in decision-making regarding the optimal treatment.

For patients with progressed degenerative spondylolisthesis (slip percentage > 10% at lateral flexion position) Osihi et al (2010) found that those defined as unstable (translatory displacement > 4 mm or rotatory displacement > 10 degrees) had significantly greater facet effusion size ($p < 0.001$) than the stable group (Oishi et al., 2010). The authors concluded from these and other data that facet effusion size was associated with the determination of whether the affected disc was *stabilized or remained unstable* at the time of operation. In particular, a smaller facet effusion size strongly suggested that the affected disc had been restabilized in the patients with lumbar degenerative spondylolisthesis.

5.7 Annulus fissure

Intervertebral discs play an important role in the biomechanical function of the spine. They provide flexibility of the spine and allow flexion, extension and lateral bending. These complex functions depend on the morphological structure of the disc, its matrix composition and cellular components. (Neidlinger-Wilke et al., 2006). The basic structure of the normal young intervertebral disc comprises:

- A central gelatinous mass known as the nucleus pulposus
- A fibrous outer ring enveloping the nucleus known as the annulus fibrosus

The annulus and nucleus cells produce and maintain the disc extracellular matrix molecules i.e. each disc cell is responsible for a large volume of matrix (Neidlinger-Wilke et al., 2006).

The gross structure of a normal disc and the location of the annulus is shown in Figure 5.7.1**.**

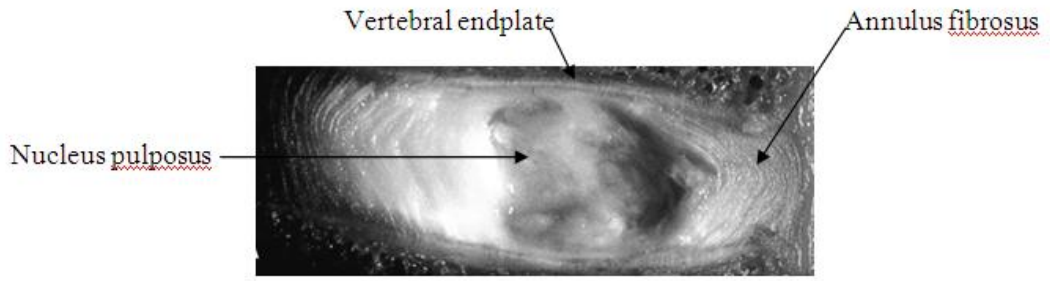

Figure 5.7.1. Cadaveric lumbar disc from a young male (35 years) sectioned in the mid-sagittal plane (M. Adams & P. Roughley, 2006)

The main function of the annulus is to *contain the NP which would otherwise extrude because of the high pressure acting on it* (Cheung & Al Ghazi, 2008).

The location of the annulus fibrosus in relation to other spinal structures is shown in Figure 5.7.2.

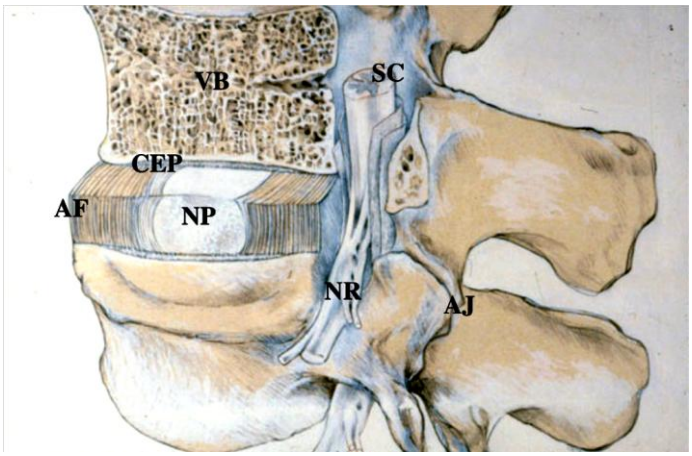

Figure 5.7.2. A schematic view of a spinal segment and the intervertebral disc. The figure shows the organization of the disc with the nucleus pulposus (NP) surrounded by the lamellae of the annulus fibrosus (AF) and separated from the vertebral bodies (VB) by the cartilaginous end-plate (CEP). The figure also shows the relationship between the intervertebral disc and the spinal cord (SC), the nerve root (NR), and the apophyseal/facet joints (AJ). From (J. Urban & Roberts, 2003)

The structure of the annulus fibrosus

At the macroscopic level, a young healthy disc consists of a highly hydrated nucleus pulposus which is surrounded laterally by a firm (but less hydrated) *annulus fibrosus* which consists of a number of concentric lamellae. In the normal state the annulus and the nucleus are distinct entities with very different structures, Figure 5.7.3.

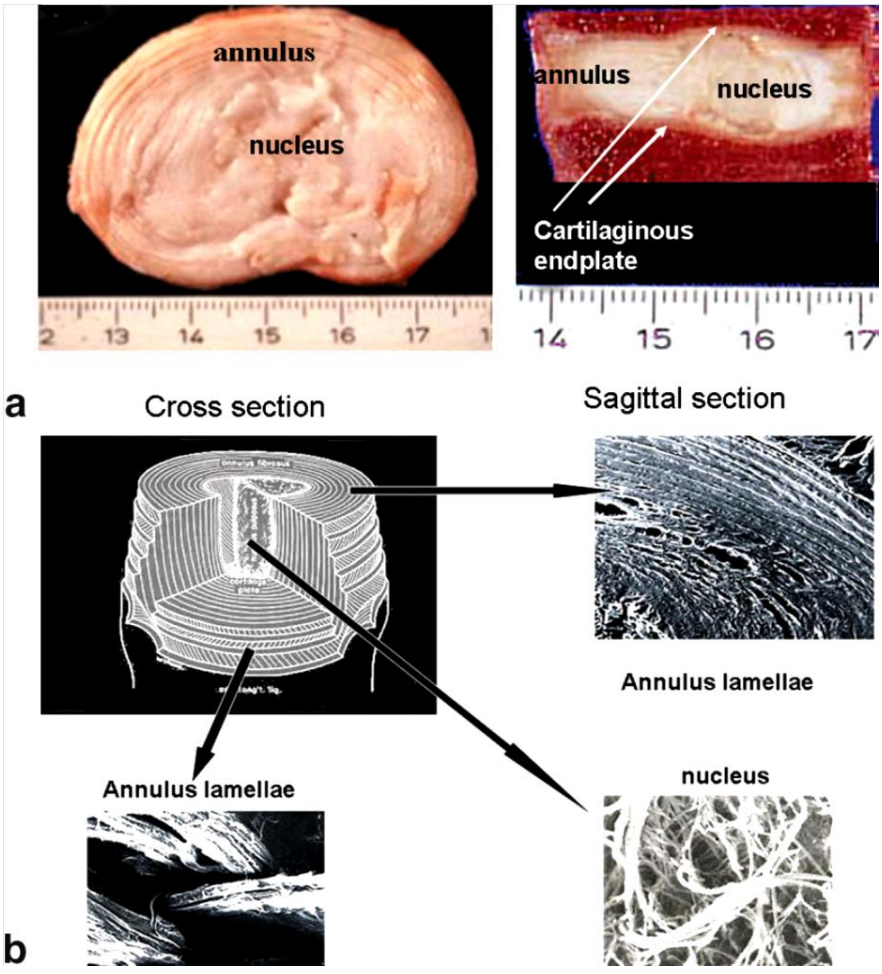

Figure 5.7.3. Morphology of a normal disc. a: Cross-section and sagittal sections through nondegenerate adult human discs showing the size of the disc and the main morphological features; i.e., the soft hydrated nucleus surrounded by the lamellae of the annulus and the thin

cartilaginous endplate interspersed between the disc matrix and the vertebral body. b: Schematic view of the collagen network of the disc showing the organization of the annulus lamellae together with details of the network revealed in scanning electron micrographs [Adapted from Inoue H. Three-dimensional architecture of lumbar intervertebral discs. Spine 1981; 6:139–146] by (J. Urban & Winlove, 2007)]

Structurally, the *annulus fibrosus* comprises large number (up to 25) lamellae or layers formed from collagen bundles firmly anchored to the adjacent vertebral bodies and running at an oblique angle to the axis of the spine, the angle reversing in adjacent lamellae, Figure 5.7.4.

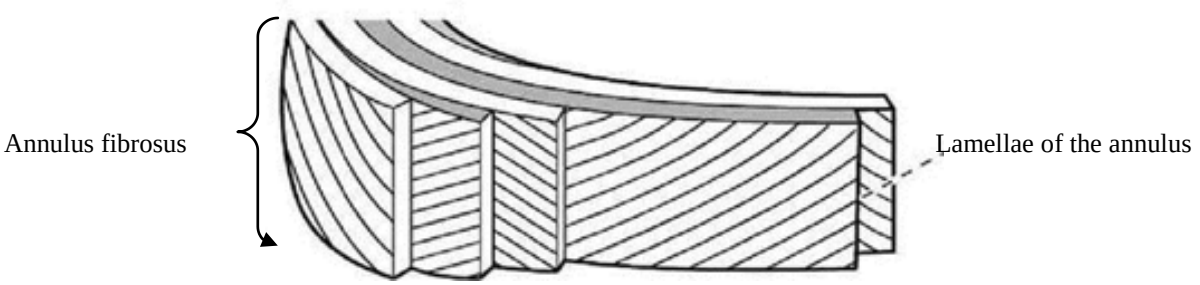

Figure 5.7.4. Lamellae structure of the annulus fibrosus (M. Adams & P. Roughley, 2006)

The composition of the annulus fibrosus

While the water content of the normal disc is highest in nucleus, the collagen content of the disc is highest in the outer annulus (as much as 70% by dry weight). The predominant molecular species of the fibrils are Type I collagen (also found in ligament, skin, and tendons) and Type II collagen (found in hyaline cartilages). Type I collagen, which is organized in dense concentric lamellae forms the fibrous network that *maintains the disc shape*, **Figure 5.7.5.**

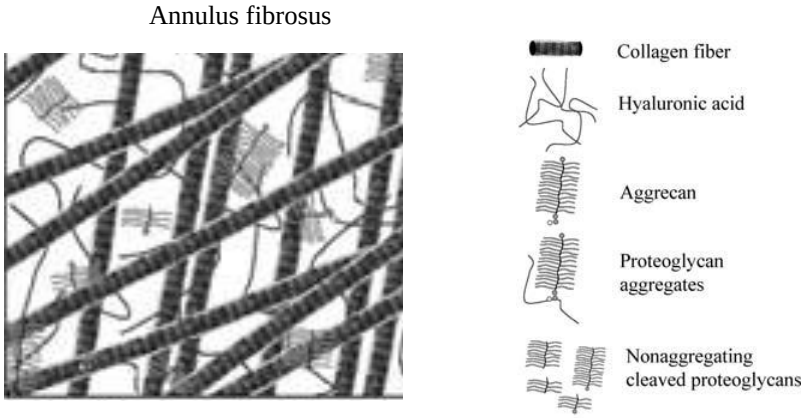

Figure 5.7.5. Schematic representation of the extracellular matrix of the annulus fibrosus (Mwale et al., 2008).

Type I collagen content is highest in the outer annulus, decreasing radially toward the nucleus, where it decreases to virtually zero. Type II collagen follows the reverse radial gradient. The collagen fibers anchor the disc to bone, and their lamellar organization in the annulus is critical for normal disc function.

Nutrition of the annulus fibrosus

The blood supply of the annulus is reported to derive from the vertebral arteries that give rise to two capillary plexuses. One plexus penetrates a small distance (1–2 mm) into the outer annulus fibrosus and the other arises in the vertebral body and penetrates the subchondral bone. Experimental evidence suggests that the microcirculation in the outer annulus supplies only the periphery of the disc and that nutrition to the bulk of the disc, including all the inner annulus and nucleus, is derived from the vertebral plexus. Blood flow to the disc capillaries and hence nutrient transport to the disc can be affected by external factors such as smoking, vibration, and vasoactive drugs (J. Urban & Winlove, 2007).

Changes with age in the annulus fibrosus

With increasing age the water content of the disc falls and the annulus becomes less easily distinguishable from the nucleus as the disc changes in morphology and becomes more and more disorganized. The annular lamellae become irregular, bifurcating and interdigitating, as the collagen and elastin networks become more disorganised. In the later stages of degeneration, gross tissue changes in the annulus fibrosus become apparent these include

- loss of lamellae organization in the annulus.
- *cracks and fissures* accompanied by ingrowth of nerves, blood vessels, and granulation tissue

These degenerative changes are associated with other gross changes in disc morphology such as disc-space narrowing, disc bulging, endplate irregularities, and osteophyte formation (J. Urban & Roberts, 2003; J. Urban & Winlove, 2007).

Classification of annular tears, cracks and fissures

In 2007 Vernon-Roberts published a cadaveric study on the pathology and sequelae of annular tears/fissures/cracks[246] (Vernon-Roberts et al., 2007). The authors distinguished 4 major types of annulus fissures or tears based on location and macroscopic features Figure 5.7.6;

- radiating tears (anterior and posterior)
- transdiscal tears
- concentric tears
- rim lesions

[246] These terms are used interchangeably in the literature, the preferred term is annulus fissure.

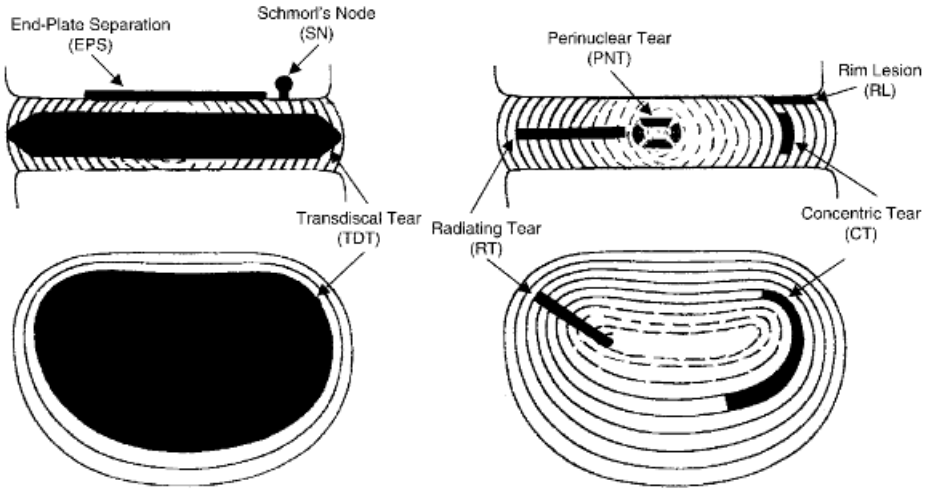

Figure 5.7.6. Diagram to illustrate the types of annulus tears (fissures) and their characteristic locations in the disc. From (Vernon-Roberts et al., 2007).

Rim lesions were further subdivide into 5 types on microscopic features;

- cleft type (50%): comprised a transverse break in the annulus lamellae close to their attachment to the bone of the vertebral rim.
- scar/healing type (20%): comprised a cleft-type rim lesion having granulation tissue within the cleft or a clearly demarcated scar composed of mature fibrous tissue.
- cystic type (13%): comprised 1 or more dilated cavities having a smooth lining and sometimes showing ingrowth of granulation tissue.
- fragmented type (13%): comprised a well defined area showing the breaking up of the attachment zone into multiple randomly arranged portions
- vasoproliferative type (5%): consisted of a well circumscribed area exhibiting a rich meshwork of small blood vessels.

Natural history of annulus fissures/tears/cracks

Vernon-Roberts et al (2007) found that the extent of the disc involved by tears increased progressively throughout life in a linear fashion irrespective of the size or number of tears in a specified zone (Vernon-Roberts et al., 2007).

According to these authors, the *first* tears to appear are *concentric tears* in the outer region of the posterior annulus at the junction between the outer narrow band of thicker lamellae and the inner thinner lamellae forming the bulk of the annulus. Benoist et al (2002) reported that concentric fissuring and radial tears may appear during the third and fourth decade of life. However, they also noted substantial individual differences with elderly persons sometimes exhibiting a “young disc” and vice versa (M. Benoist, 2002). *Perinuclear tears* are the next to form at the upper and lower

borders of the nucleus, closely followed by posterior *radiating tears* which sometimes began as extensions of a perinuclear tear Figure 5.7.7.

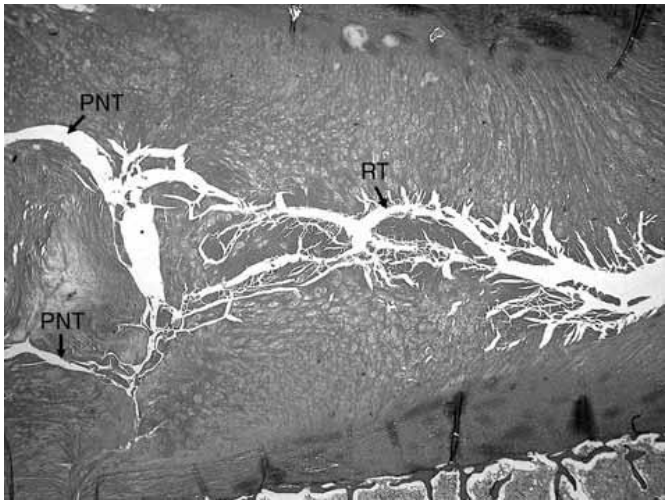

Figure 5.7.7. Medium-power (x40) microscopic image of sagittal section of the L4 –L5 disc from a 54-year-old woman, showing the linkage between upper and lower perinuclear tears (PNT) and a radiating tear (RT). (Vernon-Roberts et al., 2007)

These three tears (concentric, perinuclear and radial) were reported to often appear in the *posterior area* before any tear appeared in the *anterior annulus*. From a young age, there appears to be a high incidence of *concentric tears*, *perinuclear tears*, and *radial tears*. The remaining tears reportedly show a low incidence in young discs

Rim lesions were reported to increase progressively to become *frequent in the elderly*, while transdiscal tears were *rarely* encountered outside the elderly group, Figure 5.7.8.

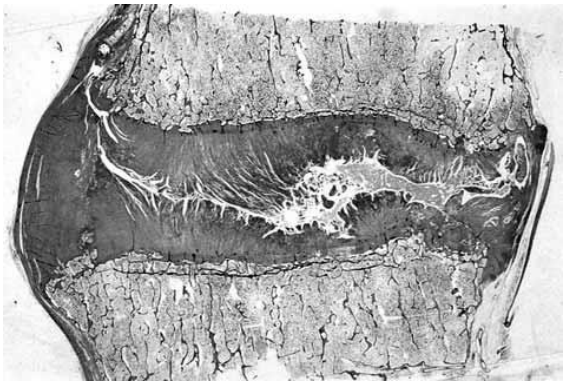

Figure 5.7.8. Low-power (x5) microscopic image of a sagittal section of the L4 – L5 disc from a 72-year-old man, showing a transdical tear with characteristic destructive cavitation of the disc center containing

free fragments and a radiating "bottle-brush" pattern of minor clefts. (Vernon-Roberts et al., 2007)

The association between annulus tear/fissure development and age as reported by Vernon-Roberts is summarised in Table 5.7.1 (Vernon-Roberts et al., 2007). All types of tears appeared to increase with age but with only rim lesions and transdiscal tears becoming frequent after the age of 50 years.

Table 5.7.1. Types of annulus fissure in excised lumbar discs reported in different age groups. From (Vernon-Roberts et al., 2007)

Type of annulus tear		Age Group		
		10-30 years	31-50 years	51-80 years
Radiating tears	Posterior	68%	Increasing	~90%
	Anterior	47%		>75%
Concentric tears	Posterior	100%	100%	100%
	Anterior	75%	75%	75%
Perinuclear tears		~90%	~82%	~98%
Transdiscal tears		Rare	Rare	50%
Rim lesions		~18%	~45%	>80%

The authors concluded that while there was a high incidence of tears below the age of 30 years the highly destructive transdiscal tears become increasingly important and pain-transmitting nerves accompany the ingrowth of vascular repair tissue into tears after the age of 50 years (Vernon-Roberts et al., 2007).

Aetiology of annulus fissures/tears/cracks

Tears are evidence of structural failure involving the annulus (Vernon-Roberts et al., 2007) and are usually described in the context of *disc degeneration and its related changes*. Disorganisation of the annulus fibrosus structure is believed to precede the formation of tears and clefts in the intervertebral disc and to strongly indicate that cleft and fissure formation are a consequence of these alterations which occur during aging and/or degeneration of the disc (M Haefeli et al., 2005). The causes of disc deterioration/degeneration are thus closely associated with the aetiology of annulus tears and fissures.

Battie et al (2006) considered that research conducted over the past decade had led to a dramatic shift in the understanding of disc degeneration and its aetiology. Previously, disc degeneration was commonly viewed as a wear and tear phenomenon exacerbated by the precarious *nutritional* status of the disc. Physical loading, often associated with occupation, was the main suspected risk factor. Recently reported studies on twins suggest that physical loading specific to occupation and sport may play a lesser role than previously thought (Battie & Videman, 2006).

Hadjipavlou et al (2009) reporting on the aetiology of disc degeneration listed a number of the most commonly implicated factors including:

- Ageing: with age the concentration of cells in the annulus is reported to decline and the collagen lamellae of the annulus becomes thicker and increasingly fibrillated – cracks and cavities develop within it. The cause of these changes is not known; declining nutrition, cell senescence, accumulation of degraded matrix products and fatigue failure in the aging disc are often implicated. However, not all annulus tears appear to correlate with age.
- Mechanical factors: circumstantial evidence has been reported associating disc degeneration with mechanical factors such as vibration and torsion. Torsional movements are reported to generate tension in half of the collagen fibres in the annulus while the other fibres become slack. For the fibres to incur damage they must be elongated further than movement in undamaged facet joints would normally allow. It has been suggested that when the spine is flexed gaping facet joints may offer less resistance to rotation which could lead to an annular tear without damaged facets. Compression has also been implicated. Excessive loading has been linked with deleterious changes in the disc through its effects on expression of genes responsible for matrix turnover. Damage to the vertebral endplate is reported to precipitate degenerative changes through interference of the flow of nutrients to the disc. Depressurisation of the nucleus leads to buckling of the inner lamellae as the nucleus is no longer able to brace the annulus and the inner lamellae of the annulus buckle inwards and the outer lamellae buckle outwards. These stresses lead to separation or delamination of the adjacent lamina
- Nutrition: the intervertebral disc is the largest avascular tissue in the body, cells
- in the centre of the disc may be up to 8mm away from the nearest blood supply. The cells in the outer annulus obtain nutrients from the blood vessels in the soft tissue around it and from a small number of capillaries that penetrate into the outer annulus. Cells in the inner annulus rely on diffusion. In the degenerate disc there is a reduction in the transport of nutrients to the annulus. A number of possible causes/contributors to impaired nutrition of the disc, some studies suggest that lack of movement may be the basis of impaired nutrition.
- Toxic materials: nicotine is reported to directly inhibit proliferation in disc cells and the manufacture of the extracellular matrix. In rats nicotine has been shown to downregulate collagen genes, a change which is reported to precede the histological changes of disc degeneration247
- Genetics : more recently evidence has accumulated on the importance of genetic factors in disc degeneration. Studies involving twins have shown a genetic predisposition to disc degeneration with environmental factors having only a modest effect in identical twins. A number of genes and genetic polymorphisms have been implicated. For example vitamin D receptor genes (Taq 1 and Fok 1), polymorphism in the MMP-3 regulator gene, and collagen related genes. However, the authors note that degeneration cannot be attributed wholly to genetic factors; genetic factors are considered to increase the risk of degeneration but do not account for all cases.

Other factors have also been causally associated with disc degeneration including:

- Metabolic disorders: such as diabetes mellitus: metabolic disorders have been reported to be a factor in disc degeneration either by interfering with the normal biochemistry of matrix synthesis or by deposition of foreign materials in the disc. In patients with diabetes mellitus, the nucleus pulposus has been reported to show a decrease in hexosamine content, an

[247] Experience is that heavy smokers heal poorly and suffer more backache than others, personal communication, Graham Martin, reviwer.

increase in hydroxyproline and an enhanced activity of enzymes involved in the metabolism of carbohydrates.

- Low grade infections: it has been proposed that low-grade infections may be a factor in disc degeneration. Some discs harvested after discectomy have been reported to have tested positive for low virulence gram-positive bacteria. These findings could not be confirmed in another study.

The authors concluded that rather than being the result of a single process, disc degeneration (and thus annulus fissure formation) can have a number of possible causes acting individually or collectively and proposed a multifactorial model, Figure 5.7.9.

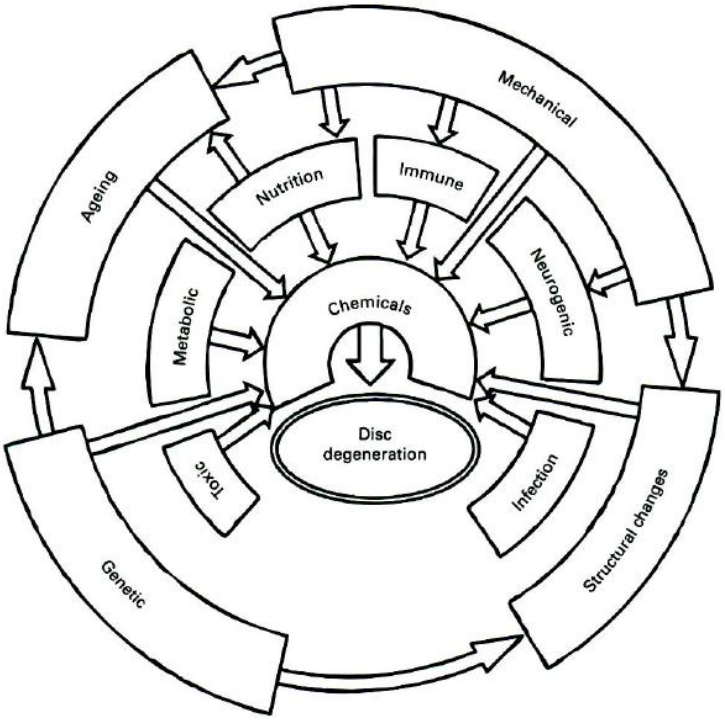

Figure 5.7.9. Model showing the multifactorial pathophysiology of disc degeneration. From (A. G. Hadjipavlou et al., 2008).

They proposed that, rather than being the result of a single process, disc degeneration (and by implication degeneration of the annulus) could have a number of possible causes and proposed that;

" Based on the available evidence, conventional wisdom dictates that the degeneration of the intervertebral disc can be defined as an age-dependent, cell mediated molecular degradation process under genetic influence that is accelerated primarily by nutritional and mechanical factors and secondarily by toxic or metabolic influences……These changes can affect the morphology of the disc, manifested as evidenced by thickening of the vertebral endplate, cracks and fissures in the matrix, delamination and tears in the annulus and in the biomechanical function of the disc."(A. G. Hadjipavlou et al., 2008)

In the same year Battie et al (2009) reported on the Twin Spine Study which was a research program on the aetiology and pathogenesis of disc degeneration (Battie et al., 2009) involving monozygous twin siblings grossly discordant for environmental exposures of interest. The study, which started in 1991, was a multidisciplinary, multinational research project with collaborators primarily in Canada, Finland, and the United States. Occupational exposures, driving and whole-body vibration exposure, and smoking exposure were examined together with anthropomorphic factors, heritability, and the identification of genotypes associated with disc degeneration. The primary suspected environmental risk factors for disc degeneration (various physical loading conditions, driving and associated whole-body vibration, and smoking) were examined in relation to a number of disc anomalies *which included annular tears*.

Among the most significant findings were a substantial influence of heredity on lumbar disc degeneration and the identification of the first gene forms associated with disc degeneration. Conversely, despite extraordinary discordance between twin siblings in occupational and leisure time physical loading conditions throughout adulthood, surprisingly little effect on disc degeneration was observed. The authors asserted that the findings of the exposure-discordant twin studies raised questions about the adequacy of an injury model or ‘‘wear and tear’’ view of disc degeneration. They concluded that:

‘‘ Disc degeneration is now considered a condition that is genetically determined in large part, with environmental factors, although elusive, also playing an important role. Most of the specific environmental factors once thought to be the primary risk factors for disc degeneration appear to have very modest effects, if any. This advance in the understanding of disc degeneration provides a foundation from which to develop new hypotheses and more fruitful research to further elucidate the etiology of disc degeneration.”

5.8 Spinal stenosis syndromes

Spinal stenosis is a focal narrowing of the spinal canal or the neural foramina. It most commonly occurs in the neck (cervical spinal stenosis CSS) or lower back region of the spine (lumbar spinal stenosis LSS).

Narrowing may be caused by developmental or acquired changes or defects in one of several possible anatomic elements in association with a number of possible aetiologies. The narrowing may cause pressure on, or compression of, the spinal nerves as they exit the spinal cord through the various vertebral canals and foramina or the spinal cord itself. Patients may be symptomatic with minimal compression or asymptomatic with a high degree of compression. The condition has been described as "a complicated condition affecting a multitude of patients" (Botwin & Gruber, 2003).

Botwin and Gruber (2003) in a historical perspective of lumbar spinal stenosis reported that the first medical report of spinal stenosis occurred in the 1800s. In 1803, Portal of France postulated that back and leg pain could be caused by bone impingement on the nerves and in 1893, Lane of England carried out a decompressive laminectomy to relieve a woman of cauda equina syndrome caused by spinal stenosis[248]. In another review of lumbar spinal stenosis storm et al (2002) noted that in 1954, Henk Verbiest, a Dutch neurosurgeon on the faculty at the City and University Hospital at Utrecht, published his classic paper entitled ''A radicular syndrome from developmental narrowing of the lumbar vertebral canal''[249]. This article is widely accepted as the first description of the *clinical syndrome* of lumbar spinal stenosis. Verbiest described a form of narrowing of the vertebral canal in middle-aged and older men with back pain, bilateral radicular pain, and disturbances of sensation and strength in the lower extremities that was precipitated by standing, walking, and hyperextension. However, although Verbiest published his findings on lumbar stenosis in the 1950s, it is only within the past two decades that this condition has been diagnosed and treated routinely.

Three areas may become stenotic, (a) the central spinal canal which carries the spinal nerves and or spinal cord, (b) the lateral recess or entrance zone through which the nerves pass, and (c) the vertebral foramina (neural foramen) that forms the exit zone of the nerve roots as they finally leave the spinal canal. (Botwin & Gruber, 2003).

The symptoms of spinal stenosis can be divided into two main categories: neurogenic intermittent claudication (to be limp)[250], and radiculopathy with or without radicular pain (S. L. Kim & Lim, 2005). Patients with spinal stenosis may also experience weakness, reflex alterations, gait disturbances, bowel or bladder dysfunction, motor and sensory changes, or atypical leg pain. The anatomic presence of spinal stenosis may be confirmed radiologically with computerized tomography (CT), myelography (rarely used now), or magnetic resonance (MR) imaging (Botwin & Gruber, 2003).

Clinically, stenosis is most commonly reported in association with degeneration in the lumbar spine with a reported incidence of 1.7% to 8% (Tan, 2003); and is age related. The same condition frequently occurs in the cervical spine however stenosis of the thoracic spine is uncommon (Aliabadi & Isaacs, 2009). The precise amount of narrowing that must occur before the canal is considered

[248] Wiltse LL. History of spinal disorders. In: Frymoyer JW, editor. Adult spine. New York: Raven Press; 1991. p. 33–5.
[249] Verbiest H. A radicular syndrome from developmental narrowing of the lumbar vertebral canal. J Bone Joint Surg(Br) 1954;36:230–7.
[250] The term neurogenic claudication defines an intermittent pain or paraesthesia in the legs brought on by walking and standing which is relieved by sitting or lying down.

stenotic differs among individuals [251](Agency for Healthcare Research and Quality (AHRQ), 2001). An identical canal size can therefore be stenotic for one person but not for another who happens to have a smaller dural sac size (Szpalski & Gunzburg, 2003).

Classification

Spinal stenosis has been classified in a number of different ways in the literature. Genevay et al (2010) noted that there were no widely accepted classification system for spinal stenosis and that as a consequence studies used widely different eligibility criteria limiting the generalizability of their findings (Genevay & Atlas, 2010). The brief outline below is taken from a selection of the most recent publications.

Classification according to aetiology

Reporting on lumbar spinal stenosis Binder et al (2002) published a comprehensive classification of stenosis by cause. They reported that stenosis was most generally divided into developmental or congenital and acquired types, although both mechanisms may be present in a given patient (D. K. Binder, Schmidt, & Weinstein, 2002), Table 5.8.1.

Table 5.8.1. Causes of Lumbar Spinal Stenosis (D. K. Binder et al., 2002)

Congenital/developmental

1. Idiopathic
2. Achondroplasia
3. Hypophosphatemic vitamin D–resistant rickets (spondyloepiphyseal dysplasia)
4. Morquio's syndrome
5. Spinal dysraphism (lipoma, myelomeningocele)

Acquired

1. Degenerative
    a. Spondylosis
    b. Spondylolisthesis
    c. Scoliosis
    d. Ossification of the posterior longitudinal ligament
    e. Ossification of the ligamentum flavum
    f. Intraspinal synovial cysts

2. Postoperative
    a. Laminectomy
    b. Fusion
    c. Fibrosis

3. Traumatic
    a. Laminectomy
    b. Kyphosis/scoliosis
    c. Burst fracture

4. Metabolic/endocrine

    a. Epidural lipomatosis
    b. Osteoporosis
    c. Acromegaly
    d. Pseudogout (calcium pyrophosphate dehydrate deposition)
    e. Renal osteodystrophy
    f. Hypoparathyroidism

[251] Alvarez and Hardy Jr, 1998; Bueff and Van der Reis, 1996; Fast and Greenbaum, 1995; Herkowitz, Abrahan, and Fischgrund, 1998; Herno, Saari, Suomalainen et al., 1999; Postacchini, 1996; Spivak, 1998.

5. Skeletal
    a. Paget's disease
    b. Ankylosing spondylitis
    c. Rheumatoid arthritis
    d. Diffuse idiopathic skeletal hyperostosis (DISH)

Not all published classifications are as extensive as this one and not all agree on the conditions that exemplify the different types given below. For example another more recent classification of lumbar stenosis also based on aetiology added ossification of the spinal ligaments, metabolic or endocrine causes, neoplasms and rheumatological diseases such as Paget disease to the above list of possible causes of secondary stenosis (Siebert et al., 2009). Under degenerative conditions disc protrusion is notably absent and under the section on traumatic causes Takata lesions are absent (personal communication, Gordon Howie, reviewer).

Primary and acquired stenosis

Primary stenosis is caused by a *congenital* narrowing of the spinal canal or a *developmental* disorder. Congenital stenosis is most often due to diffuse skeletal dysplasias, such as achondroplastic dwarfism or spondyloepiphyseal dysplasia (D. K. Binder et al., 2002). These conditions are relatively rare and usually present between the ages of 30 and 40 years (Genevay & Atlas, 2010; S. L. Kim & Lim, 2005). The vertebral neural canal reaches its adult level of cross-sectional area by 4 years of age[252] (D. K. Binder et al., 2002). In individuals who are born with a narrow spinal canal (mostly because of a shortend pedicle) even minimal changes in the structure of the spine can cause severe spinal stenosis, there is also often multilevel involvement and fewer degenerative changes (Singh et al., 2005).

Developmental stenosis is a growth disturbance of the posterior elements involving the pedicles, lamina, and/or articular processes which results in decreased volume afforded to the spinal cord (or cauda equina in the case of the lumbar spine). Examples include malrotation of the posterior elements, achondroplasia, and congenitally short pedicles (Fortin & Wheeler, 2004). Developmental lumbar stenosis requiring surgical treatment is reported to be three times more prevalent in females. Although most cases are sporadic, familial cases of stenosis not associated with dwarfism have been reported (D. K. Binder et al., 2002)

Acquired or secondary stenosis denotes changes that occur after skeletal maturity that produce narrowing in a normally developed spine (Genevay & Atlas, 2010). However, Binder et al (2002) indicated that the situation was not always straightforward:

"Most commonly, lumbar spinal stenosis arises from degenerative changes in an aging spine, which may already possess an element of congenital or developmental stenosis. Thus, patients with congenitally narrow spinal canals are more likely to develop symptomatic spinal stenosis at an earlier age."

Acquired stenosis results from a wide range of conditions including those arising from degenerative processes, local infection, metabolic disorders, neoplastic changes and physical trauma or surgery (D.

[252] Antenatal risk factors, such as prematurity and low birth weight are reported to retard the growth of the lumbar spinal canal (D. K. Binder et al., 2002)

K. Binder et al., 2002; Fortin & Wheeler, 2004; Genevay & Atlas, 2010; Siebert et al., 2009) (see Table 1). Secondary or acquired spinal stenosis resulting from degenerative conditions usually present later in life (50-60 years).

Secondary or acquired stenosis is the focus of the current report.

Classification according to anatomy

Siebert et al (2009) reported on an classification of lumbar spinal stenosis based on anatomy, Figure 5.8.1 (Siebert et al., 2009). Nerve root compression may occur at more than one site.

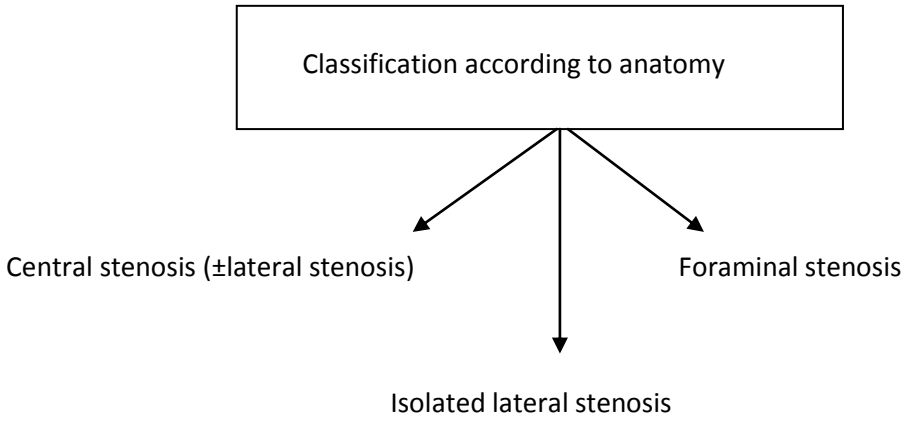

Figure 5.8.1. Classification of lumbar stenosis according to the region of restriction (Siebert et al., 2009).

Clinical classification

Siebert et al (2009) also suggested a clinical classification of lumbar spinal stenosis (LSS) according to the anterior–posterior diameter of the bony spinal canal:

- relative LSS (spinal canal 10–12 mm in diameter) is usually asymptomatic
- absolute LSS (spinal canal <10 mm in diameter) is often symptomatic

The lateral recess was considered stenotic with a diameter of <2 mm (Siebert et al., 2009).

Another useful clinical classification[253] is that developed by Schizas et al (2010) which is a 7-grade classification based on the morphology of the dural sac as observed on T2 axial magnetic resonance images based on the rootlet/cerebrospinal fluid ratio. (Schizas et al., 2010).

Comment

Given the mission and mandate of the ACC and the current brief, only forms of lumbar stenosis considered to be directly relevant to ACC are the focus of this report, i.e. acquired or secondary degenerative (primarily lumbar) and/or traumatic stenosis classified and reported, where information permits, according to anatomy (central canal stenosis, lateral recess stenosis and foraminal stenosis).

[253] As advised by Gordon Howie, reviewer.

Aetiology

In a health technology assessment reporting on the treatment options for degenerative lumbar spinal stenosis the Agency for Healthcare Research and Quality (AHRQ) used a flow chart to summarise the aetiology of degenerative lumbar spinal stenosis, Figure 5.8.2.

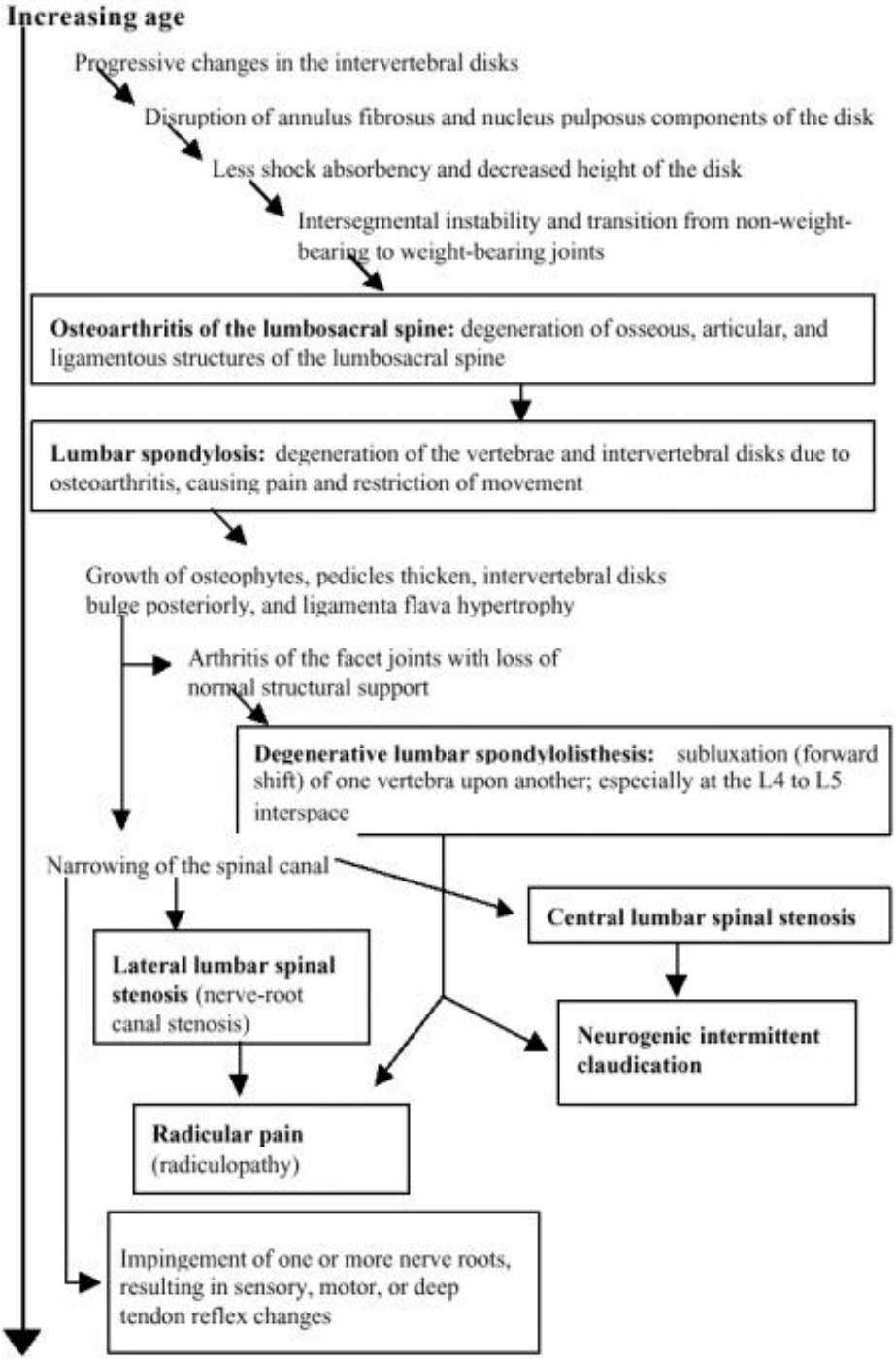

Figure 5.8.2. Aetiology of Lumbar Spinal Stenosis. From (Agency for Healthcare Research and Quality (AHRQ), 2001)

Note: spondylolisthesis is depicted in this figure as having the same aetiology as lumbar stenosis but not directly causally related.

Acquired lumbar spinal stenosis

Acquired degenerative stenosis is reported to have a tendency to lead to symptoms in women at a mean age of seventy-three years and in men at a somewhat younger age (Garfin & Rauschning, 2001). The disorder is also reported to most frequently affect L4–5, with L3–4, L5-S1, and L1–2 following in descending order (D. K. Binder et al., 2002).

It is generally agreed that the following participate in the genesis of acquired spinal stenosis (Aliabadi & Isaacs, 2009; D. K. Binder et al., 2002; Botwin & Gruber, 2003; Genevay & Atlas, 2010; S. L. Kim & Lim, 2005; Siebert et al., 2009):

- Facet joint degenerative hypertrophy and osteophytosis[254]
- Ligamentum flavum hypertrophy and calcification
- Degenerative changes in the discs

The role of spondylolisthesis in the aetiology of acquired degenerative lumbar stenosis is inconsistently reported. For example, in a number of reviews the authors reported that spondylolisthesis may contribute to the symptoms of spinal stenosis (Agency for Healthcare Research and Quality (AHRQ), 2001; Botwin & Gruber, 2003; Garfin & Rauschning, 2001; S. L. Kim & Lim, 2005) other reviews suggested that there was an aetiological connection (D. K. Binder et al., 2002; Fortin & Wheeler, 2004; Genevay & Atlas, 2010; Storm, Chou, & Tamargo, 2002). Storm et al (2002) spanned both views suggesting that spondylolisthesis could *cause* or *worsen* symptoms of stenosis because the anterior slip of the vertebra narrowed the canal and compressed the theca sac against the posterior body of the vertebra below. The authors however, then noted that this usually occurs in a canal that is already stenotic from disc bulging, facet hypertrophy, and ligamentum flavum hypertrophy (Storm et al., 2002).

Aliabadi and Isaacs (2009) focussed on physiologic stresses on the lumbar spine which over time leads to bony growth at the margins of the vertebral body. Posterior osteophytes were reported to lead to profound narrowing of the spinal canal and significant *lateral recess stenosis.* Superior articular facet joint hypertrophy was reported to further reduce the diameter of the lateral recess which was thought to result in nerve root impingement. The formation of synovial cysts at the facets was reported to cause further stenosis. The bony changes and growths that occur redwith time due to wear and tear were believed to be essentially arthritic changes. Dehydration of the nucleus pulposus and tearing of the annulus fibrosus were reported to lead to bulging herniation of the disc. Disc compression/loss of height shortens the spinal column causing the ligamentum flavum to buckle were thought to result in compression of the cauda equina, foraminal nerve root or the thecal sac (Aliabadi & Isaacs, 2009).

Binder et al (2002) noted that lumbar spinal stenosis arising from degenerative changes in an aging spine that *may already possess an element of congenital or developmental stenosis* and that these patients may develop symptomatic degenerative spinal stenosis at *an earlier age*. These authors also

[254] (Osteophytes, more commonly known as "bone spurs", are outgrowths of bone tissue that form around damaged joints.

noted that a multitude of disease processes may contribute to the development of acquired lumbar stenosis (see Table 1) and suggested that spondylolisthesis was *causally* implicated;

"Although the malaligned intervertebral joint is usually stable, severe nerve root entrapment may develop, especially beneath the hypertrophic ligamentum flavum and anteriorly displaced inferior facet in the lateral recess at the level of or just below the affected disk."

Hypertrophy and buckling of the *ligamentum flavum* secondary to loss of disc height was cited as a major cause of central canal stenosis, with hyperthrophy at the insertion point of the ligament to the lamina and facet.

The authors also highlighted spondylosis, which originated with aging and degeneration of the intervertebral disc. In the absence of a frank disc herniation, the aging lumbar disc may undergo a progressive collapse involving fissuring and desiccation of the nucleus with a consequent buckling of the dorsal annulus which can result in a broad based bulge and the slow formation of discogenic osteophytes; disc height with histologic evidence of nerve root compression in pathologic specimens were reported to be inversely correlated i.e. the narrower the disc, the larger the osteophytes, and so the more likely is nerve root compression[255]. In addition, arthritic changes in intervertebral facet joints, perhaps exacerbated by increased stresses from the collapsing disc, and manifest by bone hypertrophy and synovial tissue overgrowth, which together encroach on the lateral central canal, lateral recesses, and dorsal neural foramina (D. K. Binder et al., 2002).

Genevay et al (2010) drew attention to the "two-level stenosis concept" proposed Porter and Ward in 1992[256]. Lumbar spinal stenosis was hypothesised to be the result of vascular compromise to the vessels supplying the cauda equina (central stenosis) or from pressure on the nerve root complex (lateral stenosis) by degenerative changes[257] (Genevay & Atlas, 2010). These authors also drew attention to the fact that despite rapidly increasing rates of corticosteroid spinal injections there was limited information on the role of local inflammatory mediators in degenerative lumbar spinal stenosis. However, Siebert et al (2009) alluded to the possible role of inflammation (Siebert et al., 2009) suggesting that nerve root compression triggered localized inflammation, which affected the nerve roots excitatory state[258]. In addition, at least two interdependent vascular mechanisms were hypothesized to contribute to the development of neurogenic claudication in lumbar spinal stenosis: reduced arterial blood flow resulting in ischemia, and venous congestion with compression of the nerves and secondary perfusion deficiency[259] (Siebert et al., 2009).

Kim et al (2008) highlighted the role of disc degeneration and accompanying changes in segmental motion in the aetiology of stenosis. The authors cited compensatory responses (hypertrophy and osteophytes) in the facet joints and ligamentum flavum[260] induced by increased movement and increased stress resulting in encroachment on the neural elements. (S. L. Kim & Lim, 2005). They also highlighted the association between these degenerative changes and spine instability noting that spondylolisthesis commonly occurred with spinal stenosis (S. L. Kim & Lim, 2005).

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[255] Hasegawa T, An HS, Haughton VM, Nowicki BH. Lumbar foraminal stenosis—critical heights of the intervertebral discs and foramina: a cryomicrotome study in cadavers. J Bone Joint Surg Am 1995;77:32–38

[256] Porter RW, Ward D. Cauda equina dysfunction. The significance of two-level pathology. Spine 1992;17(1):9–15.

[257] The work that this was based on relied on ultrasound measures and is now discredited, personal communication, Gordon Howie reviwer.

[258] Kobayashi, s. *et al.* effect of lumbar nerve root compression on primary sensory neurons and their central branches: changes in the nociceptive neuropeptides substance P and somatostatin. *Spine* 30, 276–282 (2005).

[259] Porter, r. w. spinal stenosis and neurogenic claudication. *Spine* 21, 2046–2052 (1996).

[260] The Ligamentum flavum can hypertrophy and buckle into the spinal canal during disc collapse.

Szpalski and Gunzburg (2003) described stenosis secondary to degenerative spondylolisthesis in the elderly.

Kim & Lim (2005) postulated that either microvascular compromise of the cauda equina and/or an inflammatory response is required for the symptoms of lumbar spinal stenosis. Both venous congestion and/or arterial insufficiency were reported to lead to nerve root injury and to play an important role in the development of intermittent claudication (S. L. Kim & Lim, 2005). Kim et al offered some supporting evidence for these hypotheses; significant changes in the diameter of blood vessels on the cauda equina were found by Ooi et al (1990) in patients with stenosis while Baker et al. (1995) was reported to have shown a 26*%* decrease in arterial blood flow to porcine cauda equina that were mechanically compressed to simulate stenosis. Compression was performed at *more than one level*. This was shown to be important by Porter et al. (1992) who found that either multilevel central stenosis or central stenosis with root canal stenosis was necessary for these symptoms (the "two-level stenosis concept"). In addition, Inufusa et al. (1996) noted that extension significantly decreased the canal area, whereas flexion has the opposite effect contributing to vascular changes (S. L. Kim & Lim, 2005). Along with mechanical compression, Kim et al (2008) noted that an inflammatory response has been postulated to play a role in symptomatic patients; no direct evidence relating to stenosis was offered.

Note: In addition to these slowly progressive degenerative anatomical changes, it has recently been pointed out that lumbar spine stenosis has an important dynamic component. The available space in the central canal decreases in loading and extension and increases in axial distraction and flexion. The same dynamics also affect the foramen with flexion causing a 12% increase, and extension a 15% decrease, in area of foramen (Jensen et al., 2010).

Acquired central canal stenosis

Central canal stenosis is found at the intervertebral level and is caused by ligamentum flavum hypertrophy or buckling, disc protrusion or hypertrophic facet joints; it may be accompanied by degenerative spondylolisthesis. Forty percent of central stenosis is secondary to soft tissue changes within the central canal. In the lumbar region, the cauda equina can be compressed centrally from an anterior-posterior direction at the intervertebral disc level. This compression may be caused either by a *disc bulge or protrusion* anteriorly or by *hypertrophy and bulging of the ligamentum flavum* associated with *facet joint hypertrophy*, which can intrude posteriorly (Botwin & Gruber, 2003).

The main cause of hypertrophy of the ligamentum flavum is reported to be *fibrosis* (Genevay & Atlas, 2010) which is known to be related to degenerative changes related to the aging process or mechanical stresses from instability or accumulated mechanical stress from other causes. Both morphologic and immunohistochemical studies have shown that the ligamentum flavum undergoes fibrotic and chondrometaplastic changes with aging [261]. Hypertrophy of the ligamentum flavum has been described in anatomic studies to be 7 to 8 mm thick in patients with central stenosis, versus the usual 4 mm or less (Botwin & Gruber, 2003).

Acquired Foraminal stenosis

[261] Yoshida M, Shima K, Taniquchi Y, et al. Hypertrophied ligamentum flavum in lumbar spinal canal stenosis. Pathogenesis and morphologic and immunohistochemical observation. Spine 1992;17(11):1353–60.

Foraminal stenosis can be either antero-posterior resulting from a combination of disc-space narrowing and overgrowth of structures anterior to the facet joint capsule, and/or vertical resulting from posterolateral osteophytes from the vertebral endplates protruding into the foramen along with a laterally bulging annulus fibrosis or a herniated disc that compresses the nerve root against the superior pedicle. Foraminal stenosis more frequently involves the L5 nerve root, as L% is the largest root.

Lateral recess stenosis

Lateral recess stenosis has been extensively studied.

In the lumbar spine the lateral recess is the region in the lumbar canal that is bordered laterally by the pedicle, posteriorly by the superior articular facet and ligamentum flavum, and anteriorly by the vertebral body, endplate margin and disc margin. Impingement of the nerve root in this area is reported to frequently occur *without symptoms* (Bartynski & Lin, 2003).

In a study to compare the ability of different types of imaging to identify root compression in the lateral recess Bartynski and Lin (2003) identified two typical morphologic forms of acquired lateral recess stenosis (a) trefoil narrowing of the lateral recess which may be congenital or acquired and (b) angular pinch-like encroachment of the lateral margin of the canal with subsequent pinch of the nerve root, Figure 5.8.3. If early facet hypertrophy occurs, a trefoil shape of the spinal canal ensues and the laterally positioned nerve root become compressed by further facet growth or disc margin change. If facet, endplate and disc margins changes occur together the nerve root becomes displaced, pinched and compressed within this region.

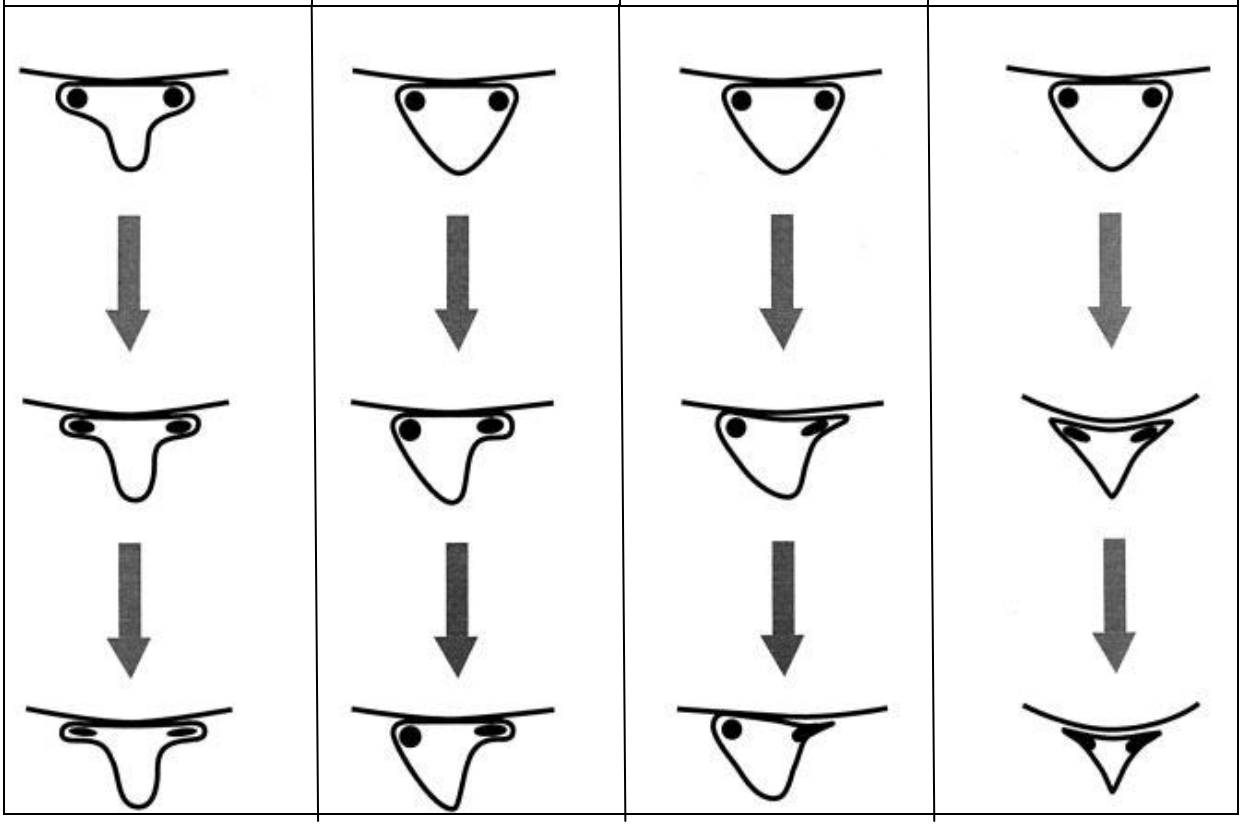
Congenital trefoil canal.	Acquired trefoil canal.	Acquired angular pinch of the lateral recess.	Bilateral acquired angular pinch of the lateral recess.
The lateral recess region becomes progressively narrowed because of either facet or endplate-disk margin degenerative changes.	Early facet degenerative changes and hypertrophy in a triangular canal develops a trefoil shape with the root positioned in a lateral recess niche. Progressive disk margin, endplate, or further facet degenerative changes leads to compression of the trapped root.	Simultaneous near equal facet, endplate, and disk margin degenerative changes lead to acute angle formation in the corner of the canal and lateral recess region. The root becomes progressively compressed in the lateral recess and may be medially deflected.	Bilateral facet, disk margin, and endplate degenerative changes can narrow the central spinal canal and the lateral recess region. This can produce both central spinal stenosis with cauda equina compression and individual nerve root compression within the abnormal lateral recess.
			

Figure 5.8.3. Illustrations show development of acquired lateral recess stenosis (Bartynski & Lin, 2003), congenital trefoil canal development is included for comparative purposes.

Botwin and Gruber (2003) suggested that a lateral recess height of 5 mm or more was normal, but that a height of 2 mm or less was pathologic, and a height of 3 to 4 mm may be considered as suggestive of lateral recess stenosis.

These authors considered lateral recess stenosis as one of *three zones of lateral stenosis*, Figure 5.8.4, (Botwin & Gruber, 2003)[262] with the lateral recess forming the first or entrance zone and foramina forming the third or exit zone: between these two there was a mid-zone located under the pars interarticularis and the pedicle.

[262] Botwin and Gruber (2003) drew on the previous work of Lee (Lee, Rauschning, & Glenn, 1988).

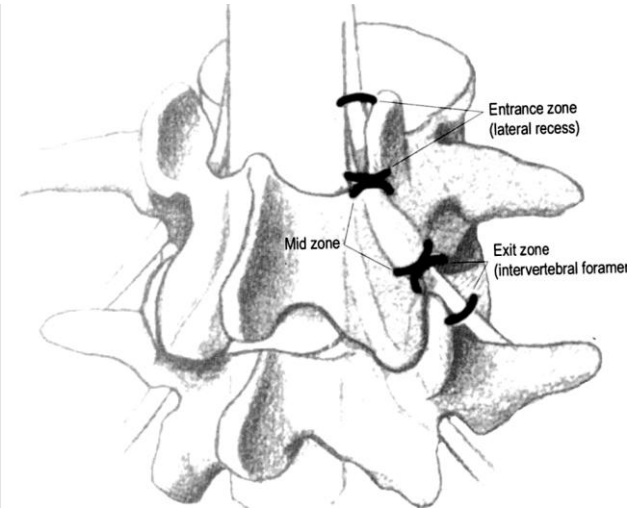


Figure 5.8.4. Three zones of lateral stenosis: (1) entrance zone (lateral recess), (2) mid zone and (3) exit zone (intervertebral foramen). (From Rothman RH, Simone FA, editors. The spine. 3rd edition. Philadelphia: W.B. Saunders; 1992).

The most common cause for lateral recess (entry zone) stenosis was reported to be *hypertrophic osteoarthritis of the facet joint*, particularly involving the superior articular process, where hypertrophy of the medial border in particular, may compress the nerve root between the facet and the dorsal aspect of the vertebral body, Figure 5.8.5, (Botwin & Gruber, 2003).

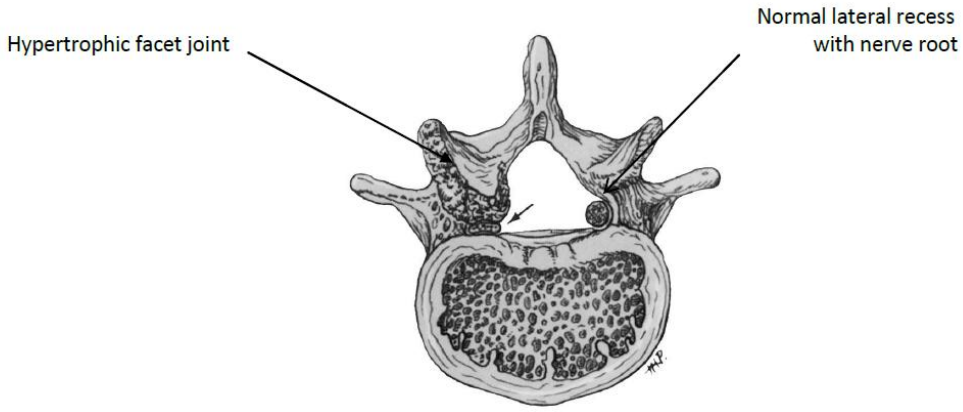


Figure 5.8.5. Entrance zone stenosis secondary to hypertrophy of the superior articular process with resultant compression of the nerve root on the right (arrow). (From Rothman RH, Simone FA, editors. The spine. 3rd edition. Philadelphia: W.B. Saunders; 1992. p. 832).

The other common cause of the narrowing of the lateral recess (entrance zone) was reported to be a *posterior disc herniation* which compresses the nerve root as it emerges from the dural sac. These two causes were reported to account for most cases of lateral spinal stenosis (Botwin & Gruber, 2003) . Genevay & Atlas (2010) reported that the same processes that induced central canal stenosis were able to induce lateral recess stenosis, citing *decreased disc height*, facet joint hypertrophy (with

or without spondylolisthesis) and/or *vertebral endplate osteophytosis* as the main causes of lateral recess stenosis (Genevay & Atlas, 2010).

In midzone stenosis, the most common cause of nerve root compression was reported to be a *defect in the pars interarticularis*. This defect may result from osteophyte formation under the pars interarticularis where the ligamentum flavum is attached or from a fibrocartilaginous or bursal tissue hypertrophy at a spondylolitic defect. The second reported cause of nerve root compression in the midzone is *pedicular kinking*. Pedicular kinking may result when advanced intervertebral disc degeneration is associated with a marked narrowing of the disc; the vertebral bodies then approach one another. As the upper vertebral body descends, its pedicle may kink the emerging nerve root to a significant degree. The nerve root may also be compressed in a gutter formed by a diffuse lateral bulge or protrusion of the intervertebral disc and the pedicle above. Pedicular kinking was reported to be most commonly seen with a L5-S1 spondylolisthesis (Botwin & Gruber, 2003).

Common causes for foraminal (exit zone) stenosis are *hypertrophic osteoarthritic changes in the facet joints* with subluxation and osteophytic ridge formation along the superior margin of the disc. A nerve root can be impinged upon vertically or horizontally. This impingement can arise secondarily from subluxation (partial dislocation) of the superior articular facet, from a lateral herniated disc or protruding annulus, or from an uncinate spur from the posteriolateral vertebral body, Figure 5.8.6.

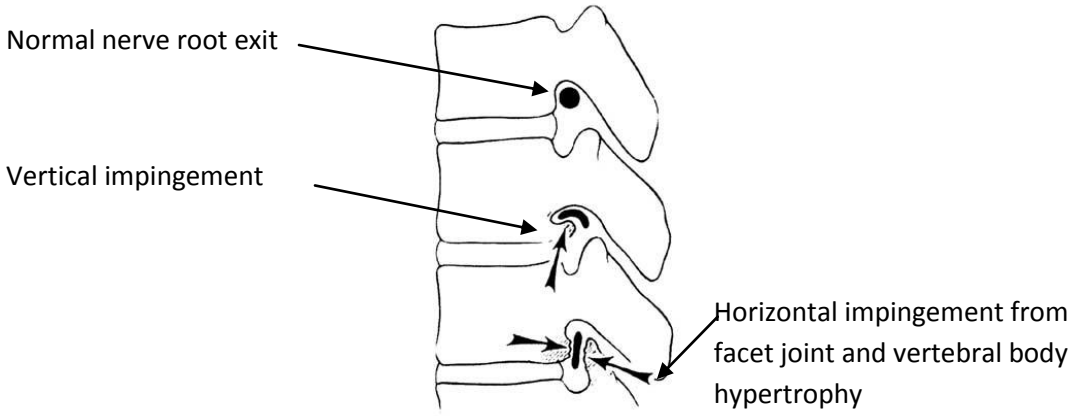


Figure 5.8.6. Diagram depicting intervertebral foramen stenosis secondary to osteophyte from posterior vertebral body and facet hypertrophy

Summary

Acquired degenerative stenosis is the most frequently observed type of spinal stenosis. It is reported to arise in conjunction with age-associated *degeneration of the lumbar discs and facet joints*. The degenerative process leads to a *loss of disc height* with associated *bulging of the disc* and *infolding and hypertrophy of the ligamentum flavum*. Facet osteoarthritis and hypertrophy (from the increased stresses associated with disc degeneration) often leads to osteophyte formation and thickening of the joint capsule. With advanced osteoarthritis of the facet joints, *cysts originating from these joints* can protrude into the spinal canal, further compromising the space available for the neural elements. Stenosis may also arise in the setting of degenerative spondylolisthesis or

spondylolisthesis arising from a prior spondylolysis (disruption in pars interarticularis). However, the role of spondylothisthesis in the *aetiology* of spinal stenosis is not well described although it is frequently described in *association* with stenosis.

The mechanism whereby compression of spinal nerve roots results in the typical symptoms and signs of spinal stenosis does not appear to have been fully elucidated. Evidence suggested that in the presence of stenosis and nerve-root compression, lumbar extension reduces the cross-sectional area of the central canal as well as the neural foramina, exerting further *pressure on the venules* surrounding the nerve roots. This process, in turn was postulated to lead to engorgement and ischemic nerve impairment. This ischemic mechanism was thought to account for the typical reversibility of symptoms when patients flex their spines forward. (Katz & Harris, 2008). The role of *inflammation was not clear and little evidence was for or against a role was offered in the studies reviewed*[263].

One or more of three areas of the lumbar vertebrae may become stenotic (a) the central canal, (b) the lateral recess and (c) the vertebral foramina, The latter (b and c) form lateral entrance and exit zones of a canal through which the spinal nerves run and are often reported together as "lateral stenosis". Most of the studies reporting specifically on lateral stenosis cite the same or similar causal process as those for central canal stenosis

- hypertrophic osteoarthritis of the facet joint,
- degenerative changes of the disc including posterior disc herniation and decreased disc height

Some studies also implicated vertebral endplate changes (osteophytosis) in the aetiology of foraminal stenosis and in midzone lateral stenosis *defect in the pars interarticularis* resulting from osteophyte formation under the pars interarticularis has been implicated.

Relationship of stenosis and heavy manual work

Szpalsk and Gunzburg (2003) in and overview of lumbar spinal stenosis in the elderly discussed the relationship between back trouble and occupation (Szpalski & Gunzburg, 2003). Some authors[264] have suggested a relationship between long-term heavy manual work and spinal stenosis. Using ultrasound measurements McDonald et al. (1984) [265] showed that a narrower spinal canal is associated with increased back related complaints in coal miners.

There are conflicting reports about the relationship of long-term heavy physical labour and/or exposure to vibration and the appearance of spinal degeneration. In very complete review Videman and Battie (1999) [266] found only a modest relation of occupational risk factors and spinal degeneration[267].

[263] Sairyo et al (2007) investigated the role of inflammation in ligamentum flavum hypertrophy and concluded that the accumulation of fibrosis/scarring caused hypertrophy of the ligamentum flavum (Sairyo et al., 2007)
[264] For example: Berney J (1994) Epidemiology of narrow spinal canal. Neurochirurgie 40: 174–178.
[265] McDonald EB, Porter R, Hibbert C et al (1984) The relationship between spinal canal diameter and back pain in coal miners. Ultrasonic measurement as a screening test.. J Occup Med 26: 23–28
[266] . Videman T, Battie MC (1999) The influence of occupation on lumbar degeneration. Spine 24:1164–1168.
[267] In New Zealand spinal stenosis is commoner in Polynesians with heavy muscles, because the musculature hypertrophies the vertebrae, reviewer.

Trauma

Fortin et al (2004) held that trauma induced stenosis due to fracture of the pars interarticularis and spondylolisthesis was the prototypical trauma-induced stenosis, but that post-surgical and post-traumatic hypertrophic changes were also implicated (Fortin & Wheeler, 2004). However, most acquired stenosis cases were reported to arise as a result of degenerative process such as discopathy and spondylosis. Combined stenosis was reported as the result of acquired changes (usually degenerative) superimposed on a congenitally or developmentally narrow canal. Normally, the reserve capacity of the spinal canal is sufficient to accommodate encroachment from adjacent structures, given that this is a relatively slow and limited process. In the context of combined stenosis, the reserve capacity is compromised such that relatively minor pathological processes may produce dramatic symptoms. Some authors stipulate that all cases of symptomatic "acquired" stenosis (secondary to degenerative processes) are more appropriately designated as combined stenosis, with some degree of precursory narrowing necessary to become manifest (Fortin & Wheeler, 2004).

Tan (2003) noted that previous trauma such as burst fractures of the spine which resulted in repulsed fragments of bone could impinge on the spinal canal causing stenosis (Tan, 2003). Zhao et al (2010) suggested that damage to the cord occurs at the time when the bone fragment is retropulsed with great energy into the spinal canal. They also proposed that the canal compromise shown on static images after the accident could not represent this dynamic fracture process and that the spinal canal was[268] almost certainly less narrowed than at the time when the cord is impacted. This could explain the clinical observation of poor correlation between the canal occlusion after trauma and the neurological dysfunction.

Natural history

Benoist et al (2002) reviewed the literature on the natural course of lumbar degenerative spinal stenosis. The authors suggested that as the general population ages the condition was becoming more common (Michel Benoist, 2002). Few studies were identified that reported on the natural evolution of the condition and only one was a randomised comparison of surgery and medical treatment the remainder were mostly small, retrospective studies with substantial methodological flaws. Differences in the methods used, the patient populations and the length of follow up made it impossible to directly compare study results. The findings of the RCT and the two largest clinical series reviewed by Benoist et al (2002)[269] are briefly summarised below.

Herno et al (1996)[3] followed the natural course of 91 patients in a retrospective study with a mean follow-up of 8 years (SD ± 3 years). Patients were assessed on radiological evidence as having a complete block (n=11), moderate stenosis (A-P diameter <10mm, n=40), mild stenosis (A-P diameter 10-12 mm, n=18) or lateral stenosis (n=22). The patients overall evaluation at follow-up showed that 30% were unchanged, 45% reported improvement and 25% reported a worsening of symptoms.

[268] Wilcox RK, Boerger TO, Allen DJ, Barton DC, Limb D, Dickson RA, et al. A dynamic study of thoracolumbar burst fractures. J Bone Joint Surg Am
2003; 85:2184–9.

[269] Herno A, Nevalainen S, Saari T, et al. The natural course of 91 nonoperated patients with lumbar spinal stenosis. Presented at the annual meeting of the International Society for the Study of the Lumbar Spine. Burlington 1996; June : 25-9. Atlas SJ, Keller RB, Robson D, et al. Surgical and non surgical management of Lumbar Spinal Stenosis. Four year outcomes from the Maine Lumbar Spine Study. Spine 2000 ; 25 : 556-62. Amundsen T, Weber H, Nordal H, et al. Lumbar spinal stenosis: conservative or surgical management. A prospective 10 year study. Spine 2000; 25 : 1424-35.

There were no differences between the four radiological groups and the authors were reported to have concluded that the natural course was benign in all 91 patients and that the subjective and physical manifestations were remarkably stable.

Atlas et al (2000) reported the four-year outcomes of the Maine lumber spine study. This was a prospective cohort study of 148 patients of whom 81 received surgical treatment and 67 received medical treatment; 80% were available for follow-up at four years. Of the medically treated patients 52% were improved and 22 patients underwent surgery during the follow-up period.

Amundson et al (2000) randomised a small group of patients (n=31) with moderate clinical symptoms to surgery or conservative treatment; a further 50 patients with mild stenosis also underwent medical treatment only. Follow-up was 10 years. Of the 18 patients randomised to conservative treatment 39% had good results after 6 months and 44% after four years; 6 patients underwent surgery. Of the 50 non-randomised patients who had mild stenosis and medical treatment, 64% had good results after 1 year and 57% after 4 years; 10 patients required surgery.

Following their reporting of all studies reviewed, Benoist et al (2002) concluded that data in the literature and their own experience suggested that that a substantial proportion of conservatively treated patients do not automatically deteriorate and will remain unchanged or even improved by medical means.

In a review of spinal stenosis published in the same year Storm et al (2002) reported that since the condition had become a recognised clinical entity, surgeons believed that surgery was required to halt progression and a cycle of instability. As a result most of the literature focussed on surgical outcomes and few studies examined non-operative treatment. With more clinical data and experience it was now clear that degenerative spinal stenosis was not necessarily progressive.

In a more recent review of lumbar spinal stenosis Genevay et al (2010) described the condition as a *slowly progressive degenerative process* in which the natural history remained poorly understood with studies reporting about a half of patients remaining clinically stable, with a quarter worsening or improving ; the authors noted that for any individual patient, the course can be unpredictable with flares and stable periods over time (Genevay & Atlas, 2010).

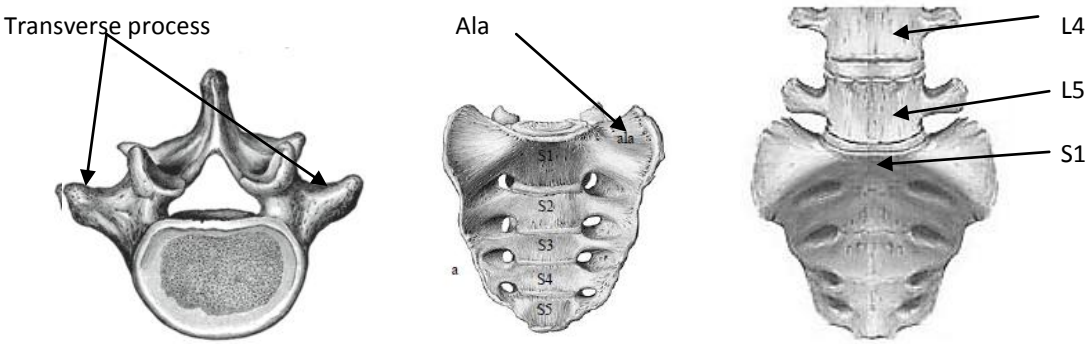
Zhao et al (2010) in a review of traumatic canal stenosis reported that a large number of clinical studies had reported the spontaneous remodelling of the spinal canal following trauma with the degree of canal stenosis reduced with time (Zhao, Fang, Zhao, & Fan, 2010).

5.9 Sacralised L5

Introduction

The lumbosacral junction

The point in the lower spine at which the lumbar vertebrae meet the sacrum[270] is called the lumbosacral junction, Figure 5.9.1.



Fifth lumbar vertebra **Sacrum (anterior view)** **Lumbosacral junction**

Figure 5.9.1. Normal vertebrae of the lumbosacral junction

Mobility at the lumbosacral junction is influenced by the *shape and disposition* of the lower lumbar and sacral vertebrae and pelvis, their *articular processes* the dic heights between L1 and L5 and the resilience of the connecting structures. In the normal spine the anatomical features of the L5-S1 joint (the lumbosacral joint) are distinctly different when compared with joints at the L1–L5 levels. For example, the L5–S1 disc orientation is different as the fifth lumbar vertebra connects to the more complex first sacral vertebra; anterior L5–S1 disc height is also greater than the disc height of L1–L5.

Defects occurring at the lumbosacral border can result in *transitional* vertebrae that have a *mixture of lumbar and sacral characteristics.* Broadly, there are two main types of transitional vertebrae (a) sacral vertebrae with the characteristics of lumbar vertebrae (lumbarised sacral vertebrae) and (b) lumbar vertebrae with the characteristics of sacral vertebrae (sacralised lumbar vertebrae). Note: there can be some features of both.

In lumbarised sacral vertebrae there has been a caudal boundary shift[271] in which the first sacral segment assumes some characteristics of the lumbar vertebra (lumbarisation). In sacralised lumbar vertebrae there has been a cranial shift[272] where the last lumbar vertebra assumes sacral characteristics and frequently becomes incorporated into the sacrum (sacralisation). Depending on the direction of the shift, an individual may gain an extra lumbar segment or loose a segment, either may have significant biomechanical and clinical implications (Savage, 2005). The shift can also be

[270] The sacrum composes a series of 5 bony segments fused together (known as S1 to S5) that create a triangular-shaped bone that serves as the base of the spine.
[271] Shift of a regional border away from the skull.
[272] Shift of a regional vertebral border towards the skull.

associated with asymmetrical accessory ribs[273].

Estimates of the prevalence of transitional vertebrae vary considerably. In those seeking healthcare for low back pain prevalence estimates range between 7% and 30%. This is slightly higher than the 4%- 24% commonly reported as the frequency of transitional vertebra in the general population (Delport et al., 2006).

Lumbosacral junction transitional states

The *lumbosacral junction* is associated with significant mechanical stress because of its terminal position in the spinal column. The biomechanics of load bearing at the junction depends on structural characteristics of vertebrae unique to the region.

This junction is frequently associated with vertebrae in ‘‘transitional’’ states between the L5 and the S1 vertebrae. These transitional states are manifest as a morphological transformation of the first sacral segment (S1) toward a L5 vertebral configuration (i.e. lumbarisation) or as fusion between the costal elements and the body of the fifth lumbar vertebrae with the first sacral segment (i.e. sacralisation). Lumbosacral transitional vertebrae have been reported to have a median frequency of 7% (Weber & Ernestus, 2011).

In the case of *sacralisation*, transitional states may range from simple unilateral or bilateral articulation between extended/dysplastic (broadened and enlarged) transverse processes of the L5 and the sacral alae, through *touching but not fused* transverse processes, to the *fusion* of entire transverse and costal elements of the L5 vertebrae with the alae of the sacrum, Figure 5.9.2.(Bron, van Royen, & Wuisman, 2007; Mahato, 2010c).

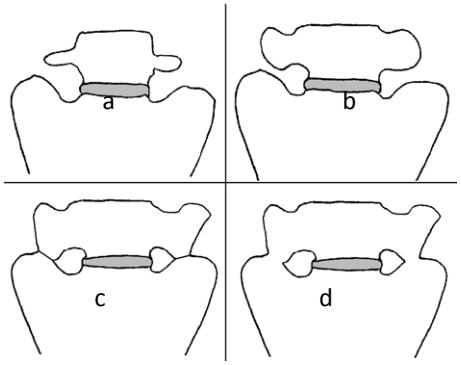


Figure 5.9.2. **Schematic representation of some of the morphological forms of transitional vertebrae found at the lumbosacral junction a. Normal arrangement, b. enlarged transvers processes, c. enlarged L5 transverse processes meeting but not fused to the alae of the sacrum, d. enlarged transverse process with bilateral fusion with the adjacent sacral ala(Bron et al., 2007).**

[273] Personal communication, Gordon Howie, reviewer.

Savage (2005) in a Master's thesis entitled "Lumbosacral transitional vertebrae: classification of variation and association with low back pain", described the *segmental variation* at the lumbosacral junction in terms of modification of the vertebral body and facet joints as well as the transverse processes, Figure 5.9.3.

Figure 5.9.3. **Variation in the transverse processes, vertebral junction and facet joints in transitional vertebrae at the lumbosacral junction after Savage (Savage, 2005)**.

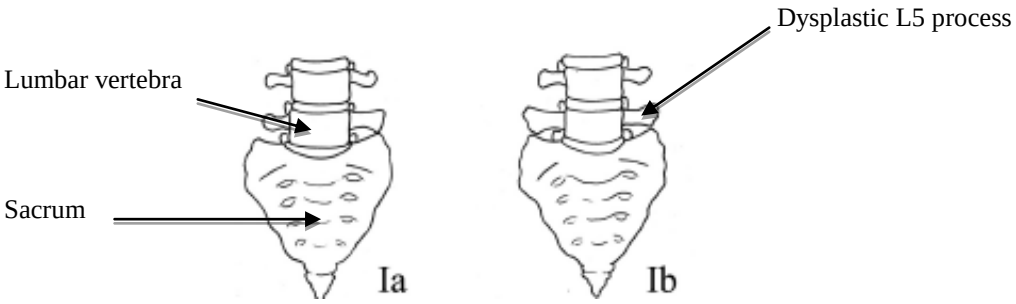
Sacralization of the L5 vertebrae

Among the transitional states encountered at the lumbosacral junction, *sacralisation of the L5 vertebra* is reported to be more commonly found than lumbarisation of the S1 sacral segment. However, complete lumbarisation of the S1 vertebra represents one end of a ''transitional spectrum'' at the lumbosacral junction with the other end being represented by absolute sacralisation of the L5 vertebra (Mahato, 2010b). Thus it may be unclear whether lumbarisation or sacralisation is taking place

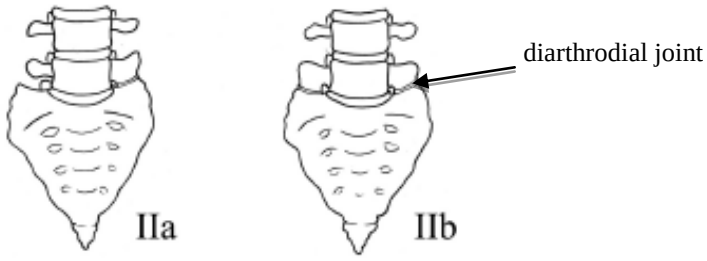
Sacralised L5 vertebrae exhibit *a range* of morphological features. Sacralised L5 vertebrae most commonly exhibit *accessory articulations* between the L5 transverse process and the ala of the sacrum. These articulations are referred to as *incomplete* sacralisation; *complete* sacralisation of the L5 vertebra entails unilateral or bilateral *fusion* between the L5–S1 transverse elements.

There have been a number of classifications of the morphological forms of sacralised L5 vertebrae. The most commonly reported is the Castellvi classification (Castellvi, Goldstein, & Chan, 1984). Castellvi et al. (1984) classified the degrees of sacralisation/lumbarisation of the L5–S1 vertebrae into four types on the basis of morphologic characteristics (Mahato, 2010a);

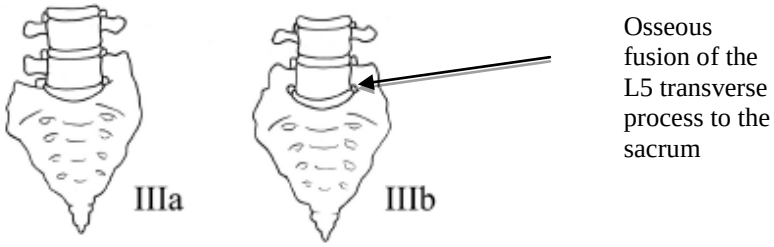
Type I: Dysplastic L5 transverse processes, measuring at least 19 mm in width: unilateral (Ia) or bilateral (Ib).



Type II: Incomplete lumbarisation/sacralisation with an enlarged transverse process that has a diarthrodial joint (a joint with two synovial facets[274]) between itself and the sacrum: unilateral (IIa) or bilateral (IIb).



Type III: Complete lumbarisation/sacralisation with osseous fusion of the transverse process(es) to the sacrum: unilateral (IIIa) or bilateral (IIIb).



[274] This definition is from Gray's anatomy. However, it says such joints are freely movable, which these joints are not. There may be a little movement between the joint surfaces, but usually there is none. Reviewer.

Type IV: Mixed lumbarisation/sacralisation: unilateral type II transition with a type III on the contralateral side .

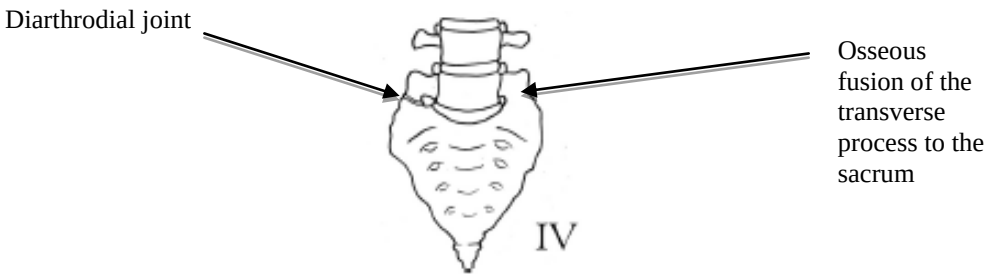


Figure 5.9.4. Classification with modifications (Konin & Walz, 2010; Weber & Ernestus, 2011)

Among individuals with transitional vertebrae, the prevalence of assimilation involving fusion of one or both transverse processes is reported with a frequency of 83% (Castellvi type III and IV) compared with only 17% of no fused transverse processes (Castellvi type II)(Weber & Ernestus, 2011) .

Aetiology

The cause of lumbosacral transitional vertebrae (LSTV) is unanimously reported to be genetic with defects arising during the development of the spine. These developmental defects are thought to be caused by a delay in the timing of threshold events occurring at the lumbosacral junction (Barnes, 1994). Disruption of developmental timing, with resultant defects, can only occur during the vulnerable time when developmental thresholds are reached. This causes developmental fields to overlap or expand beyond normal parameters resulting in caudal or cranial boundary shifts between the different regions of the vertebral column (Savage, 2005).

A number of specific genes have been implicated in relation to the determination of segmentation of the axial skeleton (Mahato, 2010a). During embryogenesis, the axial skeleton is derived from the paraxial mesenchyma that surrounds the neural tube. The mesenchyma undergoes craniocaudal segmentation, resulting in clusters of cells, the so-called somites [275]. The somites are segmentally organised in pairs on both sides of the neural tube and are specific for the axial level at which they are positioned . The segmental identity of the somites is determined by different Hox-genes in the pre-somitic mesoderm . The specific combination of Hox-genes that is expressed at a particular level seems to determine the axial identity of the resulting structures. To support this hypothesis it has been shown experimentally that *vertebral sacralisation can be induced* in transgenic mice by Hoxa11 expression. It has also been shown that in the absence of Hox11 function, *sacral vertebrae are not formed* and instead these vertebrae *assume a lumbar identity*. In addition, it has been shown that in the absence of Hox10[276] no lumbar vertebrae are formed. These studies suggest that the normal

[275] A somite is a primitive segment of the body which is mainly discernible in the embryo.
[276] Carapuco M, Novoa A, Bobola N, Mallo M. Hox genes specify vertebral types in the presomitic mesoderm. Genes Dev 2005;19: 2116–21.

patterning of lumbar and sacral vertebrae as well as the changes in the axial pattern, such as LSTV, result from mutations in the *Hox-10* and *Hox-11* genes (Bron et al., 2007).

While these is convincing support for the Hox gene complex as a primary (though not sole) contributor to final vertebra identity, there are a number of other genes that act upstream and downstream of the Hox complex that serve to regulate expression of Hox genes and ultimately the identity of each vertebra (Pilbeam, 2004). In addition to the products of Hox genes, there are regulatory genes that affect the timing of development. The genetic sensitivity of individuals, and populations, to timing disruptions may explain why some researchers have discovered that certain defects are more common in some families and populations (Savage, 2005).

The pattern of *inheritance* of vertebral developmental defects has been studied in some depth. Schmorl (1971)[277] reported that cranial shifts (sacralisation) are often at only one or two transitional borders but caudal shifts (lumbarisation) often involve three or four borders, and the shifts are often in the same direction. Schmorl (1971) also reported that the cranial shifts were dominant over the caudal shifts. Further, while the specific shift did not seem to be inherited, the direction of the shift did, i.e. the offspring may not inherit the shift at the same junction (i.e. lumbosacral or thoracolumbar) as the parent, but parent and offspring will both have either a cranial or caudal shift (Savage, 2005).

Natural history

No studies reporting on the natural history of sacralised L5 vertebrae were identified and no information relating to the natural history of the condition was reported in any of the publications examined.

Clinical considerations

An association between transitional vertebrae and *low back pain* was first reported by Bertolotti in 1917 [278] and the association has remained a topic of debate since (Mahato, 2010a). Reported clinical implications of transitional vertebrae range from direct implication or increased risk, to no associations between transitional states and low back pain (Mahato, 2010c).

Bertolotti (1917) described assimilation of the fifth lumbar vertebra into the sacrum associated with low back pain (Bertolotti syndrome). In 1984, Wiltse et al. [279] first reported pinching of the lumbar spinal nerve between the transverse process of the fifth lumbar vertebra and the sacral ala and called it “far-out syndrome” (Weber & Ernestus, 2011). Weber et al (2011) also reported that extraforaminal entrapment of the spinal nerve in transitional lumbosacral segment with unilateral transverse process anomaly (see Castellvi type IIa, Figure 1.) could result in radiculopathy mainly caused by osteophytes (Weber & Ernestus, 2011).

However, pathological conditions are reported to be much more common at the intervertebral segment *above* a transitional vertebra than below it. The cause is believed to be mechanical stress

[277] Schmorl G and Junghanns H. 1971. The human spine in health and disease (2nd American Edition). Edited and translated by Besemann EF. New York: Grune & Stratton.
[278] Bertolotti M. Contributo alla conoscenza dei vizi di differenzazione regionale del rachide con speciale riguardo all’ assimilazione sacrale della v. lombare. Radiol Med 1917;4:113–44.
[279] Wiltse LL, Guyer RD, Spencer CW, Glenn WV, Porter IS (1984) Alar transverse process impingement of the L5 spinal nerve: the far-out syndrome. Spine 9:31–41.

concentrated above the transitional vertebra because motion between the transitional vertebra and the sacrum is limited (Weber & Ernestus, 2011). Mahato et al (2010a) also reported that patients with lumbosacral transition vertebra were at increased risk of advanced disc degeneration or disc herniation *above* the lumbosacral transition vertebra (Mahato, 2010a).

Bron et al (2007) reported that patients with lumbosacral transitional anomalies were often suggested to be prone to various secondary pathologic spinal conditions including intervertebral disc herniation and/or degeneration, facet joint arthrosis and spinal canal or foraminal stenosis[280](Bron et al., 2007) rt however, convincing evidence was thought to be lacking in the scientific literature reviewed. The association between low back pain and sacralisation was also reported to be weak and the authors concluded that;

"LSTV[281] is a benign anatomical variation of the lumbosacral spine that is very often encountered by the spinal surgeon the clinical significance of the condition is still unknown and its relation with low back pain is controversial."(Bron et al., 2007)

The statistics of Delport et al 2006 suggest that the clinical significance of lumbosacral transitional vertebrae is not great, except that the first mobile joint above the transitional vertebra is more prone to wear and tear (Delport et al., 2006).

[280] Degenerative spondylolisthesis was added to this list by Gordon Howie, external reviewer who stated that " There is a known increase in the incidence of degenerative spondylolisthesis at L4/l5 in patients with sacralisation.
[281] lumbosacral transitional vertebrae (LSTV)

Section 6: Spinal fusion and adjacent segment disease

The ACC has requested an evidence based overview of the clinical outcomes of spinal fusion to provide advisors with a resource which will assist them to determine whether or not a particular claim is compensable under ACC's legislation. The focus will be on evidence pertaining to the effectiveness of spinal fusion for the management of spinal lesions on various clinical outcomes.

The overview is in three parts which cover;

1. fusion in the lumbar spine
2. fusion the cervical spine
3. the consequences of fusion surgery for adjacent spinal segments.

Section 6.1: Lumbar fusion

The current section focuses on the evidence pertaining to the effectiveness of fusion for the management of spinal lesions of the *lumbar spine* and, in particular, the *clinical outcomes* of fusion surgery.

The literature relating to lumbar fusion surgery comprises a large volume of mainly low quality studies reporting on a multiplicity of different fusion techniques and adjuncts. This voluminous and heterogeneous literature has generated a significant number of systematic and non-systematic reviews, overviews and guidelines each of which attempts to draw together key strands of the evidence to guide clinical management of specific spinal conditions. With few high quality studies available, most of the higher quality systematic reviews report on the same small group of randomised trials. Not surprisingly many of these reviews report similar conclusions.

These literature reviews have also been used to underpin clinical practice guidelines produced by professional groups/societies/associations[282] involved in the treatment of lumbar spine conditions. The resulting guidelines, written mostly by the profession for the profession, have attempted to abstract, analyse and synthesise the body of scientific evidence on lumbar fusion surgery to provide timely and graded treatment standards and practice recommendations. These professional guidelines usually contain a clear statement of the strength and quality of the evidence upon which they are based but often include expert opinion to provide advice or "options" particularly where the evidence is weak, conflicting or unsubstantial. Thus while clinical guidelines generally represent a substantial body of work, their quality, and in some cases, their impartiality, has been questioned[283].

In this ACC commissioned overview a number of difficulties were encountered when reviewing recent clinical guidelines. Firstly, a number of guideline documents tended to be lengthy and descriptive rather than analytical. Where analyses were carried out they were generally qualitative (narrative) rather than quantitative (pooling results in a metaanalysis). Secondly, there were often mismatches and omissions between the original guideline (as published on Association or Society websites) and scientific papers reporting the guidelines published subsequently in peer reviewed journals. There were also reporting discrepancies within the individual reports. These and other inconsistencies and weakness made it difficult at times to abstract the relevant data with confidence and/or track down individual pieces of information required for an evidence synthesis and quality assessment. Thirdly, different grading/ranking systems used by the different guidelines hindered comprehension and comparisons.

A number of recent and relevant clinical guidelines are reported in the current overview. However, given the weaknesses noted above and questions relating to the impartiality of guideline recommendations in some areas, this report focuses on the evidence presented in *systematic reviews* rather than guideline recommendations.

Finally, there may be difficulties relating outcomes reported in studies carried out on Japanese and North American patients to likely outcomes for New Zealanders.

[282] A large number of which are American.
[283] Guidelines vary in how closely they reflect the current evidence, different interpretations of the evidence, expert opinion and patient preference may all influence the final recommendations.

Executive Summary: Lumbar fusion

Background

Low back pain is extremely common and very costly. It is reported, for example, that between 2% and 8% of the U.S. work force is disabled or compensated for back injuries each year; 75% of the associated costs are incurred by about 5% of those with disability through back pain.

Although there are a number of management options for this small group of patients, there appears to be little consensus, either within or between specialties, on their appropriate use. Variations in the cost of care have also been of some concern; it has been reported that patients may experience broadly similar outcomes at substantially different costs.

There are now at least 11 international guidelines for management of low back pain. The recommendations of these guidelines vary. Recent critical reviews of some guidelines have suggested that there is a lack of objective analysis of the evidence and that conflicts of interest may have introduced bias. Thus for the current ACC overview it was determined that the most prudent approach would be to focus on the evidence presented in recent systematic reviews rather than treatment guidelines, but to include a brief review and summary of the recommendations reported in the most recent relevant clinical guidelines. In this way it was anticipated that evidence transparency may be maintained and any clinical guidelines idiosyncrasies/ evidence conflicts highlighted.

Methods

A systematic search of the literature for systematic reviews, meta-analyses and clinical guidelines relating to the effectiveness of surgical fusion for symptomatic conditions of the lumbar spine was carried out. Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews (i.e. evidence based). In addition bibliographic databases relevant sources/websites were searched for recent (2005 -2011) evidence based guidelines reporting substantially on fusion surgery.

The quality of most of the systematic reviews identified for this report were also reported and assessed for quality in the recent 2009 American Pain Society (APS) guidelines. Given the volume of literature in this area and the limited time and resources available for the current review, adoption of the APS quality scores rather than a re-analysis of the reviews was felt to be prudent. Additional systematic reviews not covered by the APS guidelines were assessed using the same tools as the APS guidelines. Because of the large number of low quality studies identified for the current review and their potential to distort perceptions of the effectiveness of fusion surgery, a *best evidence analysis and synthesis* was undertaken in which only recommendations based on good quality evidence that was likely to be free of significant biases was included.

Publications identified in the search procedure for the current review together with significant publications identified through pearling references from retrieved articles are cited the bibliography

at the end of this report. Other relevant references quoted to support particular statement in the reviewed studies are referenced in footnotes.

Systematic reviews

Twenty seven relevant systematic reviews focussing on or including evidence of effectiveness for lumbar fusion surgery were identified by the search procedure. Sixteen systematic reviews were considered to be eligible and included in this overview, 12 examined the effectiveness of fusion surgery for specific indications with four examining the effectiveness of different fusion techniques.

Indications/conditions

Degenerative lumbar scoliosis

One systematic review published in 2010 was identified. The purpose of the review was to compare the effectiveness corrective and non-corrective surgery for degenerative lumbar scoliosis. Interventions included anterior correction alone, instrumented fusion, combined anterior and posterior correction, and posterior correction alone. Control groups or non-corrective surgery included decompression with or without fusion. *Overall, surgical results obtained with corrective and non-corrective operations were comparable.* However, there was not enough data to assess the outcomes of the different fusion techniques employed and the studies were generally poorly reported. The authors concluded that where were insufficient good-quality studies to properly compare surgical treatment outcomes between corrective deformity and non-corrective procedures.

Fusion surgery for low back pain

Five systematic reviews published between 2005 and 2009 were identified which between them assessed a small set of randomised controlled trials. The reviews varied in the number of trials they reported, the extent of their reporting and analysis of the trials, and in the emphasis of their conclusions. However, all but one concluded that there *was no strong evidence to support the treatment of low back pain using fusion surgery,* particularly when the short-term results of fusion therapy were compared to that of an intensive rehabilitation regimen. The reviews shared a general weakness in that they were all focussed on a group of patients that shared *symptoms* rather than a specific diagnosis; this resulted in patient group overlap between these and other reviews reporting on patients with specific diagnoses.

Symptomatic degenerative lumbar spine disorders

One systematic review published in 2008 examined the effectiveness of fusion surgery for symptomatic lumbar degenerative spine disorders. The key feature of this review was its attempt to assess whether there was a difference in clinical outcomes for patients with *specific diagnoses*. The number of well-designed and adequately reported studies on interventions used to treat symptomatic lumbar degenerative disease was reported to be limited. The authors of the review concluded that substantial improvement could be expected in patients treated with fusion, regardless of technique, where an established indication such as spondylolisthesis or degenerative disc disease exists. Chronic low back pain patients were less disabled and experienced less improvement. They also reported that *definitive proof of treatment efficacy* for both fusion and nonsurgical treatment of symptomatic lumbar degenerative disease *was not provided* by the studies under review. Thus while better results were reported for some diagnoses (e.g. spondylolisthesis)

because of the low quality of the evidence, the authors concluded that overall the evidence was *unclear*.

Disc herniation

One systematic review published in 2005 examined the effectiveness of fusion surgery for disc herniation. The authors concluded that there was *no convincing medical evidence* to support the *routine use of lumbar fusion* at the time of a primary lumbar disc excision, and that there was conflicting Class III medical evidence regarding the potential benefit of the addition of fusion in this circumstance. Therefore, the increase in cost and complications associated with the use of fusion could not be justified. They did however consider that patients with preoperative lumbar "instability" may benefit from fusion at the time of lumbar discectomy. They also noted that patients with a recurrent disc herniation had been treated successfully with both reoperative discectomy and reoperative discectomy combined with fusion. In patients with recurrent lumbar disc herniation with associated spinal deformity, instability, or associated chronic low back pain, consideration of fusion in addition to reoperative discectomy was recommended

Degenerative lumbar spondylolisthesis

Five reviews published between 2005 and 2007 examined the effect of spinal fusion therapy on patients with spondylolisthesis. The reviewed studies were published between 2003 and 2005 and at least one review included studies with patients with stenosis in addition to spondylolisthesis. Results and conclusions varied. In general, there was *no strong high class evidence* to support the use of fusion as treatment for spondylolisthesis. There was some evidence to suggest that fusion may improve outcome over decompression alone, but the evidence was inconsistent and was generally based on studies with flawed designs.

Fusion techniques

Four systematic reviews published in 2005 examined evidence of effectiveness for different types of lumbar fusions. These systematic reviews were carried out by the same group of authors to underpin the 2005 AANS/CNS Guidelines for the Performance of Fusion Procedures for Degenerative Disease of the Lumbar Spine. While this series of systematic reviews represents an impressive body of work the included studies were very heterogeneous and there were a number of faults/weaknesses which increased the possibility of bias and selective selection and reporting of evidence.

Interbody techniques

In a best evidence analysis two low quality RCTs were reviewed. In one trial, circumferential instrumented fusion was not found to be superior to posterolateral fusion with regard to functional status at 2 years. In the other trial, one stand-alone posterolateral interbody fusion BAK cage and two stand-alone posterolateral interbody BAK cages for L4-L5 degenerative Grade I spondylolisthesis showed no differences between the techniques.

Pedicle screw fixation

In a qualitative systematic review reporting on the best evidence effectiveness outcomes of pedicle screw fixation as an adjunct to posterolateral fusion for non-specific back pain or degenerative spondylolisthesis, the use of pedicle screw was reported to increase radiological fusion success.

However, there was no convincing clinical correlation between radiographic fusion and clinical outcome. The largest contemporary RCT did *not show a benefit* for pedicle screw fixation.

Bone graft extenders and substitutes

In a qualitative systematic review of bone graft extenders and substitutes, a best evidence analysis included one multicentre RCT comparing recombinant human bone marrow protein-2 (rhBMP-2) with autograft used in combination with a titanium cage for an anterior lumbar interbody fusion. The authors reported that there was a slightly higher fusion rate, a slightly shorter operating room time and slightly decreased blood loss in the rhBMP-2 group. There was also an advantage for the rhBMP-2 group in terms of donor-site pain[284] .

Bone growth stimulators

In a qualitative systematic review of the use of bone growth stimulators[285] to improve outcomes of lumbar fusion a best evidence analyses reported evidence from two studies. One small RCT and one non-randomised comparative study, reported favourable (fusion) results of direct current stimulation (DCS) in a patients undergoing instrumented lumbar posterolateral fusion: functional outcome was not reported. Kucharzyk (1999) found that implantation of a DCS device improved fusion rates and clinical outcomes. A further multicenter double-blinded RCT evaluating the effect of capacitative coupling stimulation (CCS) on fusion rates and clinical outcomes reported a beneficial effect associated with CCS.

Guidelines

The search procedure developed for the current study identified three recent evidence based guidelines reporting substantially on the use of fusion techniques for the treatment of lumbar spinal disease. It should be noted that this list of eligible guidelines may not be exhaustive. Time and resource limitations did not permitted an exhaustive search to be conducted of all potentially relevant Association/Society websites.

North American Spine Society (NASS) 2009 clinical guideline for the treatment of symptomatic degenerative spondylolisthesis

There were three Grade B, one grade C and one grade I recommendations relating to lumbar fusion for degenerative lumbar spondylolisthesis; in one instance there was not enough evidence to make a recommendation.

- The addition of fusion to decompression was recommended to improve clinical outcomes in symptomatic patients (Evidence Grade: Grade B)
- The addition of instrumentation was recommended to improve fusion rates (Grade B) but not clinical outcomes (Evidence Grade: Grade B).
- Decompression with fusion was recommended as a means to provide satisfactory long-term results (Evidence Grade: Grade C).

[284] Note: a recent critical appraisal of the evidence suggests that serious adverse events were not reported in the published evidence that underpinned this recommendation.
[285] Bone growth stimulators have not been widely used in NZ (personal communication, Graham Howie, reviewer).

- Reduction with fusion and internal fixation was not recommended to improve clinical outcomes for patients with low grade degenerative lumbar spondylolisthesis (Evidence Grade: Grade I, insufficient evidence).
- There was not enough evidence to make a recommendation relating to the effectiveness of circumferential fusion compared to posterolateral fusion with decompression.

The American Pain Society (APS) 2009 Guideline for the evaluation and management of low back pain.

The evidence that underpinned the guideline was based on data from RCTs assessing the benefits and harms of surgical treatment for non-radicular low back pain with common degenerative changes, radiculopathy with herniated lumbar disc and symptomatic spinal stenosis. Lumbar fusion was a relatively small part of this guideline and was only briefly reported. Twenty systematic reviews that assessed lumbar fusion techniques were evaluated and a synthesis of the evidence produced. This evidence was used to underpin guideline recommendations.

The relevant recommendations are summarised below.

- In patients with non-radicular low back pain who do not respond to usual non-interdisciplinary interventions: Interdisciplinary rehabilitation is similar in effectiveness to fusion surgery.
- For patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms, fusion surgery is superior to nonsurgical therapy without interdisciplinary rehabilitation (1 trial) with moderate benefit but no more effective than intensive interdisciplinary rehabilitation (3 trials). (Level of evidence = fair, grade of evidence = B). The guideline also noted that instrumented fusion was associated with enhanced fusion rates compared with non-instrumented fusion, but that there was insufficient evidence to determine whether instrumented fusion improved clinical outcomes and that additional costs were substantial. There was insufficient evidence to recommend a specific fusion method (anterior, posterolateral, or circumferential), though more technically difficult procedures may be associated with higher rates of complications.
- For patients with disabling leg pain due to spinal stenosis with or without degenerative spondylolisthesis: There was insufficient evidence to determine if laminectomy with fusion was more effective than laminectomy without fusion.

American Association of Neurological Surgeons/Congress of Neurological Surgeons 2005 guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine.

A series of 17 guideline reports were published. Six of the reports related to methods and assessment techniques and were not included; three related to monitoring adjunct bracing and injection therapies and were not included. Four of the remaining eight reports focussed on specific indications (intractable low-back pain without stenosis or spondylolisthesis, disc herniation and radiculopathy, stenosis and spondylolisthesis, stenosis without spondylolisthesis) and four reports focussed on different fusion methods, graft materials and instrumentation (interbody techniques for lumbar fusion, pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain, bone graft extenders and substitutes and bone growth stimulators for lumbar fusion).

There was insufficient Class I evidence (RCTs) to recommend fusion as a treatment standard in three of the four indications examined. However, lumbar fusion was recommended as a treatment for carefully selected patients with disabling low back pain due to one- or two-level degenerative disease without stenosis or spondylolisthesis. There was not enough Class II evidence to underpin guidelines in relation to fusion surgery for any indication. A large number of treatment options resulting from low level (class III) evidence were suggested.

There was insufficient Class I evidence from RCTs to recommend the use of any particular fusion technique or adjunct as a treatment standard with the exception of autologous bone or rhBMP-2 bone graft substitute which was recommended as the treatment standard in the setting of an ALIF in conjunction with a threaded titanium cage. Class II evidence underpinned three fusion treatment guidelines:

- In the context of a single-level stand-alone ALIF or ALIF with posterior instrumentation, the addition of a PLF was not recommended as it increased operating room time and blood loss without influencing the likelihood of fusion or the functional outcome.
- Either direct current stimulation or capacitative coupling stimulation was recommended as an adjunct to spinal fusion to increase fusion rates in patients who are at high risk for arthrodesis failure following lumbar PLF.
- Pulsed electromagnetic field stimulation was recommended as an adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.

A number of treatment options resulting from low level (class III) evidence were suggested.

Best evidence synthesis: overall conclusions

Systematic reviews reporting on degenerative lumbar spondylolisthesis concluded that overall there was *conflicting evidence on the clinical effectiveness of fusion* in this populations of patients. Guidelines for symptomatic degenerative spondylothisthesis however made a recommendation *supporting fusion* as an addition to decompression, to improve clinical outcomes; this was supported by Level II or III studies with consistent findings (Grade B recommendation: Fair evidence). To improve fusion rates (but not necessarily clinical outcomes) the addition of instrumentation was recommended (level II or level III studies, Grade B recommendation: Fair evidence.)

Systematic reviews reporting on chronic low back pain concluded that *the evidence did not allow a general statement regarding the efficacy of fusion over non operative care* for discogenic back pain and that overall the evidence from RCTs suggested that any advantage was modest and, on average, near or below a minimally important clinical change in the disability score. There was evidence that *lumbar fusion was not more effective than intensive rehabilitation which included cognitive behaviour therapy.* Systematic reviews reporting on symptomatic degenerative lumbar disease (degenerative disc disease, chronic low back pain, spondylothisthesis) concluded that definite proof of treatment efficacy for both fusion and nonsurgical treatment of symptomatic lumbar degenerative disease remained *unclear*. The AANS/CNS guidelines for intractable low-back pain without stenosis or spondylolisthesis *recommended lumbar fusion as a treatment for carefully selected patients* with disabling low-back pain due to one- or two-level degenerative disease (recommendation at the level of a practice standard support by Class I evidence). For patients with

non-radicular low back pain with common degenerative changes and persistent disabling symptoms the APS guideline recommended that, in patients who do not respond to usual non- interdisciplinary interventions, clinicians consider intensive interdisciplinary rehabilitation with a cognitive/behavioural emphasis (strong recommendation, high-quality evidence).

Systematic reviews for spinal stenosis without degenerative spondylolisthesis concluded that there was good evidence that decompressive laminectomy *with or without fusion* was moderately superior to nonsurgical therapy for improvement in pain and function through 1-2 years.

Guidelines produced by the AANS/CNS on the use of bone graft extenders and substitutes recommended the use of autologous bone or rhBMP-2 bone graft substitute is recommended in the setting of an ALIF in conjunction with a threaded titanium cage (recommendation at the level of a practice standard supported by Class I evidence). Note: a recent critical appraisal of the evidence suggests that serious adverse events were not reported in the published evidence that underpinned this recommendation.

Guidelines produced by the AANS/CNS on the use of interbody techniques recommended that for lumbar fusion In the context of a single-level stand-alone ALIF or ALIF with posterior instrumentation, the *addition of a PLF was not recommended* as it increases operating room time and blood loss without influencing the likelihood of fusion or the functional outcome (recommendation at the level of a guideline supported by Class II evidence).

Background: Lumbar fusion

Reviewer's note: The background information below is paraphrased from the recent American Pain Society (APS) guidelines on interventions for the treatment of low back pain (Chou & Huffman, 2009; Chou, Loeser et al., 2009). Its purpose is to provide a context for the complex, voluminous, and at times controversial, literature relating to the treatment of disorders of the lumbar spine.

Low back pain is extremely common and very costly. It is reported, for example, that between 2% and 8% of the U.S. work force is disabled or compensated for back injuries each year (Andersson, 1999; Straus, 2002). Seventy five percent of the associated costs are incurred by about 5% of those with disability through back pain (Frymoyer & Cats-Baril, 1991).

While there are a number of management options for this small group of patients, there appears to be little consensus, either within or between specialties, on appropriate uses of the available interventions. This is demonstrated by numerous studies exhibiting unexplained variations in the treatments used and the outcomes obtained in this group of patients.

Chou et al (2009) has claimed that an important historical feature of low back pain management has been the widespread uptake and use of unproven (and sometimes invasive and costly) interventions. Some of these have reportedly later been shown to be ineffective, or even harmful (Deyo, 1991). It has also been claimed that some interventions have been widely used despite studies showing only marginal benefits (Deyo, Nachemson, & Mirza, 2004).

The cost of care has also been of some concern. It has been reported that patients may experience broadly similar outcomes, with the costs of care differing substantially both between and within specialties (Carey et al., 1995; Shekelle, Markovich, & Louie, 1995).

Given this background, not surprisingly there are now at least 11 international[286] guidelines for management of low back pain. Differences in their recommendations are thought to reflect in part (a) contextual differences between countries which can affect interpretations of the evidence and (b) how the trade-offs between benefits, side effects, and costs are weighted.

Recent guidelines for fusion or spinal surgery, such as those produced by the American Pain Society (APS)[287] the American Association of Neurological Surgeons (AANS[288]) and the North American Spine Society (NASS[289]) have been underpinned in some instances by qualitative systematic reviews of large number of studies of low scientific validity. In such circumstances the opinions of the guidelines committee (i.e. "expert opinion") can play a pivotal role (Steinbrook, 2007).

Recently, clinical guidelines for the evaluation and management of low back pain from the American Pain Society (Chou & Huffman, 2009) was critically reviewed by Manchicanti (Manchikanti et al., 2010). This review resulted in a number of damning comments:

[286] Though mostly American.
[287] http://www.ampainsoc.org/library/pdf/LBPEvidRev.pdf
[288] http://www.spinesection.org/fusion_guidelines.php
[289] http://www.spine.org/Documents/Spondylolisthesis_Clinical_Guideline.pdf

"The recent development of American Pain Society (APS) guidelines has created substantial controversy because of their perceived lack of objective analysis and recommendations perceived to be biased due to conflicts of interest."

and

"The present critical assessment review illustrates that APS guidelines have utilized multiple studies inappropriately and have excluded appropriate studies. Our integrity assessment shows deep concerns that the APS guidelines illustrating significant methodological failures which raise concerns about transparency, accountability, consistency, and independence.".

These and other comments (mostly not directed directly at surgical interventions) published in the prestigious NEJM [290] suggested that (as noted earlier) perhaps the most prudent approach to the current ACC overview was *to focus* on the evidence presented in recent[291] *systematic reviews* rather than treatment guidelines but to include a brief review and summary of the recommendations reported in the most recent relevant clinical guidelines. In this way evidence transparency may be maintained and any clinical guidelines idiosyncrasies highlighted.

[290] See for example (Blood et al., 2008; da Costa et al., 2007; Deyo, 1991, 2007; Deyo et al., 2004; Deyo, Psaty, Simon, Wagner, & Omenn, 1997; Katz & Harris, 2008; Lipson, 2004; Steinbrook, 2007, 2009)
[291] From 2000 onwards.

Lumbar fusion techniques

The techniques that are the focus of this review are not new and, in one form or another, have a long history.

Posterior fusion

Posterior fusion surgery has been practiced since the early 1900's. The procedure was first carried out to correct spinal deformity cause by tuberculosis. It was noted that it also relieved back pain.

There are multiple surgical methods for obtaining spinal fusion. The oldest and simplest method is reported to be a posterolateral gutter fusion which involved placing a bone graft in the posterolateral portion of the spine. The bone was left lying free in place, without fixing screws or plates between the lateral processes of the arch of the vertebra. This technique gave rather variable results. Sometimes the added bone just disappeared, at other times it stayed but failed to fuse with the spine, sometimes it worked as intended and fused the bones of the spine.

These inconsistent results spurred surgeons to look for better results by using some form of rigid fixation with metal plates and screws. The first attempt at improvement was to put the bone graft directly between the bodies of the vertebrae, where there were more surfaces for the graft to adhere to.

Cloward introduced modern posterior lumbar interbody fusion (PLIF) surgery in the 1950's using impacted blocks of iliac crest bone[292]. The new technique, known as posterior[293] lumbar interbody fusion (PLIF) achieved spinal fusion between vertebral elements in the low back by inserting the bone graft and/or spinal implant, such as a cage, directly into the disc space. The graft stimulated bone growth between the vertebral elements and immobilised the spinal segment. While some surgeons reported favourably on their early experience with PLIF, difficulties with inconsistent fusion rates and complications related to blood loss, dural/neural injury, graft extrusion, and arachnoiditis, limited its initial appeal.

The popularity of PLIF rose again in the 1990's with the advent of supplementary interbody implants (cages) to support and stabilize the disc space while bone graft, placed within the cages, united the bone of the vertebral end-plates. Fusion rates improved with these implants with successful fusion rates of 90-95% reported and up to 86% of patients obtaining satisfactory relief of back or radicular leg pain.

More recently, newer and more streamlined impacted implants made of titanium, plastic PEEK polymers (polyetheretheketone) or allograft bone have become available. The use of impacted allograft wedges was reported to significantly lower nerve root injury rates compared to the earlier allograft cylindrical threaded fusion cages (0% vs. 13.6% respectively). Less invasive techniques are also reported to be gaining popularity. Some surgeons perform PLIF procedures through minimal access (keyhole) approaches using either impacted or "insert and rotate" techniques[294], aided by

[292] Morselized and compacted bone chips.
[293] Surgical approach is from the back
[294] http://www.synthes.com/MediaBin/US%20DATA/Product%20Support%20Materials/Technique%20Guides/SPINE/SPTGOPALJ7671B.pdf

advances in image-guided / computer assisted technology[295]. These techniques utilize the principles developed for minimal access laminectomy surgery.

Thus, lumbar spinal fusion procedures have had a varied history and popularity for the treatment of painful conditions of the lumbar spine, but for some members of the medical community lumbar fusion surgery remains controversial.

Anterior fusion

In 1932 fusion of the lumbar spine using an anterior approach was considered to be biomechanically ideal but *technically impossible*. In an article published in 1936 on surgery for spondylolisthesis, James Jenkins (Dunedin) suggested that this approach would be the ideal for the condition but that *technical difficulties* precluded trialling the operation (Jenkins, 1936). Over the ensuing decades however, surgical technical advances allowed anterior lumbar interbody fusion to become a common procedure. In 1948 Lane and Moore, were the first to report anterior lumbar interbody fusion (ALIF) for the treatment of lumbar degenerative disc disease.

The anterior approach to the lumbar spine became increasingly utilized in the management of a variety of spinal pathologies, using a number of different grafting materials including cortico-cancellous blocks, cortico-cancellous dowels, and femoral ring allografts. Harry Crock adapted Cloward's posterior dowel technique for use with an anterior approach to the lumbar spine using cylindrical allograft. O'Brien devised a hybrid interbody graft using a biological fusion cage packed with autogenous cancellous[296] bone graft. The concept of this hybrid was that the femoral allograft ring provided the acute stability of the construct, while the autogenous iliac crest graft provided for long-term stability.

Initial reports, encompassing a heterogeneous group of patients and surgical techniques, reported fusion rates of 70% - 96% with anterior fusion. Other studies reported significantly poorer fusion rates. Thus although the technical feat of exposing the anterior lumbar spine safely was reliable in the 1970s to1980s, stand-alone anterior lumbar interbody fusion fell out of favour due to (a) sub-optimal fusion rates and (b) the advent of pedicle fixation as a supplement to posterolateral fusion by Professor Roy-Camille with fixed interval plates and Dr Art Steffee who developed the variable screw placement system and re-popularised PLIF with the addition of carbon fibre / PEEK cages (Brantigan cages)[297].

These poor outcomes resulted in a reassessment of ALIF, as a stand-alone procedure, and a gradual decline in its popularity, particularly for the treatment of lumbar degenerative disc disease and lumbar axial back pain.

The combination of anterior interbody fusion with a posterior fusion technique was developed with the aim of obtaining higher rates of fusion and improved outcome. The advantage of a very high fusion rate with these circumferential procedures, however, had to be balanced against an increased risk of morbidity related to the increased magnitude of the procedure.

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[295] Khoo LT. Palmer S. Laich DT. Fessler RG. Minimally invasive percutaneous posterior lumbar interbody fusion. Neurosurgery Nov 2002; 51 S2:166-181.

[296] Cancellous autograft, usually harvested from the iliac crest remains the gold standard for bone grafting. Cancellous autograft provides trabecular bone lined with osteoblasts providing for osteogenesis under the influence of local cytokines and growth factors. These grafts are vascularised and incorporated quickly and the low oxygen content of the graft as it is incorporated attracts host stem cells to the graft site.

[297] Personal communication (Gordon Howie, reviewer)

Techniques to increase the fusion rate of anterior lumbar interbody fusion with an anterior-only approach (with the aim of approximating to the success of circumferential constructs), began with anterior lumbar instrumentation, which was first reported in 1961. In one development, the need for autograft harvest was eliminated by packing this cage with cancellous bone chips obtained from the reaming of decompression. This novel device was designed with perforations in its walls to allow bone in-growth and enhance fusion (arthrodesis). A number of other devices were designed and currently there are a large number of interbody fusion devices available of varying design [298]and material including:

- cylindrical threaded titanium interbody cages (BAK, Spine-Tech, Minneapolis, MN, RTFC, Surgical Dynamics, Norwalk, CT, and Inter Fix, Sofamor Danek Group, Memphis, TN)
- cylindrical threaded cortical bone dowels (MD II, MD III, MD IV, Sofamor Danek Group, Memphis, TN)
- vertical interbody rings or boxes (Harms titanium-mesh cage, DePuy-Acromed, Cleveland, OH, Brantigan carbon fiber cages, DePuy-Acromed, Cleveland, OH, and Femoral Ring Allograft - FRA Spacer, Synthes, Paoli, PA).

As a result of the improved clinical results associated with the use of many of these interbody fusion devices[299] in stand-alone anterior procedures the use of anterior procedures became more wide-spread.

A recent interest in performing lumbar interbody arthrodesis with use of cages has been attributed to a high rate of fusion failure with the use of bone graft alone and a high rate of success associated with use of stand-alone anterior fusion cages and autogenous bone graft. Reported rates of fusion after anterior interbody fusion have improved from 56% to 93% with the use of the titanium cage.

[298] not all of which have gained Food and Drug Administration (FDA) approval for anterior application in the setting of a stand-alone device.
[299] Many of these devices have been abandoned. Most anterior devices now use additional screw fixation (personal communication, Gordon Howie, reviewer).

Methods

For a comprehensive description of the searches carried out for this review and the reporting of review methods see the General Methods section. Briefly, a systematic search of the literature for systematic reviews, meta-analyses and clinical guidelines relating to the effectiveness of surgical fusion for symptomatic conditions of the lumbar spine was carried out.

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews (i.e. evidence based).

Clinical guidelines were originally intended to be a key resource in the current overview undertaken for the ACC. However, as noted earlier, critical reviews of American guidelines have claimed biased reporting due to conflicts of interest in some guidelines and in the current overview systematic reviews have been employed as the primary evidence source.

In addition to bibliographic databases such as Medline and Embase the following sources/websites were searched for recent (2005 -2011) evidence based guidelines reporting substantially on fusion surgery:

American Academy of Orthopaedic Surgeons (AAOS)

American Society of Neuroradiology (ASN)

American Society of Spine Radiology

Guidelines International Network (GIN)

Institute for Clinical Systems improvement (ICSI)

Medical Services Advisory Committee

National Health and Medical Research Council (NHMRC)

National Institute for Health and Clinical Excellence (NICE)

New Zealand Guidelines Group (NZGG)

NHS Evidence

North American Spine Society (NASS)

Scottish Intercollegiate Guidelines Network (SIGN)

TRIP database

World Health Organisation (WHO)

Quality assessment

Most of the systematic reviews identified for this report were also reported and assessed for quality in the recent 2009 American Pain Society (APS) guidelines (Chou & Huffman, 2009). Given the volume of literature and the limited time and resources available for the current review, adoption of

the APS quality scores (rather than a re-analysis of the reviews using the designated tool[300]) was felt to be prudent. Additional systematic reviews not covered by the APS guidelines were assessed using the same tools as the APS guidelines.

The internal validity (quality) of systematic reviews underpinning the APS guideline was assessed using a checklist based on criteria developed by Oxman and Guyatt (Oxman & Guyatt, 1991). The concept behind the Oxman criteria is relatively simple – the greater the scientific quality (methodological rigour), the more likely a systematic review is to avoid bias and its findings reflect the truth regarding, for instance, the magnitude of the effect of a treatment. Using the Oxman criteria each study was scored between 1 and 7 based on the comprehensiveness of the search strategy, application of pre-defined inclusion criteria to select studies, appropriate assessment of validity (quality) and use of appropriate methods to synthesize the evidence. Systematic reviews with a score of four or less were considered to have a high potential for major flaws or biases which are more likely to produce positive conclusions about effectiveness; these were classified as "lower quality" systematic reviews. Systematic reviews with scores of five or more were considered to be "higher quality" with less potential for bias and a higher likelihood of valid results.

Within each systematic review, the reporting of levels of evidence and the quality of the primary studies varied. The definitions used in each study are indicated either in the text or in a footnote.

The quality of Guidelines was assessed using the AGREE tool[301].

Because of the large number of low quality studies identified for this review and their potential to distort perceptions of the effectiveness of fusion surgery, a *best evidence* analysis and synthesis was carried out in which only recommendations based on good quality evidence that was likely to be free of significant biases was included.

[300] See protocol
[301] www.agreecollaboration.org/instrument

Evidence assessment: Systematic reviews

Twenty seven relevant systematic reviews focussing on or including evidence of effectiveness for lumbar fusion surgery were identified by the search procedure. A number of reviews were excluded. For example an AHRQ (2006) review of therapy for patients over 65 years old (AHRQ, 2006), evaluated the same four randomised trials as Mirza et al (2007) and was not reported further , and recent NICE reviews which focussed on equivalence comparisons between arthrodesis and arthroplasty (NICE, 2010) were not considered to be directly relevant and excluded. Two systematic reviews relating to adjacent segment disease/instability following lumbar fusion are included in a separate report. Sixteen of the original systematic reviews were considered to be eligible and included in this overview. Fourteen examined the effectiveness of fusion surgery for specific indications. Four reviews examined the effectiveness of different fusion techniques.

It should be noted that eight reviews were undertaken as part of a larger series of literature reviews of lumbar fusion procedures for degenerative disease of the lumbar spine[302]. These reviews adhered to a single methodology and were carried out specifically to aid the executive committee of the American Association of Neurosurgeons /Congress Of Neurological Surgeons (AANS/CNS formulate fusion guidelines and recommendations for degenerative diseases of the lumbar spine (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005).

The definitions of classes of evidence for therapeutic effectiveness used by these reviews were as follows:

- Class I, evidence from one or more well-designed, randomized controlled clinical trials, including overviews of such trials;
- Class II, evidence from one or more well-designed comparative clinical studies, such as nonrandomized cohort studies, case control studies, and other comparable studies, including less well-designed randomized controlled trials; and
- Class III, evidence from case series, comparative studies with historical controls, case reports, and expert opinion as well as significantly flawed randomized controlled trials (Resnick et al., 2005a).

The reviews reported on evidence relating to the effectiveness of fusion surgery for:

- Degenerative lumbar scoliosis (Prommahachai, Wittayapirot, Jirarattanaphochai, & Sae-Jung, 2010)
- Low back pain (Andersson, Mekhail, & Block, 2006; Chou, Baisden et al., 2009; Ibrahim, Tleyjeh, & Gabbar, 2008; Mirza & Deyo, 2007; Resnick et al., 2005c)
- General and various symptomatic degenerative lumbar spine disorders (Carreon, Glassman, & Howard, 2008)
- Disc herniation (Resnick et al., 2005d)
- Degenerative lumbar spondylolisthesis(Gibson & Waddell, 2005; W. Jacobs, Vreeling, & De Kleuver, 2006; Kwon et al., 2005; Resnick et al., 2005e).

[302] These systematic reviews, and the recommendations made as a result of the evidence they provided, were published as a single guideline report (http://www.spinesection.org/fusion_guidelines.php) and as a series of 17 papers in a dedicated issue in the June 2005 volume (Volume 2, Number 6) of the Journal of Neurosurgery: spine.

- Various fusion techniques: interbody techniques (Resnick et al., 2005g), pedicle screw fixation (Resnick et al., 2005h), bone graft extenders and substitutes (Resnick et al., 2005i) and bone growth stimulators (Resnick et al., 2005j).

The main characteristics, author's conclusions and brief evidence summary for these systematic reviews are summarised in Tables 1- 11. Each table is followed by a fuller description of the reviews.

Indications:degenerative lumbar scoliosis

One systematic review was identified.

Prommahachai, 2010 "Correction with instrumented fusion versus non-corrective surgery for degenerative lumbar scoliosis: a systematic review."

The purpose of this review was to evaluate the effect of surgical treatment outcomes between corrective and non-corrective surgery for degenerative lumbar scoliosis (Prommahachai et al., 2010). The working hypothesis was that there *was a difference* between correction and non-correction surgery for this condition.

The main characteristics, author's conclusions and brief evidence summary of this systematic review are summarised in Table 6.1.1.

Table 6.1.1. Main characteristics and findings of the evidence for lumbar fusion surgery for degenerative lumbar scoliosis. Evidence overview for fusion is given in parenthesis after the indication.

Systematic review/Oxman internal validity (quality)/Focus Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes [303] measured/ Reported/ (measured by)	Authors conclusions
Degenerative lumbar scoliosis (Insufficient good quality evidence)					
Prommahacha (2010) Oxman= 5/7 FUSION Search to 2008	17 studies 3 cohort/poor RCTs 6 case series 8 case control or SR of level III studies	Corrective: Instrumented AILF PLIF **Non-corrective** (comparators): Decompression with or without fusion (laminectomy, laminotomy, laminoplasty)	Degenerative lumbar scoliosis	Oswestry Disability Index Validated pain scales SF-36 (QoL) Occupational Cost Fusion rate Adjacent segment disease Physical improvement	There were insufficient good-quality comparative studies for surgical treatment outcome comparison between corrective and non-corrective procedures. The recommendation grade for the use of deformity corrective procedures in degenerative lumbar scoliosis was classified as Level 2C (very weak recommendation).

PLIF = posterior lumbar interbody fusion/ posterior instrumented lumbar fusion. ALIF= anterior lumbar interbody fusion, AILF = anterior instrumented lumbar fusion. QoL=quality of life.
SR=systematic review.

[303] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR

The databases included in the literature search were PubMed (January 1, 1960 to March 31, 2009), EMBASE (January 1, 1985 to March 31, 2009), the Cochrane Central Register of Controlled Trials, CINAHL, and Scopus. Grey literature was searched from Scirus. The quality of the studies was graded by the Methodological Index for Non-randomized Studies (MINORS[304]). Studies that were classified as level I to IV were included.

The search identified 17 eligible studies comprising 598 patients; 451 patients received correction procedures. The majority of the studies presented Level III or Level IV evidence (i.e. non-randomized and non-comparative studies), two studies were Level II (i.e. randomised).

Interventions included anterior correction alone (anterior correction anterior lumbar intervertebral body and instrumented fusion), combined anterior and posterior correction (anterior lumbar intervertebral body and posterior instrumented fusion), and posterior correction alone (posterolateral fusion combination with instrumented fusion, posterior lumbar intervertebral body fusion with instrumentation). Control group or non-corrective surgery included decompression with or without fusion (laminectomy, laminotomy, decompressive laminectomy, decompressive laminotomy, decompression and fusion, decompression and posterior lumbar fusion, decompressive laminectomy and fusion, decompressive laminectomy and posterolateral fusion, decompression alone, or laminoplasty).

Six studies reported pain outcomes with improvements in pain ranging between 70% and 86%. Three studies measured quality of life and reported mostly good to excellent results. All studies reporting upon deformity correction noted improvement. Fusion rates ranged from 70% to 100%. Adjacent segment degeneration and/or disease was reported in seven studies.

Overall, *surgical results* obtained with corrective and non-corrective operations were comparable. However, there was not enough data to assess or compare the outcomes of the *different fusion techniques* employed and the studies were generally poorly reported. The authors concluded that where were insufficient good-quality studies to properly compare surgical treatment outcome between corrective deformity and non-corrective procedures.

Comment

This study was too recent to be included in the American Pain Society (APS) guidelines (Chou & Huffman, 2009). A quality assessment using the same criteria as the APS guidelines indicated that the review was flawed but of a reasonable quality. The main shortcomings were related to the potential for study selection bias and the assessment of study validity. The results of the study were not always clearly expressed.

Indications: low back pain

Five systematic reviews examined the effectiveness of surgery for low back pain (Andersson et al., 2006; Chou, Baisden et al., 2009; Ibrahim et al., 2008; Mirza & Deyo, 2007; Resnick et al., 2005c).

[304] Slim, K., Nini, E., Forestier, D., Kwiatkowski, F., Panis, Y. and Chipponi, J. (2003), Methodological index for non-randomized studies (MINORS): development and validation of a new instrument . ANZ Journal of Surgery, 73: 712–716. doi: 10.1046/j.1445-2197.2003.02748.x

Three (Andersson et al., 2006; Mirza & Deyo, 2007; Resnick et al., 2005c) focussed on spinal fusion, the other two (Chou, Baisden et al., 2009; Ibrahim et al., 2008) examined surgical procedures which included spinal fusion.

The main characteristics, author's conclusions and brief evidence summary of these systematic reviews are summarised in Table 6.1.2, followed by a fuller description of the reviews.

Table 6.1.2. Main characteristics and findings of the evidence for lumbar fusion surgery for degenerative low back pain. Evidence overview for fusion is given in parenthesis after the indication.

Systematic review/Oxman internal validity (quality)/Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
Low back pain; five studies (fusion equivalent to (a) IDET, (b) intensive rehab, (c) laminectomy; better than conventional non-surgical care; significant risk of complications and improvements not clinically important.)					
Resnick (2005) FUSION Oxman=2/7 Search to date not reported	2 RCTs	Lumbar fusion Instrumented lumbar fusion Comparators Non-surgical treatment – conservative care Intensive rehabilitation	Intractable low-back pain without stenosis or spondylolisthesis	VAS Oswestry Disability Index GFS Work status Function Daily use of medication Patient satisfaction	Class I medical evidence exists in support of the use of lumbar fusion as a treatment standard for carefully selected patients with low-back pain intractable to the best medical management. There is Class III medical evidence that suggests that a course of intensive cognitive and physical therapy may be an efficacious treatment option for the treatment of patients with chronic disabling low-back pain.
Andersson (2006) FUSION Oxman=2/7 Search to 2005	Meta-analysis of 9 RCTs (3 high quality)	PLF PLIF ALIF CF Comparator Conservative treatment	Intractable discogenic Low Back Pain.	Pain severity Back function Quality of life	The majority of patients reported improvement in symptoms following both spinal fusion and the IDET procedure. The IDET procedure appeared to offer sufficiently similar symptom amelioration to spinal fusion without the attendant complications.
Chou 305 (2009) SURGERY Oxman=6/7 Search to 2008	22 systematic reviews 12 additional trials	Posterior lumbar fusion± instrumentation Fusion NOS Circumferential fusion Comparators Non-surgical therapy Disc replacement Interspinal spacer	Low back pain (non-radicular) with common degenerative changes, radiculopathy with herniated lumbar disc or symptomatic spinal stenosis ± degenerative spondylolisthesis	Pain (VAS) Functional status (Oswestry Disability Index, Rowland Morris disability questionnaire)	For non-radicular back pain with common degenerative changes, there is fair evidence from RCTs that fusion is no more effective than intensive rehabilitation with a cognitive behaviour emphasis, but associated with small to moderate benefits (pain and function) compared to standard non-intensive nonsurgical therapy. For spinal stenosis with or without degenerative spondylolisthesis, there is good evidence that decompressive laminectomy with or without fusion in moderately superior to nonsurgical therapy

[305] (surgery only SR).

Systematic review/Oxman internal validity (quality)/Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
					for improvement in pain and function through 1-2 years.
Ibrahim (2008) Metaanalysis SURGERY Oxman=5/7 Search to 2005	3 RCTs (a fourth was used in a sensitivity analysis)	PLF with and without pedicle screws Comparator physical therapy with or without cognitive therapy	Chronic low back pain	Oswestry Disability Index (ODI)	Surgery was found to be associated with a significant risk of complications. Therefore, the cumulative evidence at the present time does not support routine surgical fusion for the treatment of chronic low back pain. We found that surgical fusion may improve the ODI compared to non-surgical intervention at the two-years follow-up for chronic low back pain. This improvement in the ODI was not statistically significant and is of minimal clinical importance; consequently, surgeons should recommend spinal fusion cautiously to patients with chronic low back pain. Further long-term follow-ups of the studies reviewed in this meta-analysis are required to provide more conclusive evidence in favour of either treatment.
Mirza (2007) FUSION Oxman = 5/7 Search to 2006	4 multicentre RCTs	PLF using iliac crest autograph without fixation PLF with iliac crest autograph with pedicle screw fixation ALIF or PLIF using bone blocks cut from the iliac crest Comparator Non-surgical treatment: cognitive intervention and exercise education	Chronic low back pain/discogenic back pain	back specific disability, pain general function psychological function work status radiographic complications patient satisfaction	Compared to unstructured, heterogeneous non-operative care, lumbar fusion may be more efficacious for treatment of chronic back pain. Fusion may not be more effective than a structured rehabilitation program that includes cognitive-behaviour therapy. Limitations of some of the RCTs comparing these treatments prevent more definitive conclusions.

NOS= not otherwise specified. PLIF = posterior lumbar interbody fusion/posterior instrumented lumbar fusion. ALIF= anterior lumbar interbody fusion, AILF = anterior instrumented lumbar fusion. PLF= posterolateral fusion. CF= circumferential (360º) fusion.

Resnick 2005b "intractable low-back pain without stenosis or spondylolisthesis"

Author's rationale: "Lumbar spinal fusion procedures are provided as a treatment for patients with low-back pain due to lumbar degenerative disease without stenosis or spondylolisthesis. These procedures are associated with significant cost and the potential for complications. There has been considerable debate regarding the role, if any, of lumbar fusion for the treatment of patients with low-back pain without deformity or neurological deficit. The purpose of this review is to evaluate the published literature regarding the use of lumbar fusion in this patient population."

The evidence for the effectiveness of fusion for *intractable low-back pain without stenosis or spondylolisthesis* (Resnick et al., 2005c) was reported in a qualitative analysis of two RCTs (one of higher quality) with a median follow-up of 1 and 2 years. Fusion was superior to standard non-operative treatments in one RCT (n=294) but fusion was no better than intensive rehabilitation in the other RCT (n=64).

The authors concluded that there was a Class I medical evidence study (P. Fritzell, Hagg, & Wessberg, 2001), suggesting that lumbar fusion was associated with *better outcomes* than conservative care for appropriately selected patients with disabling low-back pain. They advised that consideration for surgery should be reserved for those patients with persistent pain thought to arise from one or two motion segments despite the best medical management available to the patient. They concluded that there was Class III medical evidence to suggest that a course of intensive cognitive[306] and physical therapy may be an efficacious treatment option for the treatment of patients with chronic disabling low-back

Comment

The quality of this systematic review was rated as poor being given an overall rating quality of 2/7 (extensive flaws) in the APS guideline (American Pain Society, 2009). A possibility of selection bias, limitations in the search procedure, the assessment of quality and issues relating to the combining of studies were the main flaws

Andersson 2006 "Treatment of Intractable Discogenic Low Back Pain. A Systematic Review of Spinal Fusion and Intradiscal Electrothermal Therapy (IDET)".

The objective of this study was to conduct a systematic review of clinical outcomes in patients undergoing spinal fusion or the intradiscal electrothermal therapy (IDET) procedure for intractable discogenic low back pain.

A limited systematic search of the literature was undertaken for English-language journal articles published from January 1995 to December 2005. Articles were selected if disc degeneration or disruption was the primary indication for spinal fusion or the IDET procedure and if outcomes included evaluations of back pain severity, condition-specific functional impairment and/or health-related quality of life.

The literature search identified 33 spinal fusion articles: 10 randomized controlled trials, 1 nonrandomized controlled trial, 9 before-and-after trials, and 13 case series. The quality of all reports of randomized controlled trials was graded using the 5-point Jadad Score[307] with a score of "1" representing poor quality and a score of "5" reflecting excellent quality. This scoring system rates study quality on three fundamental methodological criteria: randomization, blinding, and completeness of follow-up.

The primary outcomes of interest were pain severity, back function, quality of life. There were similar median percentage improvements in patients treated with spinal fusion and the IDET procedure for pain severity (respectively 50% and 51%), and quality of life (respectively 46% and 43%). For back function the median percentage improvement was 42% for fusion and 14% for IDET.

[306] There are limitations in offering cognitive therapy in New Zealand (personal communication, Gordon Howie, reviewer).
[307] http://en.wikipedia.org/wiki/Jadad_scale and Haynes, R.B.; Sackett D.L., Guyatt G.H. Tugwell P. (2005). Clinical Epidemiology. Lippincott Williams & Wilkins. pp. 31. ISBN 9780781745246

Compared to other types of studies a smaller magnitude of improvement for both treatments in all 3 primary outcomes was an identified in the randomized controlled trials.

Perioperative complications were commonly associated with spinal fusion (median: 14%, range: 2% to 54%, n=31 study groups) whereas adverse events were rarely experienced with the IDET procedure (median: 0%, range: 0% to 16%, n=14 studies). Randomized controlled trials of spinal fusion were reported to have methodological limitations. The proportions of good or excellent results for fusion are shown in Table 6.1.3.

Table 6.1.3. The proportion of good or excellent results for different types of lumbar fusion techniques.

Studies reporting good or excellent results	Good or excellent results (overall median % and range)
All spinal fusion studies (16* of 33, 48%)	67% (17% to 100%)
Posterior lumbar fusion or Circumferential fusion (10 studies)	64% (41% to 100%
Posterior instrumented lumbar fusion (3 studies)	80% (52% to 80%)
Anterior instrumented lumbar fusion (6 studies)	85% (55% to 100%)
Circumferential fusion (4 studies)	61% (17% to 80%)

*Including observational studies

The authors concluded that the majority of patients reported improvement in symptoms following both spinal fusion and the IDET procedure and that the IDET procedure appeared to offer similar symptom amelioration to spinal fusion without the attendant complications. They also reported that it was it was unclear whether spinal fusion provided an advantage over conservative medical management with respect to symptomatic improvement among patients with intractable discogenic low back pain since the two randomized controlled trials comparing spinal fusion with conservative management (Brox et al., 2003; P. Fritzell et al., 2001) provided conflicting findings for both pain severity and functional impairment of the back.

Comment

The quality of this systematic review was rated as poor being given an overall rating quality of 2/7 (extensive flaws) in the APS guideline (American Pain Society, 2009), possibility of selection bias, limitations in the search procedure, the assessment of quality and issues relating to the combining of studies were reported to be the main flaws. It should also be noted that IDET is not considered to be a good comparator [308].

Chou 2009 "Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline."

This systematic review assessed the benefit and harms of *surgery* for non-radicular back pain with common degenerative changes, radiculopathy with herniated lumbar disc, and symptomatic spinal stenosis (Chou, Baisden et al., 2009).

[308] It has been reported that 35000 procedures were done before a proper trial with real control showed IDET is not better than inserting a needle in the back (personal communication, Gordon Howie, reviewer)

A limited search of the literature for RCTs and systematic reviews was conducted through to July 2008. The quality of RCTs was assessed using criteria developed by the Cochrane Back Review group; the quality of systematic reviews was assessed using the Oxman criteria[309]. This was followed by a qualitative synthesis of the evidence.

For non-radicular low back pain, four higher quality studies reporting on 3 RCTs were identified (Brox et al., 2006; Brox et al., 2003; Fairbank et al., 2005; P. Fritzell et al., 2001). These studies evaluated fusion versus non-surgical therapy in patients with moderately severe pain and have been widely reported; they feature in most of the systematic reviews that examine the effectiveness of lumbar fusion surgery[310].

The trials produced inconsistent results which were believed to be related to differences in the non-surgical comparators used (but see also footnote 27). The authors concluded that fusion was no better than intensive rehabilitation but slightly better than *standard* non-surgical therapy. The clinical benefits of instrumented versus non-instrumented fusion surgery were reported to be unclear.

Comment

The internal validity (quality) of this systematic review was relatively high with a score of 6/7 on the modified Oxman scale. The conclusions from this review were the same as that of Andersson et al (2006) reporting on the same set of trials.

Ibrahim 2008 "Surgical versus non-surgical treatment of chronic low back pain: a meta-analysis of randomised trials."

Ibrahim et al (2008) performed a meta-analysis of RCTs to investigate the effectiveness of surgical fusion versus non-surgical intervention[311] for the treatment of chronic low back pain (Ibrahim et al., 2008).

A systematic search of MEDLINE (1966–October 2005), EMBASE (1980–October 2005), CINAHL (1982–October 2005), Science Citation Index (1970–October 2005) and the Cochrane registry of clinical trials was carried out to identify all published RCTs. Eligible trials were required to have reported Oswestry Disability Index (ODI) scores as an outcome measure[312]. The types of treatment examined included surgical (spinal fusion with or without instrumentation) and non-surgical (physical therapy with or without cognitive therapy) interventions.

The search identified six studies, three of which were found to be eligible for primary analysis (Brox et al., 2003; Fairbank et al., 2005; P. Fritzell et al., 2001); a fourth RCT was included in a sensitivity analysis. The meta-analysis comparison was based on the mean difference in ODI (Oswestry Disability Index) change from baseline to follow-up of patients undergoing surgery and those

[309] Oxman, A. D. and G. H. Guyatt (1991). "Validation of an index of the quality of review articles." Journal of Clinical Epidemiology 44(11): 1271-1278.
[310] These papers are somewhat mixed. For instance the Fairbanks study population was a group of patients with low back pain of one year's duration only, not otherwise specified., while the Ekman study population was patients with adult isthmic spondylolisthesis who are generally a good group to treat surgically, (personal communication, Gordon Howie, reviewer).
[311] One of the difficulties in randomized trials surgery vs non-surgery is patients' preference. Most patients approaching a surgeon have already failed conservative treatment and do not wish to embark on further exercise programs. There is often a high cross over in these trials, eg, the SPORT trial on discectomy (personal communication, Graham Howie, reviewer).
[312] Combining ODI differences is one way of measuring outcome but what one really wants to know is how many patients achieved a meaningful improvement of 15 points and a distinction should be made between different types of patients, insured, compensation &c. Modic changes which are known to affect outcome (personal communication, Gordon Howie, reviewer).

undergoing non-surgical treatment. A sensitivity analysis was carried out using a study by Ekman[313] with a different patient population.

The mean difference in ODI together with 95% confidence intervals were extracted from studies in all of the papers; the study included in the sensitivity analysis did not report the mean change from baseline to follow-up. All studies were determined to be of good quality but prone to performance bias and detection bias since surgical interventions cannot be blinded.

The mean overall difference in the patient reported ODI between the surgical and non-surgical groups was 4.13 in favour of surgery, but this difference was not statistically significant (95% CI: −0.82 to 9.08, p=0.10), Figure 6.1.1.

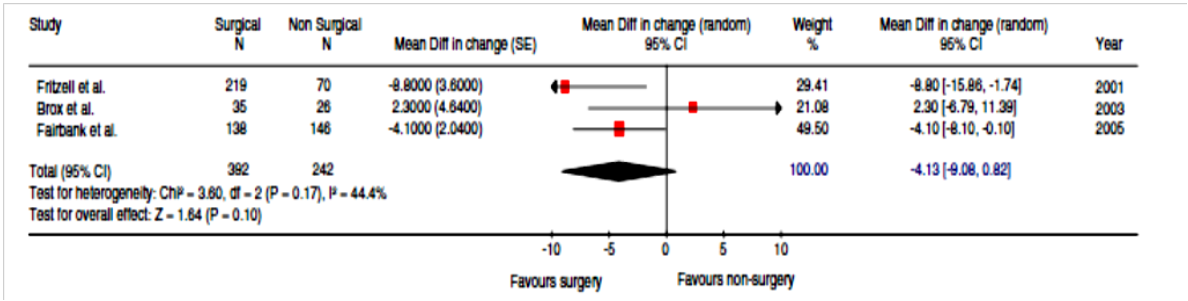


Figure 6.1.1. Meta analysis of three RCTs comparing fusion and non-surgical treatment of low back pain.

Sensitivity analyses performed to examine the effect of the imputed results from Fairbank et al. 2005, showed a mean overall difference in the ODI of 4.34 in favour of surgery, but this difference was not statistically significant (95% CI: −0.48 to 9.17, p=0.08, I_2=44.0%).

Further analyses were carried out that included the study by Ekman[314] who recruited patients with chronic low back pain caused by isthmic spondylolisthesis and was the only study to do so. Analyses including this study and using available or imputed results by Fairbank et al. 2005 (with >15% loss to follow-up) showed a mean overall difference in the ODI of 3.9 (95% CI: 0.17–7.62, p=0.04, I2=21.4%) and 4.11 (95% CI: 0.46–7.76, p=0.03, I_2=22.1%) in favour of surgery, respectively.

In summary, this systematic review identified three randomised controlled trials that compared surgical fusion and non-surgical treatment for patients with chronic low back pain and looked at the short-term outcome. An additional study recruited a different patient group with isthmic spondylolisthesis and was included in a sensitivity analysis. All studies were of good methodological quality. The pooled results showed a non-significant trend in favour of surgery with a mean ODI difference of 4.13 (p=0.10; 95% CI: −0.82 to 9.08). The results were consistent across different assumptions. Limitations included a paucity of studies, and output measures limited to ODI. Patient

[313] Ekman P, Möller H, Hedlund R (2005) The long-term effect of posterolateral fusion in adult isthmic spondylolisthesis: a randomized controlled study. Spine J 5:36–44
[314] Ekman P, Möller H, Hedlund R (2005) The long-term effect of posterolateral fusion in adult isthmic spondylolisthesis: a randomized controlled study. Spine J 5:36–44

satisfaction and return to work, were not included in all of the original studies and thus were not considered in the meta-analysis. A placebo effect and publication bias may have also affected the results.

The authors concluded that currently available evidence did not support the routine use of surgery for the treatment of chronic low back pain. Surgical treatment was associated with a 16% pooled rate of early complication (95%CI: 12–20, I_2=0%).

Comment

This review received a score of 5/7 in the APS guideline (Chou & Huffman, 2009) indicating that the review was flawed but of a reasonable quality.

Mirza 2007 "Systematic review of randomized trials comparing lumbar fusion surgery to non-operative care for treatment of chronic back pain.

The objective of the systematic review of RCTs reported by Mizra et al (2007) was to compare lumbar fusion surgery and non-surgical treatment of chronic back pain associated with lumbar disc degeneration. Four relevant studies were identified using a systematic search of Medline and the bibliographies of eligible studies;[315] these studies[316] were also reviewed in the systematic reviews carried out by Carreon et al (2008) and Ibraim (2008) and this earlier review by Mirza is only reported briefly here for the purpose of completeness.

Four studies reporting the results of three RCTs were eligible for this review (Brox et al., 2006; Brox et al., 2003; Fairbank et al., 2005; Peter Fritzell, Hägg, Wessberg, Nordwall, & the Swedish Lumbar Spine Study, 2002) (Appendix I). Following an analysis of the results and quality of these trials the following points were made by the authors;

- limitations in some of the RCTS comparing these treatments prevent definitive conclusions as to which is more efficacious,
- compared to unstructured, heterogeneous non-operative care, lumbar fusion surgery may be more efficacious for the treatment of chronic back pain,
- fusion may not be more effective than a structured rehabilitation program that includes cognitive behaviour therapy.

The authors concluded that:

"These trials do not allow a general statement regarding the efficacy of fusion over non-operative care for discogenic back pain. All four trials suggest that any advantage of surgery over nonsurgical care is modest, on average near or below the minimally important change in the disability score. The differences in the magnitude of nonsurgical improvement suggest that the nature of nonsurgical treatment may be critical."

Comment

The quality of this systematic review was rated as good, being given an overall rating quality of 5/7 in the APS guideline (Chou & Huffman, 2009)

[315] The search was restricted to "randomized controlled trial" which may not have identified all eligible studies.
[316] At least two of these RCTs were reviewed in all of the other systematic reviews of lumbar fusion.

Conclusions: fusion for low back pain

All five systematic reviews (Andersson et al., 2006; Chou, Baisden et al., 2009; Ibrahim et al., 2008; Mirza & Deyo, 2007; Resnick et al., 2005c) between them assessed a small set of randomised controlled trials.

They varied in the number of these trials they reported, the extent of their reporting and analysis of the trials, and in the emphasis of their conclusions. However, all but one concluded that there was *no strong evidence* to support the treatment of low back pain using fusion surgery, particularly when the short-term results of fusion therapy were compared to that of an intensive rehabilitation regimen.

The systematic reviews of fusion for low back pain share a general weakness in that they are focussed on a group of patients that share symptoms rather than a specific diagnosis resulting in patient group overlap with other reviews reporting on patients with specific diagnoses. So, for example, in one review of fusion for low back pain (Resnick et al., 2005c), where the diagnostic groups were very varied, there was a separate assessment of the evidence for fusion for spinal stenosis with or without degenerative spondylolisthesis.

Indications: various symptomatic degenerative lumbar spine disorders.

One systematic review examined the effectiveness of fusion surgery for symptomatic lumbar degenerative spine disorders (Carreon et al., 2008). The main characteristics, author's conclusions and brief evidence summary of this review are summarised in Table 6.1.4, followed by a fuller description of the review.

Table 6.1.4. Main characteristics and findings of the evidence for general/various symptomatic degenerative lumbar spine disorders. Evidence overview for fusion is given in parenthesis after the indication.

Systematic review/Oxman internal validity (quality)/Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
General/various symptomatic degenerative lumbar spine disorders; one study (unclear)					
Carreon (2008) FUSION Oxman=5/7 Search to 2007	24 trials (16 included surgical treatment)	Posterior spinal fusion† N=16 Anterior spinal interbody fusion N=4‡ Circumferential (N=2): 270°, 360° Fusion not specified (N=2) Comparator Non-surgical intervention	Various symptomatic degenerative spine disorders (degenerative disc disease (DDD), chronic low back pain (CLBP), and spondylolisthesis)	Oswestry Disability Index (ODI) MOS Short Form-36 outcomes	The three fusion types produced similar amounts of improvement in ODI. Nonsurgical patients did not improve as much but had a lower baseline ODI. Improvements in the SF-36 PCS were fairly consistent across diagnostic groups and treatment types. Chronic low back pain patients were less disabled and experienced less improvement. In conclusion, the number of well-designed and adequately reported studies on interventions used to treat symptomatic lumbar degenerative disease is limited. Definite proof of treatment efficacy for both fusion and

Systematic review/Oxman internal validity (quality)/Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
					nonsurgical treatment of symptomatic lumbar degenerative disease remains unclear.

Carreon 2008 "Fusion and nonsurgical treatment for symptomatic lumbar degenerative disease: a systematic review of Oswestry Disability Index and MOS Short Form-36 outcomes."

The objective of this study was to evaluate lumbar fusion and nonsurgical interventions for various symptomatic degenerative spine disorders using the Oswestry Disability Index as a primary outcome measure in a systematic review. A secondary objective was to determine whether there was a difference in clinical outcomes based on specific diagnoses (Carreon et al., 2008).

A computer-aided search of Medline, Embase, HealthSTAR, Cumulative Index to Nursing & Allied Health Literature, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, PsycINFO, and PsychLit, from the beginning of the databases up to February 2007 was carried out using the search recommended by the Back Review Group of the Cochrane Collaboration.

This search yielded 24 RCTs for analysis, 16 of these trials included at least one arm in which patients received lumbar spinal fusion, Table 6.1.5.

Table 6.1.5. Summary of randomised controlled trials reported by Carreon 2008.

Fusion type and technique	Studies (RCTs)
Posterior spinal fusion (eight studies):	
Instrumented	Brox et al 2003
Non-instrumented	Brox et al 2006
Iliac crest bone graft	Boden et al 2002
Bone morphogenetic protein	Dimar et al 2006
Autologous growth factor	Haid et al 2004
Ceramic	Jenis et al 2006
Texas Scottish rite hospital instrumentation	Korovessis et al 2005
	Vacarro et al 2005
Anterior lumbar interbody fusion (four studies):	
Bagby and Kuslich (BAK) cage	Blumenthal et al 2005
Iliac crest bone graft	Burkus et al 2003
Bone morphogenetic protein	Chung et al 2003
Titanium cage	Sasso et al 2004
Femoral ring allograft	
Laparoscopic	
Mini-laparoscopic	
Circumferential (two studies):	
270°	McKenna et al 2005

Fusion type and technique	Studies (RCTs)
360°	Schoefferman et al 2001
Fusion not specified (two studies)	Fairbanks, 2005 Fritzell, 2002

Between diagnostic groups, the highest mean baseline ODI was in patients with degenerative disc disease (DDD) (51.4) followed by patients with chronic low back pain (CLBP) (47.7) and spondylolisthesis (46.3). Between surgical treatment groups, the mean baseline ODI was similar. Patients with spondylolisthesis had the greatest improvement in ODI (43.7). Patients with DDD (24.9) showed greater improvement in ODI than those with CLBP (11.5).

Posterior, anterior and combined fusion types produced similar amounts of improvement in ODI (posterior, 24.7; anterior, 24.6; combined, 18.2). SF-36 PCS data for patients with CLBP or patients who had a combined anterior-posterior fusion were not available. In the other diagnostic and treatment groups, the mean baseline SF-36 PCS was 528.4, range 27.7–29.2, and mean change in SF-36 PCS 513.0, range 11.2–13.4. Fusion rates among the different diagnostic and treatment groups were similar with an overall mean fusion rate of 86.7%.

The authors of the review concluded that substantial improvement could be expected in patients treated with fusion, regardless of technique, when an established indication such as spondylolisthesis or DDD exists. CLBP patients were less disabled and experienced less improvement. However, the number of well-designed and adequately reported studies on interventions used to treat symptomatic lumbar degenerative disease was reported to be limited and *definite proof* of treatment efficacy for both fusion and nonsurgical treatment of symptomatic lumbar degenerative disease not provided by the studies under review.

Comment

This review was too recent to be included in the APS guideline (American Pain Society, 2009) a quality assessment for this overview using the same criteria as the APS guideline resulted in a score of 5/7 suggesting that the review was not very likely to be prone to serious biases. The key feature of this review was its attempt to assess whether or not there was a difference in clinical outcomes for patients with *specific diagnoses*. While better results were reported for some diagnoses (e.g. spondylolisthesis) because of the low quality of the evidence, the authors concluded that overall the evidence was *unclear*.

Inidcations:disc herniation

One systematic review examined the effectiveness of fusion surgery for disc herniation (Resnick et al., 2005d). The main characteristics, author's conclusions and brief evidence summary of this review are summarised in Table 6.1.6, followed by a fuller description of the review.

Table 6.1.6. Main characteristics and findings of the evidence for surgery for disc herniation. Evidence overview for fusion is given in parenthesis after the indication.

Systematic review/Oxman internal validity (quality)/Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
Disc herniation; one study (no convincing medical evidence that fusion should be added to discectomy)					
Resnick (2005) FUSION Oxman =2/7 Search to 2003	20 class III studies	PLF PLIF ALIF Comparators Discectomy Laminectomy	Disc herniation and radiculopathy	Back pain Japanese Orthopaedic Association Activities of daily living Oswestry Disability Index	There is no convincing medical evidence to support the routine use of lumbar fusion at the time of a primary lumbar disc excision. There is conflicting Class III medical evidence regarding the potential benefit of the addition of fusion in this circumstance. Therefore, the definite increase in cost and complications associated with the use of fusion are not justified.

PLIF = posterior lumbar interbody fusion/posterior instrumented lumbar fusion. ALIF= anterior lumbar interbody fusion, PLF= posterolateral fusion.

Resnick 2005 "Lumbar fusion for disc herniation and radiculopathy"

Author's rationale*:*

"Spinal fusion is a commonly performed procedure, often conducted following a decompressive procedure. In cases of lumbar disc herniation, the primary problem is usually limited to radicular pain due to nerve compression. Typically, patients with a symptomatic herniated disc refractory to medical management undergo discectomy without fusion. Spinal fusion has, however, been used as a treatment for patients with primary and recurrent disc herniations. The purpose of this review is to examine the medical evidence concerning the role of lumbar fusion in the operative treatment of patients with radiculopathy and back pain caused by a herniated lumbar intervertebral disc."

There were no Class I or II[317] studies that supported the use of lumbar fusions for this group of patients. The scientific foundation for the recommendations arising from the review were underpinned by 20 reported Class III studies[318] (Yorimitsu et al (2001), Loupasis et al (1999), Dvoral (1988), Takeshima, et al (2000), Donceel and Du Bois (1998), Young et al (1962), Kotilainen & Valtonen (1993), Kotilainen (1998), Cauchoix et al (1978), Padua et al (1999), Inoue et al (1984) , Eie (1978) , Matsunga et al, Suk et al (1993), Cinotti et al (1998), Ozgen et al (1999) Glassman et al (1998), Chitnavis et al (2001), Vishtech & Dickman (2001), Eule et al (1999), Huang & Chen (2003).

The authors concluded that there was *no convincing medical evidence* to support the routine use of lumbar fusion at the time of a primary lumbar disc excision, and that there was *conflicting* Class III medical evidence regarding the potential benefit of the addition of fusion in this circumstance. Therefore, the increase in cost and complications associated with the use of fusion could not be justified. They did however, consider that patients with preoperative lumbar "instability"[319] may benefit from fusion at the time of lumbar discectomy but noted that the incidence of such "instability" appeared to be very low (<5%) in the general lumbar disc herniation population. They

[317] Class I, evidence from one or more well-designed, randomized controlled clinical trials, including overviews of such trials; Class II, evidence from one or more well-designed comparative clinical studies, such as nonrandomized cohort studies, case control studies, and other comparable studies, including less well-designed randomized controlled trials;
[318] Class III, evidence from case series, comparative studies with historical controls, case reports, and expert opinion as well as significantly flawed randomized controlled trials.
[319] There is no universally accepted and objective definition of "instability". It is the opinion of the operating\ surgeon at the time.

also noted that patients who suffer from chronic low-back pain, or are heavy labourers or athletes with axial low-back pain in addition to radicular symptoms may also be candidates for fusion at the time of lumbar disc excision.

The authors reported that patients with a recurrent disc herniation have been treated successfully with both reoperative discectomy and reoperative discectomy combined with fusion. In patients with recurrent lumbar disc herniation with associated spinal deformity, instability, or associated chronic low back pain, consideration of fusion in addition to reoperative discectomy was recommended.

Indications: degenerative lumbar spondylolisthesis

Five reviews examined the effect of spinal fusion therapy on patients with spondylolysthesis (Gibson & Waddell, 2005; W. Jacobs et al., 2006; Kwon et al., 2005; C. R. Martin et al., 2007; Resnick et al., 2005e). All of these studies focussed on spondylolisthesis, however only two focussed on *fusion surgery* for spondylolysthesis (W. Jacobs et al., 2006; Resnick et al., 2005e), the remainder (Gibson & Waddell, 2005; Kwon et al., 2005; C. R. Martin et al., 2007) focussed on surgery and included fusion techniques.

The main characteristics, author's conclusions and brief evidence summary of the effect of spinal fusion therapy for patients with degenerative spondylolisthesis are summarised in Table 6.1.7, followed by a fuller description of the review.

Table 6.1.7. Main characteristics and findings of the evidence for surgery for degenerative lumbar spondylolisthesis . Evidence overview for fusion is given in parenthesis after the indication.

Systematic review/Oxman internal validity (quality)/ Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
Degenerative lumbar spondylolisthesis: five studies (some evidence to suggest that fusion may improve outcome over decompression alone but the evidence is inconsistent)					
Resnick (2005j) FUSION Oxman = 2/7 Search to 2003	32 studies Class I=1[320]† Class II=3† Class III=29†	Posterolateral Fusion +/- instrumentation <u>Comparators</u> Laminectomy Foraminectomy Facetectomy; Foraminotomy	Lumbar stenosis and spondylolisthesis	Various including; Japanese Orthopaedic Association Oswestry Disability Index Lower limb pain Back pain walking	A single Class II (non-randomised comparative study) medical evidence study (Herkowitz & Kurz) provided medical evidence in support of the use of fusion at the time of decompression to improve functional outcome. The majority of evidence from other studies comparing outcomes after decompression alone or decompression combined with PLF in patients with stenosis and spondylolisthesis also favoured the performance of PLF. The medical evidence regarding the use of pedicle screw fixation in this patient population is rated as Class III (mostly case series) and is inconsistent
Jacobs (2006) FUSION Osman=6/7 Search to 2004	8 RCTs 21 case series (4 prospective consecutive studies 17 retrospective studies, of which 11 used consecutive and 6 non-consecutive patient selection).	Posterolateral fusion Anterior instrumented lumbar fusion Instrumentation <u>Comparators</u> Fusion with or without decompression, with or without reduction, anterior versus posterior fusion,	Low-grade lumbar isthmic spondylolisthesis	Fusion rates Clinical outcomes (not otherwise specified)	Posterolateral fusion appears to be the general gold standard for the treatment of adult isthmic low-grade lumbar spondylolisthesis, although there is no scientific evidence to support this choice. Further, only one randomised trial has shown superior results for PLF as compared to conservative treatment (exercises). The use of PLF (or surgery for that matter) as a gold standard is thus not supported by rigorous scientific evidence. Supplemental to PLF, there is still no evidence to support the use of

Systematic review/Oxman internal validity (quality)/ Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
		non-instrumented fusion versus instrumented fusion			posterior instrumentation as clinical and radiological outcomes are not better and complication rates are higher.
Gibson (2005) SURGERY Oxman=6/7 Search to 2005	31 RCTs	Anterior fusion Posterior fusion Circumferential fusion Instrumented fusion (various) Interbody fusion (various) Comparators Laminectomy Laminotomy	Degenerative lumbar spondylosis	Patient self-assessment Pain Function/disability Occupational Fusion rate Physical improvement Neurological signs	There is limited evidence that adjunct fusion to supplement decompression for degenerative spondylolisthesis produces less progressive slip and better clinical outcomes than decompression alone. There is also limited evidence that fusion alone may be as effective as fusion combined with decompression for grade I or II isthmic spondylolisthesis with no significant neurology. Fusion is more effective than continued, failed, standard 1990s, 'usual care'; it does not appear to be any more effective than a modern rehabilitation programme
Kwon (2005) SURGICAL Oxman=1/7 Search to 2003	34 studies 4 prospective RCTs 6 comparative studies 24 case series	PLF AILF Comparators Laminectomy Spinal internal fixation	Low grade isthmic spondylolisthesis	Clinical (not otherwise specified) Radiological	A pooling of the surgical literature on adult low-grade spondylolisthesis indicates that a combined anterior and posterior procedure most reliably achieves fusion and a successful clinical outcome. The literature, however, is primarily retrospective and heterogeneous with respect to indications for surgery and methods of evaluating outcome, providing a compelling rationale for a prospective randomized controlled trial of the various surgical approaches to this problem. A number of authors reported a strong association between the achievement of solid fusion and a successful clinical outcome; this association as primarily borne out in the patients with combined procedures that had both high fusion rates and successful

Systematic review/Oxman internal validity (quality)/ Focus/ Search to date	Studies	Main fusion technique(s) Main comparator(s)	Indication	Main outcomes measured/ reported/ (measured by)	Author's conclusions
Martin (2007) SURGERY Oxman =5/7 Search to 2005	13 studies (4 RCTs and 9 comparative observational studies)	<u>RCTs</u> Laminectomy vs laminectomy + bilateral transverse process fusion. Laminectomy+ posterolateral fusion vs laminectomy+ posterolateral fusion + pedicle screw and plate instrumentation. Posterolateral fusion vs posterolateral fusion + pedicle screw and plate instrumentation. Decompression vs decompression + posterolateral fusion vs decompression + posterolateral fusion + mixed pedicle fixation. <u>Non-randomised comparative studies</u> Laminotomy/laminectomy/decompression/instrumented fusion (posterior and anterior)/conservative treatment – various combinations and comparisons	Degenerative lumbar spondylolisthesis	VAS Japanese Orthopaedic Association Oswestry Disability Index Patient/physician Composite rating Fusion rate Radiographic Reoperation rate Complications Medication use	There is moderate evidence that spinal fusion may lead to a better clinical outcome than decompression alone. No conclusion about the clinical benefit of instrumenting a spinal fusion could be made. However, there is moderate evidence that the use of instrumentation improves the chance of achieving solid fusion. Conclusions made in the current review should be interpreted with recognition of the low methodological quality and poor reporting of the primary studies.

Resnick 2005 "Fusion in patients with stenosis and spondylolisthesis"

Author's rationale:

"Patients with lumbar stenosis often present with concomitant degenerative spondylolisthesis. Decompression alone in this population may result in deformity progression. Lumbar PLF has been used as a means to prevent postoperative deformity progression and to improve functional outcome after decompressive surgery in this population. The purpose of this review is to examine the literature concerning the role of fusion after decompression surgery in patients with degenerative spondylolisthesis and stenosis."

The effectiveness of fusion in patients with *stenosis and spondylolisthesis* was examined in a qualitative systematic review of four RCTs (one of higher quality) with a median follow-up of 2-3 years and a sample size range of 44-130 (Resnick et al., 2005e).

The authors concluded that:

- A single Class II medical evidence study (Herkowitz & Kurz) provided medical evidence in support of the use of fusion at the time of decompression to improve functional outcome in patients with lumbar stenosis and spondylolisthesis.
- The majority of evidence from other studies comparing outcomes after decompression alone or decompression combined with posterior lumbar fusion in patients with stenosis and spondylolisthesis also favoured the performance of posterior lumbar fusion.
- The medical evidence regarding the use of pedicle screw fixation in this patient population was rated as Class III and was inconsistent, however, a consistent benefit associated with the use of pedicle screw fixation had been reported in patients with preoperative instability or kyphosis.
- Iatrogenic instability following decompression (which is associated with poor outcomes) may also be treated with PLF involving supplemental instrumentation.
- The best evidence suggested that fusion was superior for excellent or good outcome at 3 years (1 RCT, 96% vs. 44%), for degenerative spondylolisthesis .

Comment

The quality of this systematic review was rated as poor being given an overall rating quality of 2/7 (extensive flaws) in the APS guideline (American Pain Society, 2009). A high possibility of selection bias, limitations in the search procedure, the assessment of quality and issues relating to the combining of studies were the main flaws.

Jacobs 2006 "Fusion for low-grade adult isthmic spondylolisthesis: a systematic review of the literature."

Jacobs et al (2006) reported the findings of a systematic review undertaken to evaluate which fusion technique provided the best clinical and radiological outcome for adult low-grade lumbar isthmic spondylolisthesis, and to assess the overall clinical and radiological outcome of each fusion technique (W. Jacobs et al., 2006) . Randomised controlled trials (RCTs) were used to evaluate the best treatment; controlled studies and non-controlled studies were used to determine the outcomes after surgery.

Medline, Embase, Current Contents, and Cochrane databases as well as reference lists of selected articles were searched. The search (through to March 2004) identified 684 publications. Twenty nine studies met the inclusion criteria, of which eight were RCTs and 21 were cases series. The case series

included four prospective consecutive studies and 17 retrospective studies; 11 of the retrospective studies used consecutive and 6 non-consecutive patient selection. All of the eight RCTs evaluated the effect of different techniques of posterolateral fusion (PLF). Where sufficient data were available, subgroup analyses were conducted to assess the effects of age, gender, disease severity, and length of follow-up time on outcomes.

The methodological quality of the RCTs was assessed with the aid of a checklist used in systematic literature reviews of spine surgery by van Tulder[321]; the quality of non-controlled studies (i.e. cohort, prospective, cross sectional, and historical study designs) was assessed using a checklist of items developed by Cowley[322].

Four of eight (50%) RCTs and 2 of 21 (9.5%) non-controlled studies were reported to be of high quality. Using only RCTs, evidence on the best treatment available was sought based on following anticipated contrasts;

- with or without decompression,
- with or without reduction,
- anterior versus posterior fusion,
- non-instrumented fusion versus instrumented fusion

Four RCTs meeting 50% or more of the quality criteria on the van Tulder list contributed to the synthesis; all four RCTs evaluated PLF with or without instrumentation. No benefits from additional instrumentation were found in any of these studies. A meta-analysis was not performed on these four trials due to their treatment heterogeneity.

Outcomes after surgery

For the non-controlled studies, a best evidence synthesis was performed for those providing consecutive patient selection and completeness of treatment description; five of 21 studies provided adequate cohorts for the synthesis. These studies contained outcome information about posterior instrumentation, decompression and reduction. Fusion rates of 80%-100% were reported for these studies and the proportion of patients with good or excellent clinical outcomes ranged from 45%-98% (median 90%).

The authors concluded from the evidence examined that:

"Posterolateral fusion appears to be the general gold standard for the treatment of adult isthmic low-grade lumbar spondylolisthesis, although there is no scientific evidence to support this choice. Further, only one randomised trial has shown superior results for PLF as compared to conservative treatment (exercises). The use of PLF or surgery for that matter as a gold standard is thus not supported by rigorous scientific evidence. Supplemental to PLF, there is still no evidence to support the use of posterior instrumentation as clinical and radiological outcomes are not better and complication rates are higher. Decompression has not proven to be necessary (and may be detrimental [2]), but may be used in the clinical setting in case of nerve root pain. However, nerve

[321] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
[322] Cowley DE (1995) Prostheses for primary total hip replacement A critical appraisal of the literature. Int J Technol Assess Health Care 11(4):770–778.

root pain may also be caused by a dynamic stenosis due to instability. This is addressed by fusing the motion segment, and this may already be sufficient to treat the nerve root pain without decompression. The role of sagittal alignment and the related possible benefits of reduction (and therefore also instrumentation) of the listhesis have not been adequately studied. This is immensely important, as these factors may be confounding variables that have made it impossible for us to determine the optimum surgical treatment strategy, and they may well influence the long-term outcome. Despite the unproven effect of instrumentation, reduction, or anterior column support, many surgeons now use these modalities. This may be unscientific, but it may well be based on the surgeons' empirical experience. This implies that due to improved surgical possibilities, we may in the future be able to show beneficial effects. The challenge for us, as the spine surgical community, is to prove this."

Comment

This review was not assessed or reported in the APS guideline (American Pain Society, 2009). A quality assessment using the same checklist as the APS guideline performed for this report assessed the quality of this review as "good" with a score of 6/7.

Kwon 2005 "A critical analysis of the literature regarding surgical approach and outcome for adult low-grade isthmic spondylolisthesis"

Kwon et al, 2005 reported on a systematic review of the radiographic and clinical outcomes of adult patients undergoing surgery for low-grade isthmic spondylolisthesis to determine whether conclusions could be drawn regarding the optimal choice of surgery for patients with adult low-grade isthmic spondylolisthesis (Kwon et al., 2005). Radiographic and clinical outcomes of patients who underwent a posterior procedure alone, an anterior procedure alone, or a combined anterior and posterior procedure were examined. The influence of laminectomy, spinal internal fixation, smoking, and secondary gain issues on outcomes were reported.

Clinical outcomes varied (i.e. patient reported or surgeon reported, with or without independent observers, using a 4-point scale, 3-point scale, or some other outcome measure), and the review authors were forced to report clinical outcomes as simply "successful" or "unsuccessful."

A systematic search of the literature identified 34 studies (4 RCTs and 30 retrospective case series) in which the clinical and/or radiographic outcomes of over 1000 patients with low-grade isthmic spondylolisthesis were reported. Twenty six studies described the radiographic or clinical outcomes of adult patients undergoing an isolated posterior fusion procedure (posterolateral fusion with or without decompression or spinal fixation). Five studies described the results of patients undergoing an isolated anterior lumbar interbody fusion (ALIF). Nine studies evaluated patients undergoing a combined anterior and posterior stabilization procedure [323].

Fusion rates were 98.2% (167/170) for patients undergoing combined anterior and posterior procedures, 83.3 % (741/890) for those undergoing a posterior procedure alone, and 74.0% (57/77) for those undergoing anterior stabilization.

[323] The sum of these studies exceeds 34 because some studies included a mixture of patients undergoing two surgical approaches (eg, posterior and combined anterior–posterior).

The rate for the combined procedure was significantly higher than that of the posterior or anterior procedures alone ($P < 0.0001$). There was a trend (P=0.059) for a higher fusion rate with posterior procedures alone. Clinical outcomes were superior for patients undergoing a combined anterior and posterior fusion with a successful clinical result in 86.4% of cases (108/125), compared to a clinical success rate of 74.8% of patients (609/814) who had a posterior procedure ($P = 0.0045$). A clinical success rate of 89.6% in patients (60/67) who had an anterior procedure was not significantly different from that of the combined procedures ($P = 0.65$) but was significantly better than that of posterior procedures alone ($P = 0.0047$).

Sub-group analysis in studies describing combined procedures revealed no significant difference in radiographic or clinical outcomes between patients with an ALIF–posterior–posterolateral fusion and those with a PLIF– posterolateral fusion ($P = 0.068$ and $P = 0.43$, respectively) .

Covariate analysis suggested that the performance of a laminectomy did not significantly influence radiographic fusion or clinical outcome, although there was a trend toward a higher pseudoarthrosis rate ($P = 0.093$) and unsuccessful clinical outcome ($P = 0.11$) in patients undergoing a laminectomy. There was a significantly higher fusion rate and more successful clinical outcomes with spinal internal fixation[324].

The authors noted that although a strong correlation between radiographic fusion and positive clinical outcome had not been clearly established for many lumbar indications in the literature, in this review of isthmic spondylolisthesis, a number of authors did report a strong association between the achievement of solid fusion and a successful clinical outcome; this association was most apparent in patients who underwent *combined procedures.*

The authors concluded that a pooling of the surgical literature on adult low-grade spondylolisthesis indicated that a combined anterior and posterior procedure most reliably achieved fusion and a successful clinical outcome. The literature, however, was primarily retrospective and heterogeneous with respect to indications for surgery and methods of evaluating outcome.

Comment

There were a number of methodological problems with this review. These comprised reporting omissions including the reporting of validity criteria and assessment, measures to avoid bias, methods for combining studies and a weak search strategy. These faults increased the likelihood of study omission and biased reporting and led to the review being given an overall rating quality of 1/7 (poor) in the APS guideline(American Pain Society, 2009).

Gibson 2005 "Surgery for degenerative lumbar spondylosis"

In the same year Gibson et al (2005) published an updated Cochrane review of surgery for degenerative spondylosis (Gibson & Waddell, 2005).

A total of 31 randomized controlled trials were identified. Most of the earlier trials primarily reported on surgical outcomes; more recent trials reported patient-centred outcomes of pain or

[324] The higher fusion rate is consistent with previous literature that has demonstrated that pedicle screw fixation facilitates bony fusion and reduces the pseudoarthrosis rate of posterolateral fusions. The more successful clinical outcome, however, conflicts with four independent prospective randomized studies that have evaluated posterolateral fusions with or without pedicle screw supplementation fixation, all of which have failed to identify any significant improvement in self-reported clinical outcomes with the addition of pedicle screw fixation

disability. The interventions reviewed included laminectomy; laminotomy; anterior lumbar intervertebral body fusion (ALIF), postero-lateral, posterior lumbar intervertebral body (PLIF) fusion alone or in combination, or other forms of instrumented fusion; intradiscal electrotherapy (IDET), disc replacement and combinations of the preceding interventions. The majority of the trials compared two or more surgical techniques.

The authors grouped the trials into three sections which comprised trials of;

- decompression with or without fusion for spinal stenosis and/or nerve root compression (N=8); one trial compared surgical treatment with conservative therapy, and one compared different techniques of decompression for spinal stenosis. Three trials compared decompression alone with decompression and some form of fusion. One trial compared outcomes following the use of an interspinous spacer with those after a non-operative regime, including epidural injection. A further two trials of surgery for isthmic spondylolisthesis were included.
- fusion, intra-discal electrotherapy (IDET) or disc arthroplasty for back pain (N=7; two trials of fusion to relieve discogenic back pain compared with different forms of conservative treatment, preliminary results from three small trials of IDET, and two trials of disc arthroplasty
- comparison of different techniques of spinal fusion. (N=19); 15 trials considered the role of instrumentation in fusion and four trials considered electrical stimulation (direct current and pulsed electromagnetic stimulation) in posterolateral fusion.

Five trials included subgroups of participants, these trials are included in more than 1 section.

In their discussion Gibson et al (2005) reported a summary[325] of the status quo as of 2005 which is summarised below:

- The surgical literature on lumbar fusion over past 20 years is “incomplete, unreliable, haphazard”.
- Instrumentation appears to increase the overall fusion rate, but only slightly.
- Instrumentation does not improve overall clinical outcomes, although there is currently insufficient evidence to judge for particular subgroups of patients.

Clinical conclusions of relevance to the current overview reported by Gibson et al (2005) are summarised below.

- There was limited evidence that fusion, to supplement decompression for degenerative spondylolisthesis, produced less progressive slip and better clinical outcomes than decompression alone.
- There was limited evidence that fusion alone was as effective as fusion combined with decompression for Grade I or II isthmic spondylolisthesis with no significant neurology.

[325] This summary was taken from a recently completed a comprehensive review by Bono and Lee (2004) of a much wider range of randomized and nonrandomized, prospective and retrospective studies of lumbar fusion (Bono & Lee, 2004), which Gibson et al (2005) used to provides a check on their more rigorous but more limited Cochrane Review.

- There was conflicting evidence on the effectiveness of fusion compared with conservative treatment; one RCT (P. Fritzell et al., 2001) provided strong evidence in favour of fusion, but another RCT (Brox et al., 2006; Brox et al., 2003) refuted this. Different treatments were given to the control groups in the two trials. It has been this has been postulated that this was the primary reason for the discrepancy in the results of the two RCTs.
- There was some evidence from trials of low quality and clinical and statistical heterogeneity326 that instrumentation of a posterolateral fusion led to a higher fusion rate, though it was noted that there were problems assessing fusion in the presence of metalwork, which few of these trials considered. Also despite enhancing fusion rates improvement in clinical outcome appeared to be marginal.

It was not possible for the authors to draw any conclusions about relative morbidity or complications arising from instrumentation, and it was not possible for the authors to draw any conclusions about the possible role of instrumented fusion for any particular pathological condition, or about the relative benefits of any particular instrumentation system.

The authors concluded that there was some evidence on various issues of surgical techniques of decompression and fusion for individuals with lumbar spondylosis, but that there was insufficient evidence on the effectiveness of surgery on *clinical outcomes* [327]to draw any firm conclusions. They also called for higher quality RCTs, preferably comparing surgical treatments with natural history, placebo, or conservative treatment. They further noted that surgeons should seek expert methodological advice when planning trials.

Comment

The quality of this systematic review was rated as good with an overall rating quality of 6/7 in the APS guideline (Chou & Huffman, 2009).

Martin 2007 "The surgical management of degenerative lumbar spondylolisthesis: A systematic review"

Martin et al (2007) reported on a systematic review of the relevant literature to determine if there was an advantage to instrumented or non-instrumented spinal fusion over decompression alone for patients with degenerative lumbar spondylolisthesis (C. R. Martin et al., 2007).

The search identified 13 relevant RCTs and comparative observational studies published between 1966 and June 2005. These studies were reported to be of a generally low methodological quality. Outcomes included clinical results, reoperation rate, and fusion status. This systematic review was included in the guidelines reported by Watters et al (2009) and is only briefly reported here for the purpose of completeness.

When fusion was compared to decompression alone a satisfactory clinical outcome was significantly more likely with fusion than with decompression alone (RR relative risk, 1.40; 95% confidence interval, 1.04–1.89; *P* <0.05). The use of adjunctive instrumentation significantly increased the probability of attaining solid fusion (relative risk, 1.37; 95% confidence interval, 1.07–1.75; *P* <0.05), but not of achieving a significant improvement in clinical outcome (relative risk, 1.19; 95%

[326] Most of the trials used different instrumentation systems. Many of these trials were of low methodological quality with inadequate randomisation, lack of blinding and therefore a potential for bias.
[327] Expert opinion " There is little doubt that instrumentation makes for more frequent fusion, but failure of fusion with instruments is still not uncommon. The real question……. is whether successful fusion makes for better patient outcome."

confidence interval, 0.92–1.54). There was a non significant trend toward lower repeat operations with fusion compared with both decompression alone and instrumented fusion.

Comment

The quality of this systematic review was rated as good being given an overall rating quality of 6/7 in the APS guideline (Chou & Huffman, 2009)**.**

Conclusions: degenerative lumbar spondylolisthesis

Five systematic reviews examined the evidence relating to the effectiveness of fusion surgery for degenerative lumbar spondylolisthesis. The reviews were published between 2005 and 2007 and they reviewed studies published between 2003 and 2005. At least one review included studies with patients with stenosis in addition to spondylolisthesis.

Results and conclusions varied. In general, there was no strong high class evidence to support the use of fusion as treatment for spondylolisthesis. There was some evidence to suggest that fusion may improve outcome over decompression alone, but the evidence was inconsistent and generally from studies with flawed designs.

Fusion techniques

Four systematic reviews examined evidence of effectiveness for different types of lumbar fusions including;

- interbody techniques (Resnick et al., 2005g)
- pedicle screw fixation (Resnick et al., 2005h)
- bone graft extenders and substitutes (Resnick et al., 2005i)
- bone growth stimulators (Resnick et al., 2005j).

These systematic reviews were carried out to underpin the AANS/CNS Guidelines for the Performance of Fusion Procedures for Degenerative Disease of the Lumbar Spine. (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005). The rationale, evidence and findings for each type of fusion is summarised below.

Resnick 2005 "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion."

The authors' rational for this review is given below:

"The surgical treatment of low-back pain has evolved over the last several decades, and interbody techniques have been proposed as surgical alternatives to posterolateral lumbar fusion. Placement of the graft within the load bearing column of the spine has biomechanical advantages and has been reported to result in higher fusion rates with improved patient outcomes compared with PLF techniques. A variety of techniques are available for the application of interbody grafts, and each technique has its particular advantages, disadvantages, and champions. The purpose of this review is to examine the literature reporting experience with interbody fusion techniques and their relative

safety and efficacy compared with posterolateral fusion techniques for the treatment of patients with low-back pain."

The main characteristics and brief evidence summary of the effectiveness of different interbody techniques in spinal fusion are summarised in Table 6.1.8, followed by a summary of the best evidence outcomes.

Table 6.1.8. Summary of the characteristics and reported evidence of the systematic review of interbody techniques for lumbar fusion (Resnick et al., 2005g).

Systematic review	Fusion techniques	Indications	Evidence
Interbody techniques for lumbar fusion			
Resnick, D. K., T. F. Choudhri, et al. (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion." J Neurosurg Spine 2(6): 692-9.	Anterior lumbar interbody fusion Posterolateral fusion Posterolateral interbody fusion Transformal lumbar interbody fusion (TLIF) Authors of several studies compared the results of ALIF, PLIF, or TLIF techniques with each other as well as with PLF.	Degenerative disease of the lumbar spine	Evidence from seventeen studies was reported. Three studies offered class I evidence for outcomes or complications (Schofferman et al 2001, Fritzell et al 2003, Fritzell et al 2002), four studies provided class II evidence (Christensen et al 2002, Pradhan et al 2002, Vamvanij et al 1998, Humphreys et al 2001). Thirteen studies provided class III evidence.[328] **The best quality evidence** came from one Class I study (Schofferman et al 2001) and two Class II studies (Pradhan et al 2002, Humphreys et al 2001)[329], there was also Class I evidence for one outcome within a Class III study (Fritzell et al 2002) and Class II evidence for outcome in a Class III study (Christiansen et al 2002).

The *best evidence* outcomes reported in this systematic review of interbody techniques are summarised below.

- The effectiveness of interbody techniques for lumbar fusion was examined in this qualitative[330] systematic review (Resnick et al., 2005g) which included two low quality RCTs with a median follow-up of 2 years and study sizes of 25 and 147 respectively. In one study circumferential instrumented fusion was not found to be superior to posterolateral fusion with regard to functional status at 2 years, but was reported to result in a lower re-operation rate through 2 years (7% vs. 22%), leg pain at 1 year ($p<0.03$), and peak back pain at 2 years ($p<0.04$). One stand-alone posterolateral interbody fusion BAK cage versus two stand-alone posterolateral interbody BAK cages for L4-L5 degenerative Grade I spondylolisthesis (1 lower-quality RCT) showed no differences .

Resnick (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 12: pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain."

[328] Some studies gave different classes of evidence for different outcomes i.e. had more than one class of evidence..
[329] This is not reported further due to conflicting quality assessment reported in the text and tables. Due to time and resource limits the conflicts could not be resolved.
[330] No quantitative/metaanalysis.

The authors' rationale for the review is given below:

"The use of instrumentation as an adjunct to lumbar fusion procedures has increased over the past two decades. Multiple techniques have been described for the surgical treatment of patients with chronic low-back pain. Posterolateral fusion is one of the more widespread techniques and may be performed with or without the use of pedicle screw fixation to provide internal fixation as a surgical adjunct to the fusion procedure. The addition of instrumentation is associated with higher costs and higher complication rates. The purpose of this review is to establish whether the medical evidence in the scientific literature demonstrates a clinical benefit of internal pedicle screw fixation as an adjunct to PLF in the treatment of patients with low-back pain due to degenerative lumbar disc disease or low-grade degenerative spondylolisthesis."

The main characteristics and brief evidence summary of the effectiveness of pedicle screw fixation as an adjunct to spinal fusion are summarised in Table 6.1.9, followed by a summary of the best evidence outcomes.

Table 6.1.9. Summary of the characteristics and reported evidence of the systematic review of pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain (Resnick et al., 2005h).

Systematic review	Techniques	Indications	Evidence
Pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain			
Resnick, D. K., T. F. Choudhri, et al. (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 12: pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain." J Neurosurg Spine 2(6): 700-6.	Posterolateral fusion with and without pedicle screw fixation	Low back pain	Fourteen eligible studies were identified providing evidence relating to fusion rates, radiographic and clinical outcomes. For clinical outcomes there were four class I studies (Thomson et al 1997, Fritzell et al 2004, Bjarke Christensen et al 2002 and Fritzell et al 2002) and two class II studies (Lorenz et al 1991, Fischgrund et al 1997). Seven studies were considered to provide class III evidence. For fusion rates there were two class I studies (Zdeblick 1993, Fischgrund et al 1997), two class II studies (Lorenz et al 1991, Thomsen et al 1997) and three class III studies.

The *best evidence* outcomes reported in this systematic review of pedicle screw fixation are summarised below.

- This qualitative systematic review of the effectiveness of lumbar fusion with pedicle screw fixation as an adjunct to posterolateral fusion for non-specific back pain or degenerative spondylolisthesis (Resnick et al., 2005h) was reported to increase radiological fusion success, but there was no convincing clinical correlation between radiographic fusion and

clinical outcome. The largest contemporary RCT did not show a benefit for pedicle screw fixation.

Resnick (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes.

The authors' rationale for the review is given below:

"Successful arthrodesis following lumbar fusion requires osseous bridging between the vertebral bodies, which is usually achieved by placing graft material between the vertebral bodies, which then heal over time. The standard graft material is harvested autogenous bone331, which may be limited by availability and may be associated with donor- site morbidity. Allograft bone332 may also be used for various applications; however, availability, cost, risk of disease transmission, and lack of osteoinductive capacity limit the utility of allograft in some applications. For these reasons, bone graft substitutes have been developed for application in the lumbar spine. These substitutes have variable mechanical properties and biological activities, and they may or may not be efficacious for specific situations. The purpose of this review is to examine the medical evidence regarding the use of bone graft substitutes in lumbar spinal surgery."

The main characteristics and brief evidence summary of the effectiveness of bone graft extenders as an adjunct to spinal fusion are summarised in Table 6.1.10, followed by a summary of the best evidence outcomes.

Table 6.1.10. Summary of the characteristics and reported evidence of the systematic review of bone graft extenders and substitutes (Resnick et al., 2005i)

Systematic review	Techniques	Indications	Evidence
Bone graft extenders and substitutes			
Resnick, D. K., T. F. Choudhri, et al. (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes." J Neurosurg Spine 2(6): 733-6.	Posterolateral fusion Anterior lumbar interbody fusion <u>Bone graft substitutes</u> Autologous growth factor Recombinant human bone morphogenetic protein (rhBMP-2)	Degenerative diseases of the lumbar spine	One Class I study (Burkus, et al., 2002) and five Class III studies (Lowery, et al., 1999 III , Boden, et al., 2002 III, , Linovitz & Peppers, 2002 III , Burkus, et al, 2003 III, Kasai, et al., 2003 III) were identified. The best available evidence (Burkus, et al., 2002) indicated that rhBMP-2 was a viable alternative to autograft bone for interbody fusion procedures (Class I).

The *best evidence* outcomes reported in this systematic review of bone graft extenders are summarised below.

[331] Bone graft taken from one person's body and implanted into another individual's body.
[332] Bone graft taken from one portion of the patient's body and implanted into another portion of the individual's body.

- This qualitative systematic review of bone graft extenders and substitutes (Resnick et al., 2005i) included one multicenter RCT comparing recombinant human bone marrow protein-2 (rhBMP-2) with autograft when used in combination with a titanium cage for an anterior lumbar interbody fusion. In a group of 279 well-matched patients with lumbar degenerative disease, there were significant improvements in the Oswestry disability index, back pain, leg pain, and patient satisfaction scores in both treatment groups. There was a slightly higher fusion rate in the rhBMP-2 group and a slightly shorter operating room time (24 minutes) and slightly decreased blood loss (44 ml). There was also an advantage for the rhBMP-2 group in terms of donor-site pain.

Resnick (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 17: bone growth stimulators and lumbar fusion."

The authors' rationale for the review is given below:

"One of the goals of a lumbar fusion is to produce a solid arthrodesis across the unstable motion segment(s). Laboratory studies and human studies performed over the last 30 years have demonstrated that bone healing is associated with electrical potentials developing at the fusion site. Attempts have been made to harness this electrical–biological link through the use of applied electrical fields to promote bone healing. Several bone growth stimulators are now available as adjuncts to promote osseous fusion. These devices are expensive, require different ES[333] techniques, and are not universally accepted as efficacious. The purpose of this paper is to review the evidence for the efficacy of these devices as adjuncts for bone fusion following lumbar surgery."

The main characteristics and brief evidence summary of the effectiveness of bone graft extenders as an adjunct to spinal fusion are summarised in Table 6.1.11, followed by a summary of the best evidence outcomes.

[333] ES = electrical stimulation.

Table 6.1.11. Summary of the characteristics and reported evidence of the systematic review of bone growth stimulators and lumbar fusion (Resnick et al., 2005j).

Systematic review	Techniques	Indications	Evidence
Bone growth stimulators and lumbar fusion			
Renwick, D. K., T. F. Choudhri, et al. (2005). "Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 17: bone growth stimulators and lumbar fusion." J Neurosurg Spine 2(6): 737-40.	Posterolateral fusion <u>Bone growth stimulators</u> Capacitative coupled stimulation Direct current stimulation electrical stimulation Pulsed electromagnetic field stimulation	Degenerative diseases of the lumbar spine	One review assessed the evidence for the efficacy of these devices as adjuncts for bone fusion following lumbar surgery. Nine studies were identified, two (Rogozinski & Rogozinski, 1996, Kucharzyk, 1999) providing Class II evidence of effectiveness. Rogozinski and Rogozinski reported favourable (fusion) results of direct current stimulation (DCS) in a small randomized sample of patients undergoing instrumented lumbar PLF. These authors did not assess functional outcome. Kucharzyk (1999) found that implantation of a DCS device improved fusion rates and clinical. Both of these studies provide Class II medical evidence supporting the efficacy of DCS as a means to improve fusion rates. The Kucharzyk study also provides Class III medical evidence supporting a beneficial effect on functional outcome.

The *best evidence* outcomes reported in this systematic review of bone growth stimulators are summarised below.

- The final qualitative systematic review in this series examined the evidence for the use of bone growth stimulators to improve outcomes of lumbar fusion (Resnick et al., 2005j) . Two studies, one small RCT and one non-randomised comparative study, reported favourable (fusion) results of direct current stimulation (DCS) in a patients undergoing instrumented lumbar posterolateral fusion. These authors did not assess functional outcome. Kucharzyk (1999) found that implantation of a DCS device improved fusion rates and clinical outcomes. A further multicenter double-blinded RCT evaluating the effect of capacitative coupling stimulation (CCS) on fusion rates and clinical outcomes reported a beneficial effect associated with CCS.

Comment

This series of systematic reviews represents and impressive body of work on lumbar fusion techniques. However, due to the heterogeneity of the included studies, the approach and analysis was largely descriptive (qualitative) and there were a large number of reporting errors and omissions. Mismatches between the body text and the data reported in the tables were common which made data extraction problematic and there were omissions in the reporting of study

inclusion criteria, study quality assessment and methods for combining studies. These and other faults which increased the possibility of bias and selective selection and reporting of evidence, led to these reviews being given an overall rating quality of 2/7 (poor) in the APS guideline (Chou & Huffman, 2009).

Evidence Assessment: Guidelines

The search procedure developed for the current study identified three *recent* evidence based guidelines reporting *substantially* on the use of *fusion techniques* for the treatment of lumbar spinal disease (Chou & Huffman, 2009; Resnick & Groff, 2006; Watters et al., 2009)[334]. This list of eligible guidelines may not be exhaustive[335]. Time and resource limitations did not permit an exhaustive search to be conducted of all potentially relevant Association/Society websites.[336].

The characteristic of these guidelines are given below (and in Appendix II), followed by a brief description of the findings and recommendations of each of the guidelines and an assessment of how far the guidelines conform to the AGREE[337] criteria for the reporting of guidelines.

North American Spine Society (NASS) 2009 clinical guideline for the treatment of symptomatic degenerative spondylolisthesis.

Watters et al (2009) published a North American Spine Society (NASS) clinical guideline to provide evidence-based recommendations to address key clinical questions surrounding the diagnosis and treatment of *degenerative lumbar spondylolisthesis* (Watters et al., 2009). The guideline was intended to reflect contemporary treatment concepts for *symptomatic* degenerative lumbar spondylolisthesis as reflected in the *highest quality* clinical literature available on this subject as of June 2007.

The characteristic of the 2009 North American Pain Society guidelines, their overall recommendations for the reported indications and an assessment of how far the guidelines conform to the AGREE[338] criteria for the reporting of guidelines are summarised in Appendix II. Guideline recommendations relating *specifically to surgical fusion* are discussed below.

The goals of the guideline recommendations were to assist in delivering optimum, efficacious treatment and functional recovery from this spinal disorder. These guidelines were underpinned by two of the systematic reviews reported in the previous section of this report Martin et al (2007) and Gibson et al (2005).

The patient population for the guideline encompassed adults (18 years or older) with a chief complaint of low back pain and/or lower extremity symptoms related to spinal stenosis.

The NASS guideline was underpinned by a systematic review of the evidence with studies assigned to one of five levels of evidence (ranging from Level I=high quality randomized controlled trial, Level V =expert consensus) and grades of recommendation[339] which indicated the strength of the recommendations based on the quality of the literature.

The grades of recommendation for summaries or reviews of studies are show in Table 6.1.12.

[334] An earlier NASS guideline by the same authors (http://www.spine.org/Documents/NASSCG_Stenosis.pdf) is not assessed as the more recent guideline includes its evidence and findings.
[335] See methods section for the guideline sources searched.
[336] For a list of websites search see Methods section in this report and accompanying documents.
[337] www.agreecolaboration.org
[338] www.agreecolaboration.org
[339] A: Good evidence (Level I studies with consistent finding) for or against recommending intervention. B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention. C: Poor quality evidence (Level IV or V studies) for or against recommending intervention. I: Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

Table 6.1.12. Grades of recommendation used in the North American Spine Society clinical guideline.

Grade A:	Grade B	Grade C	Grade I
Good evidence (Level I Studies with consistent findings) for or against recommending intervention	Fair evidence (Level II or III Studies with consistent findings) for or against recommending intervention.	Poor quality evidence (Level IV or V Studies) for or against recommending intervention.	Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

The *best research evidence available was employed* to answer the targeted clinical questions. The review also included an assessment of outcome measures.

The Surgical Intervention section of the guideline (Part D) examined and assessed the effectiveness of lumbar fusion. Five clinical questions were posed:

- Does the addition of lumbar fusion, with or without instrumentation to surgical decompression, improve surgical outcomes in the treatment of degenerative lumbar spondylolisthesis compared to treatment by decompression alone?
- Does the addition of instrumentation to decompression and fusion for degenerative lumbar spondylolisthesis improve surgical outcomes compared with decompression and fusion alone?
- How do outcomes of decompression with posterolateral fusion compare with those for 360° fusion in the treatment of degenerative lumbar spondylolisthesis?
- What is the role of reduction (deliberate attempt to reduce via surgical technique) with fusion in the treatment of degenerative lumbar spondylolisthesis?
- What is the long-term result (four+ years) of surgical management of degenerative lumbar spondylolisthesis?

The recommendations and evidence from 14 relevant studies relating to these questions are shown in Table 6.1.13.

Table 6.1.13. Clinical questions, evidence and recommendations reported in the North American Spine Society (NASS) Guidelines for the treatment of symptomatic degenerative spondylolisthesis.

Guideline question	Intervention and comparator	Evidence	Recommendation and Grade of recommendation
Q1 Does the addition of lumbar fusion, with or without instrumentation to surgical decompression, improve surgical outcomes in the treatment of degenerative lumbar spondylolisthesis compared to treatment by decompression alone?	Lumbar fusion (with or without instrumentation) and surgical decompression vs. Surgical decompression	**5 studies** Meta-analysis of level III studies (Mardjetco et al 1994) Systematic review of randomised and non-randomised comparative studies (Martin et al 2007). Two prospective comparative studies (Bridwell et al 1993; Herkowitz et al 1991) One retrospective comparative study (Matsudaira et al 2005).	Surgical decompression with fusion is recommended for the treatment of patients with symptomatic spinal stenosis and degenerative lumbar spondylolisthesis to improve clinical outcomes compared with decompression alone. Grade of Recommendation: B
Q2 Does the addition of instrumentation to decompression and fusion for degenerative lumbar spondylolisthesis improve surgical outcomes compared with decompression and fusion alone?	Decompression and fusion with instrumentation vs Decompression and fusion without instrumentation	5 studies Meta-analysis of level III studies (Mardjetco et al 1994) Systematic review of 31 RCTs (Gibson et al 2005) Randomised comparative study (Fischgrund et al 1997) Prospective comparative study (Bridwell et al 1993), Retrospective comparative study (Kimura et al 2001)	The addition of instrumentation i recommended to improve fusion rates in patients with symptomatic spinal stenosis and degenerative lumbar spondylolisthesis. Grade of Recommendation: B The addition of instrumentation is not recommended to improve clinical outcomes for the treatment of patients with symptomatic spinal stenosis and degenerative lumbar spondylolisthesis. Grade of Recommendation: B
Q3 How do outcomes of decompression with posterolateral fusion compare with those for 360° fusion in the treatment of degenerative lumbar spondylolisthesis?	Decompression with posterolateral fusion vs. 360° fusion	Paucity of evidence	Because of the paucity of literature addressing this question, the work group was unable to generate a recommendation to answer this question.
Q4 What is the role of reduction (deliberate attempt to reduce via surgical technique) with fusion in the treatment of degenerative lumbar spondylolisthesis?	Reduction (deliberate attempt to reduce via surgical technique) with fusion	3 studies Three case series (Bedner et al 2001 , Lee et al 1994, Sears et al 2005)	Reduction with fusion and internal fixation of patients with low grade degenerative lumbar spondylolisthesis is not recommended to improve clinical outcomes. Grade of Recommendation: I (Insufficient Evidence)

Guideline question	Intervention and comparator	Evidence	Recommendation and Grade of recommendation
Q5 What is the long-term result (four+ years) of surgical management of degenerative lumbar spondylolisthesis?	Long-term result (four+ years) of surgical management of degenerative lumbar spondylolisthesis?	3 studies Two follow-up studies (Kornblum et al 2004, Postacchini et al 1992) Retrospective study (booth et al 1999)	Decompression and fusion is recommended as a means to provide satisfactory long-term results for the treatment of patients with symptomatic spinal stenosis and degenerative lumbar spondylolisthesis. Grade of Recommendation: C

Summary: NASS

- There were three Grade B, one grade C and one grade I recommendations relating to lumbar fusion for degenerative lumbar spondylolisthesis; in one instance there was not enough evidence to make a recommendation.
- The addition of fusion to decompression was recommended to improve clinical outcomes in symptomatic patients (Evidence Grade: Grade B), the addition of instrumentation was recommended to improve fusion rates (Grade B) but not clinical outcomes (Evidence Grade: Grade B)
- Decompression with fusion was recommended as a means to provide satisfactory long-term results (Evidence Grade: Grade C).
- Reduction with fusion and internal fixation was not recommended to improve clinical outcomes for patients with low grade degenerative lumbar spondylolisthesis (Evidence Grade: Grade I, insufficient evidence).
- There was not enough evidence to make a recommendation relating to the effectiveness of circumferential fusion compared to posterolateral fusion with decompression.

The American Pain Society (APS) 2009 Guideline for the evaluation and management of low back pain.

In 2009 the American Pain Society published Clinical Practice Guideline for low back pain (Chou & Huffman, 2009)[340]. The surgery section of these guidelines was supported by a published systematic review published in the same year (Chou, Baisden et al., 2009). The evidence that underpinned the guideline was based on data from RCTs assessing the benefits and harms of surgical treatment for;

- non-radicular low back pain with common degenerative changes
- radiculopathy with herniated lumbar disc
- symptomatic spinal stenosis.

The guidelines were very wide ranging and included interventional diagnostic tests, interventional therapies, surgery and interdisciplinary rehabilitation with the evidence reported in a document which was nearly 500 pages long (Chou & Huffman, 2009). The evidence and recommendations for surgery were published separately (Chou, Baisden et al., 2009; Chou & Huffman, 2009).

[340] The original guideline was published on the APS website without explicit recommendations (i.e. evidence base only), the recommendations relation to surgery and rehabilitation were published in a separate publication in the same year.

The characteristic of the 2009 American Pain Society guidelines, their overall recommendations for the reported indications and an assessment of how far the guidelines conform to the AGREE[341] criteria for the reporting of guidelines are summarised in Appendix II. Recommendations relating specifically to surgical fusion are discussed below.

Lumbar fusion was a relatively small part of this guideline and was relatively briefly reported[342]. The systematic review of surgical interventions for low back pain (Chou, Baisden et al., 2009) that informed the fusion recommendations (reported in the earlier systematic review section) identified and evaluated 24 systematic reviews and 12 RCTs not included in any of the previous systematic reviews.

Twenty systematic reviews that assessed lumbar fusion techniques were evaluated to produce a synthesis of the evidence for the purposes of producing recommendations. Fifteen of these systematic reviews are reported or covered individually in the section on systematic reviews above; of the five not considered to be eligible for the current ACC review, two were not considered to be systematic and were prior to 2005, three were disc replacement comparisons. It was not clear how many additional RCTs (i.e. RCTs not already reported in the systematic reviews) were included in the synthesis due to conflicting statements.

The overall *quality* (validity) of the evidence for the body of literature was evaluated using methods adapted from the U.S. Preventive Services Task Force[343]. To assign an overall strength of evidence (good, fair, or poor) for each comparison and outcome, the type, number, size and quality of studies; strength of association; consistency of results within and between study designs; and directness of evidence were considered, Table 6.1.14.

[341] www.agreecolaboration.org

[342] It should also be noted that parts of this guideline published by Chou under the auspices of the APS Chou R, Huffman L. Guideline for the Evaluation and Management of Low Back Pain: Evidence Review. American Pain Society; Glenview, IL: 2009; http://www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf, has been vociferously criticised by Manchikanti, L., Datta, S., Gupta, S., Munglani, R., Bryce, D. A., Ward, S. P., et al. (2010). A critical review of the American pain society clinical practice guidelines for interventional techniques: Part 2. therapeutic interventions. Pain Physician, 13(4), E215-E264.

[343] Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force. Am J Prevent Med. 2001;20(3S):21-35.

Table 6.1.14. American Pain Society (APS) 2009 guidelines study quality (validity) ratings

Rating of good quality	Rating of fair quality	Rating of poor quality
Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least two consistent, higher-quality RCTs or studies of diagnostic test accuracy).	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalisability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; two or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least two consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

The *strength* of the evidence base upon which the recommendations were made was graded from A to D. Table 6.1.15.

Table 6.1.15. Strength of evidence grading used in the APS 2009 guidelines. From (Chou, Loeser et al., 2009)

Grade	Definition
A =	The panel strongly recommends that clinicians consider offering the intervention to eligible patients. The panel found good evidence that the intervention improves health outcomes and concludes that benefits substantially outweigh harms
B =	The panel recommends that clinicians consider offering the intervention to eligible patients. The panel found at least fair evidence that the intervention improves health outcomes and concludes that benefits moderately outweigh harms, or thatbenefits are small but there are no significant harms, costs, or burdens associated with the intervention.
C =	The panel makes no recommendation for or against the intervention. The panel found at least fair evidence that the intervention can improve health outcomes, but concludes that benefits only slightly outweigh harms, or the balance of benefits and harms is too close to justify a general recommendation.
D =	The panel recommends against offering the intervention. The panel found at least fair evidence that the intervention is ineffective or that harms outweighs benefits
I=	The panel found insufficient evidence to recommend for or against the intervention. Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

The *evidence summaries and levels of evidence/ratings* for the four indications considered in the guidelines are given in Table 6.1.16.

Table 6.1.16. Evidence summaries and levels of evidence/ratings for the four indication considered in the American Pain Society guidelines.

Indication	Evidence summary (taken from the full guideline)	Level of evidence
Non-radicular low back pain with common degenerative changes	• Three higher quality trials found spinal fusion to be no better or only slightly superior to intensive rehabilitation plus a cognitive intervention for the improvement in pain or functional status. • For mixed degenerative conditions evidence relating to the efficacy of instrumented versus non-instrumented fusion is inconsistent. • Evidence of efficacy of anterior, posterior or combined fusion is inconsistent. • Electrical stimulation may improve fusion rates in non-instrumented fusion but there was no clear effect on clinical outcomes. • Early complications following fusion occur in up to 20% of patients, the rate of in hospital mortality is <1%. Rates vary between studies. • Complications from spinal fusion were more frequent in the more technically difficult methods of fusion.	Fair
Isthmic spondylolisthesis	• PLIF was moderately superior to an exercise program for pain and disability after 2 years but differences no longer significant at 9 years (Grade or II slip, 1 trial). • Fusion with or without instrumentation plus laminectomy and decompression was associated with higher rates of non-fusion and unsatisfactory results compared to fusion (with or without instrumentation) alone (slip Grade I or II without neurological defects, 1 trial). • Instrumented fusion was no better than non-instrumented fusion (mild disease, two trials). • Pooled data from observational studies found anterior fusion or a combined approach to have higher success rates than posterior fusion and instrumented fusion superior to non-instrumented fusion. • There was insufficient evidence to reliably judge the safety of surgery for this condition.	Poor
Symptomatic spinal stenosis. with or without degenerative spondylolisthesis	• There was a trend towards superior clinical outcomes following laminectomy plus posterolateral fusion compared to decompression alone (3 small trials, degenerative spondylolisthesis). • No difference between instrumented and non-instrumented fusion in 3 trials (degenerative spondylolisthesis). • Circumferential instrumental fusion was moderately superior for pain through 5-9 years follow-up.(degenerative spondylolisthesis and isthmic spondylolisthesis)	Poor to fair
Radiculopathy with herniated lumbar disc	• Lumbar fusion for lumbar disc prolapse with radiculopathy: No convincing evidence to support routine use of lumbar fusion at the time of primary lumbar disc excision [344]	Not graded

†For patients with isthmic or degenerative spondylolisthesis in mixed populations evidence of efficacy is summarised in the sections on surgery for spinal stenosis or degenerative spondylolisthesis.

Based on the evidence and the level of the evidence reported in the evidence review (Chou & Huffman, 2009), a number of recommendations were made relating to surgical intervention (Chou &

[344] Based on evidence from one systematic review included in the current systematic review section..Resnick DK, Choudhri TF, Dailey AT, et al. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. J Neurosurg Spine. 2005;2:673-678.

Huffman, 2009) . Three recommendations (Recommendations 2, 4 and 7) included lumbar fusion in their statements, Table 6.1.17

Table 6.1.17. American Pain Society recommendations which include reference to fusion surgery.

In patients with non-radicular low back pain who do not respond to usual non-interdisciplinary interventions:	For patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms:	For patients with disabling leg pain due to spinal stenosis with or without degenerative spondylolisthesis:
Interdisciplinary rehabilitation is similar in effectiveness to fusion surgery. (Recommendation 2)	Fusion surgery was superior to nonsurgical therapy without interdisciplinary rehabilitation (1 trial) with moderate benefit (Recommendation 2) but no more effective than intensive interdisciplinary rehabilitation (3 trials) (Recommendation 4; Level of evidence = fair, grade of evidence = B). The guideline also noted that instrumented fusion was associated with enhanced fusion rates compared with non-instrumented fusion, but that there was insufficient evidence to determine whether instrumented fusion improved clinical outcomes, and that additional costs were substantial (Recommendation 4). There was insufficient evidence to recommend a specific fusion method (anterior, posterolateral, or circumferential), though more technically difficult procedures may be associated with higher rates of complications (Recommendation 4).	There was insufficient evidence to determine if laminectomy with fusion was more effective than laminectomy without fusion. (Recommendation 7)

American Association of Neurological Surgeons/Congress of Neurological Surgeons 2005 guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine.

The June 2005 (Volume 2, Number 6) issue of the Journal of Neurosurgery:spine was devoted to the reporting of the AANS/CNS Guidelines for the Performance of Fusion Procedures for Degenerative Disease of the Lumbar Spine (Full guideline, 2005 Lumbar Fusion Guidelines[345]). The guideline committee was composed of 11 neurological and orthopaedic surgeons who focussed on *seventeen* topics relating to the lumbar spine. Six of the topics related to methods and assessment techniques and are not reported further here, three related to monitoring adjunct bracing and injection therapies and were not included. Four of the remaining 8 reports focussed on specific indications;

- intractable low-back pain without stenosis or spondylolisthesis, Part 7 (Resnick et al., 2005c)
- disc herniation and radiculopathy, Part 8 (Resnick et al., 2005d)
- stenosis and spondylolisthesis, Part 9 (Resnick et al., 2005e)
- stenosis without spondylolisthesis, Part 10 (Resnick et al., 2005f)

[345] http://www.spinesection.org/fusion_guidelines.php

A further four reports[346] focussed on different fusion methods, graft materials and instrumentation;

- interbody techniques for lumbar fusion, Part 11 (Resnick et al., 2005g)
- pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain, Part 12 (Resnick et al., 2005h)
- bone graft extenders and substitutes, Part 16 (Resnick et al., 2005i)
- bone growth stimulators and lumbar fusion, Part 17 (Resnick et al., 2005j)

Class I[347] evidence was required to support treatment recommendations of the strongest type called practice **standards,** reflecting a high degree of clinical certainty.

Class II evidence was required to support recommendations called **guidelines,** reflecting a moderate degree of clinical certainty.

Class III evidence (i.e. other sources of information, including observational studies such as case series, expert opinion, and fatally flawed randomized controlled trials[348]) supported practice **options** reflecting unclear clinical certainty.

Indications

The guideline recommendations for four conditions are summarised in Table 6.1.18 .

[346]Reviews reporting injection therapies, low-back pain, and lumbar fusion (part 13), brace therapy as an adjunct to or substitute for lumbar fusion (part 14), electrophysiological monitoring and lumbar fusion (part 15) were not considered to be relevant to the current ACC review and were not included.

[347] The definitions of classes of evidence for therapeutic effectiveness were as follows: Class I, evidence from one or more well-designed, randomized controlled clinical trials, including overviews of such trials; Class II, evidence from one or more well-designed comparative clinical studies, such as nonrandomized cohort studies, case control studies, and other comparable studies, including less well-designed randomized controlled trials; and Class III, evidence from case series, comparative studies with historical controls, case reports, and expert opinion as well as significantly flawed randomized controlled trials

[348] Options may also reflect widely accepted practices which may be preceded by a variable amount of conservative treatment.

Table 6.1.18. American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) guideline recommendations for specific indications.

Part	Performance topic /Recommendations
Part 7: Resnick (2005) Intractable low-back pain without stenosis or spondylolisthesis,	**Intractable low-back pain without stenosis or spondylolisthesis** **Standards** Lumbar fusion is recommended as a treatment for carefully selected patients with disabling lowback pain due to one- or two-level degenerative disease without stenosis or spondylolisthesis. **Guidelines** There is insufficient evidence available to support a treatment guideline. **Options** An intensive course of physical therapy and cognitive therapy is recommended as a treatment option for patients with low-back pain in whom conventional medical management has failed.
Part 8: Resnick (2005) Disc herniation and radiculopathy.	**Lumbar fusion for disc herniation and radiculopathy.** **Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** • Lumbar spinal fusion *is not* recommended as routine treatment following primary disc excision in patients with a herniated lumbar disc causing radiculopathy. • Lumbar spinal fusion *is* recommended as a potential surgical adjunct in patients with a herniated disc in whom there is evidence of preoperative lumbar spinal deformity or instability. • Lumbar spinal fusion *is* recommended as a potential surgical adjunct in patients with significant chronic axial low-back pain associated with radiculopathy due to a herniated lumbar disc. • Reoperative discectomy is recommended as a treatment option in patients with a recurrent lumbar disc herniation. • Reoperative discectomy combined with fusion is recommended as a treatment option in patients with a recurrent disc herniation associated with lumbar instability, deformity, or chronic axial low-back pain.
Part 9: Resnick (2005) Stenosis and spondylolisthesis	**Fusion in patients with stenosis and spondylolisthesis** **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** • The performance of a lumbar PLF is recommended for patients with lumbar stenosis and associated degenerative spondylolisthesis who require decompression. • Pedicle screw fixation as an adjunct to lumbar PLF should be considered as a treatment option in patients with lumbar stenosis and spondylolisthesis in cases in which there is preoperative evidence of spinal instability or kyphosis at the level of the spondylolisthesis or when iatrogenic instability is anticipated.
Part 10: Resnick (2005) Stenosis without spondylolisthesis	**Fusion following decompression in patients with stenosis without spondylolisthesis** **Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** • In situ posterolateral lumbar fusion is not recommended as a treatment option in patients with lumbar stenosis in whom there is no evidence of pre-existing spinal instability or likely iatrogenic instability

Part	Performance topic /Recommendations
	due to facetectomy. • In situ lumbar PLF is recommended as a treatment option in addition to decompression in patients with lumbar stenosis without deformity in whom there is evidence of spinal instability. 3) The addition of pedicle screw instrumentation is not recommended in conjunction with PLF following decompression for lumbar stenosis in patients without spinal deformity or instability.

Summary: indications

There was insufficient Class I evidence (RCTs) to recommend fusion as a treatment standard in three of the four indications examined. However, lumbar fusion was recommended as a treatment for *carefully selected* patients with *disabling low back pain* due to one- or two-level degenerative disease without stenosis or spondylolisthesis. There was not enough Class II evidence to underpin guidelines in relation to fusion surgery for any indication. A large number of options resulting from low level (class III) evidence were reported.

Fusion techniques

The guidelines reported on evidence of effectiveness for six different techniques or adjuncts to lumbar fusions including, interbody techniques, pedicle screw fixation, brace therapy, electrophysical monitoring, bone graft extenders and substitutes, bone growth stimulators.

The recommendations for each indication are given in Table 6.1.19.

Table 6.1.19. American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) guideline recommendations for specific interventions

Part	Performance topic /Recommendations
Part 11: Resnick (2005) Interbody techniques for lumbar fusion	**Interbody techniques for lumbar fusion** **Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines** In the context of a single-level stand-alone ALIF or PLIF with posterior instrumentation, the addition of a PLF is not recommended as it increases operating room time and blood loss without influencing the likelihood of fusion or the functional outcome. **Options** • It is recommended that both PLF and interbody fusion (PLIF, TLIF, or ALIF) techniques be considered as treatment options for patients with low-back pain due to DDD at one or two levels. • Placement of an interbody graft is recommended as a treatment option to improve fusion rates and functional outcome in patients undergoing surgery for low-back pain due to DDD at one or two levels. The surgeon is cautioned that the marginal improvement in fusion rates and functional outcome with these techniques is associated with increased complication rates, particularly when combined approaches (that is, 360°) are used. • The use of multiple approaches (anterior and posterior) to accomplish lumbar fusion is not recommended as a routine option for the treatment of patients with low-back pain without deformity.
Part 12: Resnick (2005) Pedicle screw fixation	**Pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain** **Standard** There is insufficient evidence to recommend a treatment standard. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** • Pedicle screw fixation is recommended as a treatment option for patients with low-back pain treated with PLF who are at high risk for fusion failure because the use of pedicle screw fixation improves fusion success rates. • Pedicle screw fixation as a routine adjunct to PLF in the treatment of patients with chronic low-back pain due to DDD is not recommended because there is conflicting evidence regarding a beneficial effect of pedicle screw fixation on functional outcome, and there is consistent evidence that the use of pedicle screw fixation is associated with higher costs and complications.
Part 16: Resnick (2005) Bone graft extenders	**Bone graft extenders and substitutes.** **Standards** The use of autologous bone or rhBMP-2 bone graft substitute is recommended in the setting of an ALIF in conjunction with a threaded titanium cage. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** • Recombinant human BMP-2 in combination with HA and tricalcium phosphate may be used as a substitute for autograft bone in some cases of PLF. • Several formulations of calcium phosphate exist and are recommended as bone graft extenders, especially when used in combination with autologous bone.
Part 17: Resnick	**Bone growth stimulators[349] and lumbar fusion.** **Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines**

[349] Bone growth stimulators have not been widely used in NZ (personal communication, Graham Howie, reviewer)

Part	Performance topic /Recommendations
(2005) Bone growth stimulators	Either direct current stimulation (DCS) or capacitative coupling stimulation (CCS) is recommended as an adjunct to spinal fusion to increase fusion rates in patients who are at high risk for arthrodesis failure following lumbar PLF. Pulsed electromagnetic field stimulation is recommended as an adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.

Summary: fusion techniques

There was insufficient Class I evidence from RCTs to recommend the use of any particular fusion technique or adjunct as a treatment **standard** with the exception of autologous bone or rhBMP-2 bone graft substitute which was recommended as the treatment **standard** in the setting of an ALIF in conjunction with a threaded titanium cage.

Class II evidence underpinned three fusion treatment **guidelines;**

- in the context of a single-level stand-alone ALIF or ALIF with posterior instrumentation, the addition of a PLF was not recommended as it increased operating room time and blood loss without influencing the likelihood of fusion or the functional outcome
- either direct current stimulation or capacitative coupling stimulation was recommended as an adjunct to spinal fusion to increase fusion rates in patients who are at high risk for arthrodesis failure following lumbar PLF
- pulsed electromagnetic field stimulation was recommended as an adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.

A number of **options** resulting from low level (class III) evidence were reported.

Best evidence synthesis: systematic reviews

A best evidence synthesis was carried out based on;

- National Health and Medical Research Council, Australia ,Evidence Level I systematic reviews
- better quality reviews (modified Oxman scores >4)

Five of eight systematic reviews were considered to be high quality reviews based on the conditions above (Carreon et al., 2008; Chou, Baisden et al., 2009; Gibson & Waddell, 2005; Ibrahim et al., 2008; Mirza & Deyo, 2007). These reviews contributed to the best evidence synthesis below.

Degenerative lumbar spondylolisthesis

Gibson and Waddell (2005) reported that there was;

- limited evidence that adjunct fusion to supplement decompression for degenerative spondylolisthesis produced less progressive slip and better clinical outcomes than decompression alone ,
- limited evidence that fusion alone was as effective as fusion combined with decompression for grade I or II isthmic spondylolisthesis with no significant neurology.

Gibson and Waddell (2005) also reported that;

- fusion was more effective than continued, failed, standard 1990s, 'usual care'
- fusion did not appear to be any more effective than a modern rehabilitation350 programme.

Because of apparently contradictory evidence from three RCTs (Brox et al., 2003; P. Fritzell et al., 2001; Keller et al., 2004) the authors concluded that *overall* there was conflicting evidence on the clinical effectiveness of fusion in this populations of patients[351].

Fusion surgery versus non-surgical therapy for chronic low back pain

Mirza et al (2007) compared fusion surgery versus non-surgical therapy for patients with chronic and moderately severe back pain (VAS mean score 63-65) or disability (mean ODI score 45) for at least one year and who were unresponsive to standard nonsurgical therapy (Mirza & Deyo, 2007). They determined that:

- Compared to unstructured, heterogeneous non-operative care, lumbar fusion may be more efficacious for treatment of chronic back pain.

[350] Although the composition of interdisciplinary rehabilitation programs varies, the most effective programs generally involve cognitive/behavioural and supervised exercise components with at least several sessions a week, with over 100 total hours of treatment. Barriers to use of intensive interdisciplinary rehabilitation include relatively high cost, unavailability in some areas, and limited insurance coverage. In workers disabled due to low back pain, some studies suggest that costs of interdisciplinary rehabilitation may be offset by fewer lost wages or days off of work (Chou et al 2009).

[351] This conclusion did not acknowledge the fact that the control arms in the various studies differed significantly

- Fusion may not be more effective than a structured rehabilitation program that includes cognitive-behaviour therapy.

The authors noted that the evidence did not allow a general statement regarding the efficacy of fusion over non operative care for discogenic back pain and that that overall the evidence from RCTs suggested that any advantage was modest and on average near or below a minimally (clinically) important change in the disability score. They also noted that the difference in the magnitude of improvement with *different nonsurgical* treatments suggested that the *type* of non-surgical treatment offered was critical to comparative effectiveness of fusion.

Chou et al (2009) reported that for patients with non-radicular back pain and common degenerative changes there was FAIR evidence that:

- lumbar fusion was associated with small to moderate benefits relating to pain and function compared to usual none-intensive non surgical care
- lumbar fusion was not more effective than intensive rehabilitation which includes cognitive behaviour therapy.

One of the issues raised in this review was the availability of intensive rehabilitation programmes and the ability/willingness of the patient to participate in them (Chou, Baisden et al., 2009).

Comment

This review reiterated the conclusions/recommendations of Mirza et al (2007). Both systematic reviews (Chou, Baisden et al., 2009; Mirza & Deyo, 2007) evaluated the same four higher quality trials[352].

Ibrahim et al (2008) also reported evidence that surgical lumbar fusion for patients with chronic low back pain:

- may improve clinical outcome (ODI) in the short term (2 years) surgical intervention when compared to non-surgical treatment.

However, due to the risk of surgical complications and a small non-significant increase in ODI which was of minimal clinical importance, the authors did not feel that the evidence was strong enough to support the *routine* use of surgical fusion for the treatment of chronic low back pain. A cautious approach to spinal fusion was recommended (Ibrahim et al., 2008).

Spinal stenosis without degenerative spondylolisthesis

For patients with spinal stenosis with or without degenerative spondylolisthesis, there was GOOD evidence from Chou et al (2009)

- that decompressive laminectomy with or without fusion was moderately superior to nonsurgical therapy for improvement in pain and function through 1-2 years .

[352] Brox et al 2003, Brox et al 2006, Fairbank et al 2005, Fritzell et al 2001 (see systematic review publications for full references)

Symptomatic degenerative lumbar disease (degenerative disc disease, chronic low back pain, spondylothisthesis).

Using the Oswestry Disability Index (ODI) and MOS Short Form-36 as outcome measures, Carreon et al (2008) reported that evidence that;

- anterior, posterior and circumferential lumbar fusion produced similar amounts of improvement in ODI across diagnostic groups
- nonsurgical patients did not improve as much as those who underwent fusion but had a lower baseline ODI.
- improvements in the SF-36 PCS were fairly consistent across diagnostic groups and treatment types.

In conclusion, the authors considered that *definite* proof of treatment efficacy for both fusion and nonsurgical treatment of symptomatic lumbar degenerative disease remained unclear (Carreon et al., 2008).

Best evidence synthesis: guidelines

This synthesis comprises the best evidence recommendations. Since the three included guidelines used different systems to grade/rank their evidence and recommendations it was not possible to determine a common best evidence level/rank. To accommodate this clinical recommendations or advice supported by the **top two grades** of the particular ranking system used in each guideline was used. Thus the synthesis below includes recommendations supported by high or reasonably *high levels of evidence* and receiving the *highest or second highest recommendation grading*. The results are summarised below by (a) indication and (b) intervention.

Indications

Symptomatic degenerative spondylolisthesis (Grade B and above evidence)

A recommendation supporting fusion, as an addition to decompression, to improve clinical outcomes was supported by Level II or III studies with consistent findings (Grade B recommendation: Fair evidence). To improve fusion rates (but not necessarily clinical outcomes) the addition of instrumentation was recommended (level II or level III studies, Grade B recommendation: fair evidence (NASS guidelines, Walters et al 2009)

Non-radicular low back pain with common degenerative changes and persistent disabling symptoms (strong recommendation)

The APS guideline (Chou & Huffman, 2009) recommended that, in patients with non-radicular low back pain who do not respond to usual,non interdisciplinary interventions, clinicians consider intensive interdisciplinary rehabilitation with a cognitive/behavioural emphasis (strong recommendation, high-quality evidence).

Intractable low-back pain without stenosis or spondylolisthesis (practice standard)

Lumbar fusion was recommended as a treatment for *carefully selected patients* with disabling low-back pain due to one- or two-level degenerative disease without stenosis or spondylolisthesis (recommendation at the level of a practice standard support by Class I [353]evidence) (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005)

Interventions

Bone graft extenders and substitutes (practice standard)

The use of autologous bone or rhBMP-2 bone graft substitute is recommended in the setting of an ALIF in conjunction with a threaded titanium cage (recommendation at the level of a practice standard supported by Class I evidence) (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005)[354].

Interbody techniques for lumbar fusion (guideline)

In the context of a single-level stand-alone ALIF or ALIF with posterior instrumentation, the addition of a PLF was not recommended as it increases operating room time and blood loss without

[353] Class I evidence=one or more well-designed randomised controlled trials including overviews of such trials.
[354] More recently Caragee eal (2011) published a critical review of the evidence that found that adverse events (including an increased risk of malignancy) associated with the use of rhBMP2 has been an underreported/underestimated ((Eugene J. Carragee, Hurwitz, & Weiner, 2011)).

influencing the likelihood of fusion or the functional outcome (recommendation at the level of a guideline supported by Class II [355]evidence) (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005).

Either direct current stimulation or capacitative coupled simulation was recommended as an adjunct to spinal fusion to increase fusion rates in patients who were at high risk for arthrodesis failure following lumbar PLF (recommendation at the level of a guideline supported by Class II [356]evidence) (American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), 2005)

[355] Class II evidence =one or more well designed comparative clinical studies such as non-randomised cohort studies, case control studies and other comparable studies including less well-designed randomized controlled trials.
[356] Class II evidence =one or more well designed comparative clinical studies such as non-randomised cohort studies, case control studies and other comparable studies including less well-designed randomized controlled trials.

Conclusions: Lumbar fusion

The literature encompasses a *wide range of indications* and an *ever-increasing number of different fusion techniques and fusion adjuncts* reported; in certain areas the volume of literature is sparse. Increasingly stringent quality assessments of randomised controlled trials have downgraded the evidence provided by poor examples of this study type and the most recent systematic reviews are still asking for better quality studies to be performed to direct clinical practice[357].

Over the last decade a constant editorial theme has been the proliferation of fusion techniques and adjuncts and the suspicion that the drivers of a steep increase in the number of fusion operations carried out (at least in America) are not related to clinical effectiveness or an increase in back problems. The literature surveyed in this ACC commissioned report gives some support to this idea.

The literature identified formed an evidence pyramid with the base comprising a large number of poor quality clinical or surgical series reporting different fusion techniques across different populations with *generally favourable conclusions for fusion.* At the narrow apex of the pyramid *was a small number of much higher quality studies (RCTs*) reporting over a narrow range of techniques and patient populations and with rather *less favourable fusion outcomes*.

A best evidence synthesis of systematic reviews and guidelines identified for the current review at times produced conflicting interpretations of the evidence.

[357] Given the expense and recruitment difficulties associated with the conduct of RCTs in this area, an alternative may be to set up a national register of of spinal surgical procedures to act as a repository of prospectively collected economic and clinical data. This would provide data of direct relevance to of the New Zealand population (personal communication, Gordon Howie, reviewer).

Appendix I: Trials of fusion vs non-surgical therapy

Table 94 from the APS guideline (Chou & Huffman, 2009).

Table 94. Trials of fusion versus non-surgical therapy for non-radicular low back pain with common degenerative changes

Author, year Population evaluated	Surgical intervention	Number of patients Duration of follow-up	Main results	Quality score*
Brox, 2003[245] Chronic low back pain with degenerative disc disease at L4/L5 or L5/S1 (no prior discectomy)	Instrumented posterolateral fusion	n=64 1 year	**Surgery versus intensive rehabilitation with a cognitive-behavioral component** ODI score, mean difference in change from baseline: 2.3 (-6.8 to 11.4) Back pain, mean difference in change from baseline: 8.6 (-3.0 to 20.1) Overall rating 'success': 71% vs. 63%, p=0.59	8/9
Brox, 2006[244] Chronic low back pain with degenerative disc disease at L4/L5 or L5/S1 following discectomy	Instrumented posterolateral fusion	n=60 1 year	**Surgery versus intensive rehabilitation with a cognitive-behavioral component** ODI score, mean difference in change from baseline: -7.3 (-17.3 to 2.7) Back pain, mean difference in change from baseline: -5.2 (-18.0 to 7.6) Overall rating 'success': 50% vs. 48%, p=0.91	8/9
Fairbank, 2005[246] MRC Spine Stabilization Trial Chronic low back pain and considered a candidate for spinal fusion	Graf ligamentoplasty (15%) or fusion with technique left to discretion of surgeon (85%)	n=349 2 years	**Surgery versus intensive rehabilitation with a cognitive-behavioral component** ODI, mean difference in change from baseline: -4.1 (-8.1 to -0.1), p=0.045 SF-36 physical component score, mean difference in change from baseline: 2.0 (-1.2 to 5.3) SF-36 mental component score, mean difference in change from baseline: -0.2 (-2.9 to 2.6)	6/9
Fritzell, 2001[247] Swedish Lumbar Spine study Chronic low back pain with degenerative disc disease at L4/L5 or L5/S1	Non-instrumented posterolateral fusion (1/3), instrumented posterolateral fusion (1/3), or instrumented circumferential fusion (1/3)	n=294 2 years	**Surgery versus non-intensive physical therapy** Back pain VAS score, mean change from baseline (0 to 100 scale): 21.0 vs. 4.3, p=0.0002 ODI score, mean change from baseline: 11.6 vs. 2.8, p=0.015 Overall rating 'better' or 'much better': 63% vs. 29%, p<0.0001	7/9

*Excludes criteria involving blinding of patients and care providers, for maximum score of 9
(VAS): Visual Analogue, (RDQ): Roland Morris Disability Questionnaire, (ODI): Oswestry Disability Index, (SF-36):Short-form 36

Appendix II: Characteristics of guidelines for lumbar fusion

Guideline Title AGREE quality score Indication	Fusion technique Non-fusion comparator (s)	Recommendations
Low back pain (two guidelines)		
APS (Chou et al 2009) [358] Evaluation and Management of Low Back Pain (48%) 83% Non-radicular low back pain with common degenerative changes	PLF ± instrumentation Fusion NOS Circumferential fusion <u>Comparators</u> Non-surgical therapy	**Recommendation Two** In patients with non-radicular low back pain who do not respond to usual, non interdisciplinary interventions, it is recommended that clinicians consider intensive interdisciplinary rehabilitation with a cognitive/behavioural emphasis <u>(strong recommendation, high-quality evidence).</u> Chronic back pain is a complex condition that involves biologic, psychological, and environmental factors. For patients with persistent and disabling back pain despite recommended non interdisciplinary therapies, clinicians should counsel patients about interdisciplinary rehabilitation (defined as an integrated intervention with rehabilitation plus a psychological and/or social/occupational component) as a treatment option. **Recommendation four** In patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms, it is recommended that clinicians discuss risks and benefits of surgery as an option <u>(weak recommendation, moderate-quality evidence).</u> It is recommended that shared decision-making regarding surgery for nonspecific low back pain include a specific discussion about intensive interdisciplinary rehabilitation as a similarly effective option, the small to moderate average benefit from surgery versus non-interdisciplinary nonsurgical therapy, and the fact that the majority of such patients who undergo surgery do not experience an optimal outcome (defined as minimum or no pain, discontinuation of or occasional pain medication use, and return of high level function).
AANS/CNS Resnick† (2005) Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 7: intractable low-back pain without stenosis or spondylolisthesis	Lumbar fusion Instrumented lumbar fusion <u>Comparators</u> Non surgical treatment – conservative care Intensive rehabilitation	**Standards** Lumbar fusion is recommended as a treatment for carefully selected patients with disabling low back pain due to one- or two-level degenerative disease without stenosis or spondylolisthesis. **Guidelines** There is insufficient evidence available to support a treatment guideline. **Options** An intensive course of physical therapy and cognitive therapy is recommended as a treatment option for patients with low-back pain in whom conventional medical management has failed.
Herniation and radiculopathy (one guideline)		
AANS/CNS Resnick† (2005) Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine.	Posterolateral fusion (PLF) Posterolateral instrumented fusion Anterior instrumented fusion	**Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** Lumbar spinal fusion is not recommended as routine treatment following primary disc excision in patients with a herniated lumbar disc causing radiculopathy. Lumbar spinal fusion is recommended as a potential surgical adjunct in patients with a herniated disc in whom there is evidence of preoperative lumbar spinal deformity or instability.

[358] Full guideline at http://www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf

Guideline Title AGREE quality score Indication	Fusion technique Non-fusion comparator (s)	Recommendations
Part 8: lumbar fusion for disc herniation and radiculopathy	<u>Comparators</u> Discectomy Laminectomy	Lumbar spinal fusion is recommended as a potential surgical adjunct in patients with significant chronic axial low-back pain associated with radiculopathy due to a herniated lumbar disc. Reoperative discectomy is recommended as a treatment option in patients with a recurrent lumbar disc herniation. Reoperative discectomy combined with fusion is recommended as a treatment option in patients with a recurrent disc herniation associated with lumbar instability, deformity, or chronic axial low-back pain.
Stenosis without spondylolisthesis (one guideline)		
AANS/CNS Resnick† (2005) Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 10: fusion following decompression in patients with stenosis without spondylolisthesis	Posterolateral fusion Posterolateral instrumented fusion <u>Comparators</u> <u>Laminectomy</u> <u>Laminotomy</u> <u>Partial Medial Facetectomy</u> <u>Foraminotomy</u> Discetomy	**Standards** There is insufficient evidence to recommend a treatment standard. **Guidelines** There is insufficient evidence to recommend a treatment guideline. **Options** In situ posterolateral lumbar fusion is not recommended as a treatment option in patients with lumbar stenosis in whom there is no evidence of pre-existing spinal instability or likely iatrogenic instability due to facetectomy. In situ lumbar PLF is recommended as a treatment option in addition to decompression in patients with lumbar stenosis without deformity in whom there is evidence of spinal instability. The addition of pedicle screw instrumentation is not recommended in conjunction with PLF following decompression for lumbar stenosis in patients without spinal deformity or instability.
Spondylolisthesis (four guidelines)		
NASS (Walters et al 2009) Diagnosis and treatment of degenerative spondylolisthesis 65% Symptomatic degenerative lumbar spondylolisthesis	Lumbar fusion NOS Instrumented lumbar fusion Posterolateral fusion <u>Comparators</u> Decompression Reduction	The addition of fusion to decompression was recommended to improve clinical outcomes in symptomatic patients.[359] <u>(Grade B, fair evidence from level II or level III studies)</u> The addition of instrumentation was recommended to improve fusion rates (Grade B, fair evidence from level II or level III studies) but not clinical outcomes <u>(Grade B, fair evidence from level II or level III studies)</u> Decompression with fusion was recommended as a means to provide satisfactory long-term results <u>(Grade C, poor quality evidence from level IV or V studies).</u> Reduction with fusion and internal fixation was not recommended to improve clinical outcomes for patients with low grade degenerative lumbar spondylolisthesis <u>(Grade I insufficient or conflicting evidence not allowing a recommendation for or against intervention).</u> There was not enough evidence to make a recommendation relating to the effectiveness of circumferential fusion compared to posterolateral fusion with decompression.
Chou[360] (2009) APS Guidelines Isthmic spondylolisthesis	Posterolateral fusion with or without instrumentation Fusion with or without instrumentation + decompressive laminectomy	No specific recommendation

[359] It may be noted that orthopaedic decompressions are a lot wider and remove very much more bone, joint, ligament and muscle than neurosurgical decompressions carried out with a microscope, this distinction was not apparent in the literature reviewed.
[360] Full guideline at http://www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf

Guideline Title AGREE quality score Indication	Fusion technique Non-fusion comparator (s)	Recommendations
	Posterior fusion Anterior fusion Combined approach Comparators Non-surgical treatment	
Chou[361] (2009) APS Guidelines Spinal stenosis with or without degenerative spondylolisthesis	Posterolateral fusion Circumferential fusion Posterolateral interbody fusion Comparators Laminectomy Non surgical therapy	Insufficient evidence exists to guide recommendations for interdisciplinary rehabilitation for persistent radiculopathy or symptomatic spinal stenosis. **Recommendation seven** In patients with persistent and disabling radiculopathy due to herniated lumbar disc or persistent and disabling leg pain due to spinal stenosis, it is recommended that clinicians discuss risks and benefits of surgery as an option (strong recommendation, high-quality evidence). It is recommended that shared decision-making regarding surgery include a specific discussion about moderate average benefits, which appear to decrease over time in patients who undergo surgery
AANS/CNS Resnick† (2005) Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 9: fusion in patients with stenosis and spondylolisthesis	Posterolateral fusion Posterolateral instrumented fusion Comparators Decompression Facetectomy Laminectomy	The performance of a lumbar posterolateral fusion is recommended for patients with lumbar stenosis and associated degenerative spondylolisthesis who require decompression. There is insufficient evidence to recommend a treatment guideline. **Options.** Pedicle screw fixation as an adjunct to lumbar PLF should be considered as a treatment option in patients with lumbar stenosis and spondylolisthesis in cases in which there is preoperative evidence of spinal instability or kyphosis at the level of the spondylolisthesis or when iatrogenic instability is anticipated.

[361] Full guideline at http://www.ampainsoc.org/pub/pdf/LBPEvidRev.pdf

Section 6.2: Cervical fusion

The current section focuses on the clinical evidence pertaining to the effectiveness of fusion for the management of spinal lesions of the *cervical spine* and, in particular, the clinical outcomes of fusion surgery.

One of the problems that was encountered during the preparation of the current overview for the ACC was that the impartiality of a number of clinical guidelines, written mostly by the profession for the profession, had been questioned[362], (see the accompanying report on lumbar fusion surgery). Thus although clinical guidelines were originally intended to be a key resource the claimed biased reporting due to conflicts of interest in some guidelines determined that systematic reviews provide the primary evidence source.

[362] Guidelines vary in how closely they reflect the current evidence, different interpretations of the evidence, expert opinion and patient preference may all influence the final recommendations.

Background: Cervical fusion

Cervical degenerative disease is one of the most common causes of acquired disability in patients over the age of 50 years (Fehlings & Arvin, 2009). With improvements in medical imaging of the cervical spine, the diagnosis of surgical degenerative disease has become easier. These improvements have been accompanied by technological advances in the surgical treatment of cervical spinal disease.

Cervical spinal fusion is designed to eliminate the normal motion of one or more vertebral segments. The idea behind fusion is that, *if* the motion itself is the root cause of pain (due to the inability of the degenerative vertebral segment to support the weight of the body comfortably) when the problematic segment is fused it no longer moves and therefore cannot cause pain. However, it should be noted that confirming and documenting that the cause of pain is the intervertebral disc is problematic (C. Martin, 2005).

Anterior cervical discectomy and fusion (ACDF) has gained popularity for the treatment of a number of conditions including degenerative spondylosis, intervertebral disk herniation, radiculopathy and spinal instability. However, the need for an interbody fusion has been questioned with proponents of anterior cervical discectomy (ACD) emphasising its simplicity, low cost and the lack of graft complications that can occur with interbody fusion. Despite arguments and uncertainties relating to the application of anterior interbody fusion for the treatment of cervical degenerative disc disease, the overall trend in the USA and Canada has been a steep increase in the number of cervical fusions, Figure 6.2.2

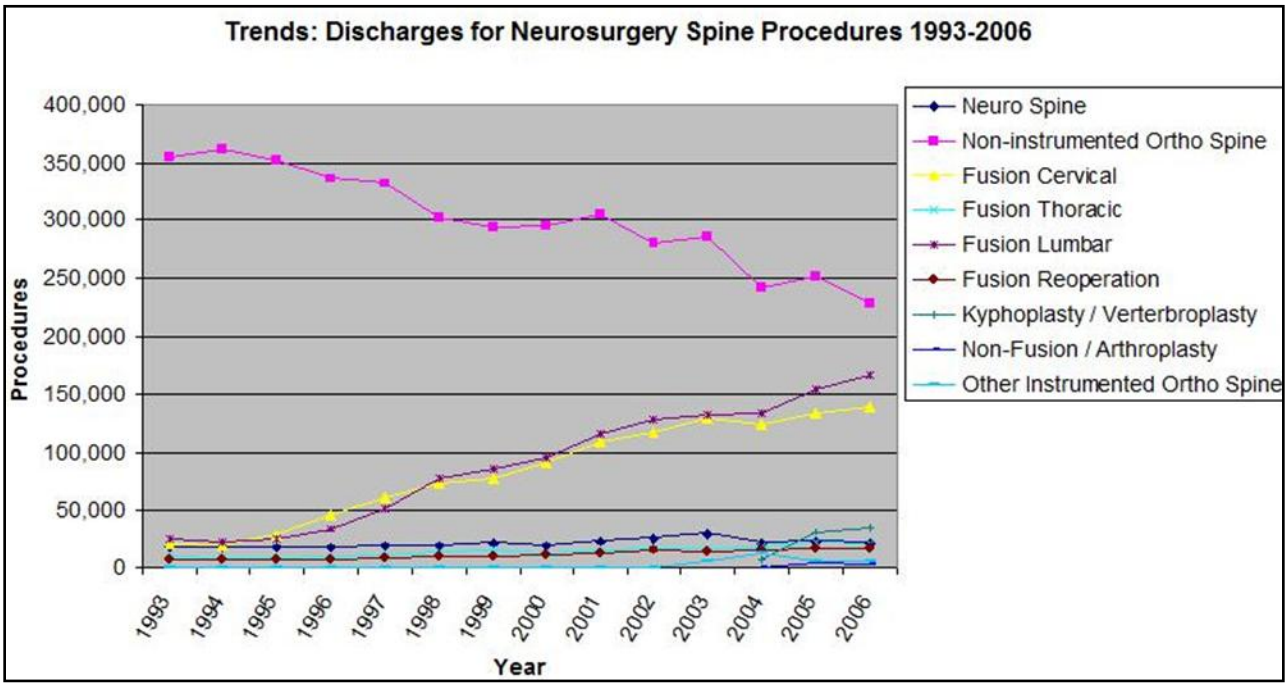


Figure 6.2.1. Trends in instrumented procedures in the United States 1993-1999 to 2000-2006 (from Chia et al, Clinical neurosurgery, Abstract ID 4899, 2009http://2009.cns.org/AbstractPop2.aspx?ID=4899)

In New Zealand, cervical fusion is primarily carried out to help decompress the emerging nerve root or to treat post-traumatic instability; few New Zealand surgeons perform cervical fusion for neck pain and fusion of the cervical vertebrae is usually for trauma or after discectomy or decompression[363].

[363] Personal communication, Gordon Howie, reviewer.

Cervical fusion techniques

Early surgical treatment of neural decompression of the cervical spine used a posterior approach to perform cervical laminectomy[364] for trauma and degenerative disease. However, in the1950s, anterior cervical discectomy with fusion[365] (ACDF) was pioneered by Smith-Robinson and Ralph Cloward. However, the addition of fusion was not shown to be more effective than discectomy alone, except that in longer term studies the union rate with discectomy alone was reported to be lower, and there appeared to be a greater loss of disc height. New Zealand followed overseas trends. For historical reasons anterior cervical fusion for radiculopathy was largely carried out by neurosurgeons and a small number of orthopaedic surgeons. In several centres trauma cases were more likely to be treated by Orthopaedic surgeons using both posterior and anterior approaches.

The graft source for interbody fusion has commonly been the iliac crest (autograft). However autografts have been associated with a wide range of complications (e.g. pain[366], deformity, wound infection and rarely fracture) and alternative interbody implants have been sought. The first successful allograft implant was reported in 1958, however fusion rates and clinical outcomes were not superior to autograft implants and other solutions were sought.

In the early 1980s anterior cervical plates to protect the bone graft and add extra stability to the spine were introduced for the management of trauma cases. Later they were added to fusion for degenerative disc disease / radiculopathy Figure 6.2.3.

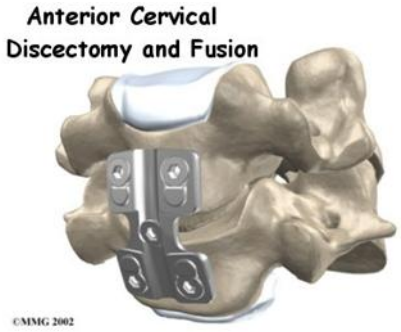


Figure 6.2.2. Anterior cervical fusion with plates and screws.

Anterior cages were also introduced in the 1980s by Bagby and Kuslich (BAK interbody cage). The use of plates and cages was in part driven by the surgical industry but the addition of an extra fee for use of these devices probably increased their use. In New Zealand the fee paid by ACC for inserting a cage was greater than for doing a cervical fusion with bone graft, even though the latter procedure takes longer; currently every fusion incorporates an interbody cage.

[364] Laminectomy is an operation to remove the portion of the vertebral bone called the lamina to relieve pressure on the spinal nerves.
[365] Achieved with a bone graft which is used to promote two bones growing together into one. The patient's own bone grows into and around the bone graft and incorporates the graft bone creating one continuous bone surface and eliminating motion at the fused joint.
[366] Pain is occasionally permanent and annoying.

A large number of different interbody materials and constructs[367] to aid interbody fusion have been developed and investigated in numerous surgical series. Fusion using interbody titanium cages has showed promising clinical results and low rates of implant failure. Instrumentation (screws, plates etc) developed to increase the stability of the cervical segment fusion reportedly increased fusion rates and maintained sagittal balance[368] more effectively[369]. Postoperative loss of lordosis and cervical kyphosis has been associated with ACD and ACDF without this added stabilizing instrumentation. However,as noted above the use of instrumentation increases cost and complications.

It is clear from this brief overview of the development of techniques for cervical fusion that there has been a stepwise and cumulative increase in the number of these techniques and in their complexity. Their increasing use and escalating costs have stimulated the development of a number of reviews and overviews to assess the quality of the primary scientific evidence and the validity of claims of fusion success and superior clinical outcomes to that provided by other surgical, medical and physical therapies. These reviews have in turn been used to underpin clinical guidelines published by medical and surgical Associations.

Fusion surgery is still evolving and advocacy for one or other fusion method/technique often appears to be based on small surgical series providing a low level of evidence because of a high risk of bias. The nature of these methodological biases is such that there is a high likelihood that these low level studies will report more positive results for the intervention than would be obtained from high quality RCTs; however large high quality RCTs pose a number of difficulties and alternative study types have been suggested as more practicable.

[367] For example, polymethylmethacrylate, ceramics, cylindrical titanium mesh carbon fibre or resorbable cages..
[368] Considered, but not proven to be, important for good clinical outcome, see Kim et al 2011. Impact of sagittal balance on clinical results after posterior interbody fusion for patients with degenerative spondylolisthesis : a pilot study. BMC Musculoskeletal disorders, Vol 12 (1),69.
[369] Plates did increase fusion rates and stopped bone graft extrusion but at a cost of swallowing difficulties and quite frequent screw misplacement into the disc below, personal communication, Graham Howie, reviewer.

Methods

For a comprehensive description of the searches carried out for this review and the reporting methods see the General Methods section. Briefly, a systematic search of the literature for high evidence level studies and overviews (systematic reviews, metaanalyses and clinical guidelines) relating to the effectiveness of fusion for degenerative diseases of the cervical spine was carried out.

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study).

Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews. In addition to searching bibliographic databases such as Medline and Embase for guidelines, the following sources/websites were searched for recent (2005 onwards) evidence based guidelines reporting substantially on fusion surgery:

American Academy of Orthopaedic Surgeons (AAOS)

American Society of Neuroradiology (ASN)

American Society of Spine Radiology

Guidelines International Network (GIN)

Institute for Clinical Systems improvement (ICSI)

Medical Services Advisory Committee

National Health and Medical Research Council (NHMRC)

National Institute for Health and Clinical Excellence (NICE)

New Zealand Guidelines Group (NZGG)

NHS Evidence

North American Spine Society (NASS)

Scottish Intercollegiate Guidelines Network (SIGN)

TRIP database

World Health Organisation (WHO)

Clinical guidelines were originally intended to be a key resource in the current overview undertaken for the ACC. However, as noted earlier, critical reviews of American guidelines which claimed biased reporting due to conflicts of interest in some guidelines, in the current overview, systematic reviews provide the primary evidence source.

Because of the large number of low quality studies identified for this review and their potential to distort perceptions of the effectiveness of fusion surgery, a best evidence summary was carried out in which only recommendations based on good quality evidence, which was likely to be free of significant biases, is presented.

Quality assessment

The internal validity (quality) of the systematic reviews was assessed using a checklist based on criteria developed by Oxman and Guyatt (Oxman & Guyatt, 1991). The concept behind the Oxman criteria is fairly simple – the greater the scientific quality (methodological rigour), the more likely an overview/systematic review is to avoid bias, and its finding reflect the truth regarding, for instance, the magnitude of the effect of a treatment.

Using the Oxman criteria each systematic review was scored between 1 and 7 based on (a) the comprehensiveness of the search strategy, (b) the application of pre-defined inclusion criteria to select studies, (c) the appropriate assessment of validity (quality) and (c) use of appropriate methods to synthesize the evidence.

Using this system, systematic reviews with a score of four or less were considered to have potential major flaws or biases[370] and were classified as "lower quality" systematic reviews. Systematic reviews with scores of five or more were considered to be "higher quality" with less potential for bias and a higher likely hood of valid results. Within each systematic review, the reporting of levels of evidence and the quality of the primary studies varied. The AGREE tool was used to assess guideline quality.

Publications identified in the search procedure for the current review together with significant publications identified through pearling references from retrieved articles are cited the bibliography at the end of this report. Other relevant references quoted to support particular statement in the reviewed studies are referenced in footnotes.

Search results

The search strategy developed for the review of the effectiveness of cervical surgical fusion for identified eight systematic reviews (SRs) and two guidelines. These studies examined the effectiveness of different surgical approaches to cervical fusion and compared the effectiveness of fusion to non-surgical and other surgical techniques. Most of the reviews were relatively recent with seven published within the last 3 years(P. A. Anderson, 2009; Cunningham, Hershman, & Bendo, 2010; Dvorak et al., 2007; W. Jacobs et al., 2011; Matz et al., 2009; Mummaneni et al., 2009; Ryken, 2009; van Limbeek,

[370] and were therefore more likely to produce positive conclusions about effectiveness.

Jacobs, Anderson, & Pavlov, 2000), and one (van Limbeek et al., 2000) published over 10 years ago. There was overlap between these reviews in the primary studies they assessed.

Within each systematic review, the reporting of levels of evidence and the quality of the primary studies varied. The scales and grading used in each study for levels of evidence and study quality are indicated either in the text or in a footnote.

Evidence assessment: Systematic reviews

Eight systematic reviews were eligible for review. Four were *standard systematic reviews* i.e. systematic reviews incorporating a quality assessment and evidence synthesis, four were systematic reviews with *recommendations for surgical management.* The latter fall short of the standards and methods of clinical guidelines and are reported here with other systematic reviews but in a separate section.

Systematic reviews without recommendations for management

Four standard systematic reviews (i.e. systematic reviews without management recommendations) were identified (Cunningham et al., 2010; Dvorak et al., 2007; W. Jacobs et al., 2011; van Limbeek et al., 2000).

The main characteristics, author's conclusions and brief evidence summary for these systematic reviews are summarised in Tables 1-4 . Each table is followed by a fuller description of the review (s). A side-by side summary of the key features and conclusions for all systematic reviews ordered by indication/diagnosis is given in Appendix I.

Van Limbeek 2000 "A systematic literature review to identify the best method for a single level anterior cervical interbody fusion".

The earliest systematic review (van Limbeek et al., 2000) aimed to determine, for patients with degenerative disc disease, which method of anterior cervical interbody fusion (ACIF) (single level), gave the best clinical and radiological outcome. Only RCTs with a follow-up of at least 6 months were eligible for inclusion. The qualities of the studies were assessed using the criteria developed by Chalmers et al (1981)[371] and the Cochrane Collaboration. The search yielded 214 references. Eight RCTs were eligible but upon assessment only three met the strict quality requirements of the review. These three RCTs assessed four different interbody fusion techniques and were used by the review authors to provide a *best evidence synthesis*.

The main characteristics and author's conclusions for this systematic review are summarised in Table 6.2.1.

[371] Chalmers TC, Smith HJ, Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A (1981) A method for assessing the quality of a randomized control trial. Control Clin Trials 2 :31–49

Table 6.2.1. Key features and findings from Limbeek et al (2000): A systematic literature review to identify the best method for a single level anterior cervical interbody fusion.

Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [372]	Conclusions
Degenerative disc disease				
Van Limbeek et al (2000) 5/7	3 good RCTs[373] Van den Bent et al (1996) Martins (1976) Savolainen et al (1998)	Anterior cervical interbody fusion with either polymethylmethacrylate, Clowerd fusion with an iliac crest graft, Smith-Robinson or Caspar plating Comparator Discectomy	Fusion (radiological) Kyposis (radiological) Clinical (questionnaires)	With low fusion rates varying between 28% and 63% and clinical outcomes of between 67%-82% (which were not always in favour of fusion with instrumentation), none of the reported techniques had a clear advantage in terms out radiographic and clinical outcomes and the reviews authors concluded that none of the techniques provided a gold standard for treatment of degenerative disc disease.

Clinical outcomes were variously assessed based on either (a) pain scores obtained from independent reports made by the patient and an observer, (b) a four-point scale to measure clinical outcome, or (c) a clinical outcome questionnaire that evaluated benefit and complaints on a three-point scale.

The findngs/results for three studies included in the best evidence synthesis are summarised below:

- Van den Bent et al (1996) compared anterior cervical discectomy in which polymethylmethacrylate (PMMA)374 was used to promote fusion with discectomy alone in order to evaluate whether using PMMA improves the results of anterior discectomy. Fusion was observed in 63% of the discectomy-alone group and in 28% of the PMMA group. Clinical outcome was excellent or good in 77% (95%CI 61–89) for discectomy alone and 70% (95%CI 53–83) for discectomy with PMMA. Clinical outcome after 6 months was excellent or good for 82% (Cloward fusion) and 67% (12 of 18) for discectomy alone (P=0.65).
- Martins et al (1976) compared discectomy alone to the Cloward fusion procedure using an iliac crest graft. The Cloward fusion group had 6 excellent, 8 good, 2 fair and 1 poor results and the discectomy-alone group had 4 excellent, 8 good, 5 fair and 1 poor results. Outcomes were based on radiograph and clinical measures. There was no difference between the two treatments (P = 0.65) but the number of patients in this study was small.
- Savolainen et al. (1998) compared discectomy alone to two different fusion techniques: Smith-Robinson or Caspar plating. Clinical outcome after 4 years showed 76% of the patients had a

[372] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR
[373] There were eight eligible RCTs however five failed to meet strict the strict methodological requirements of the review.
[374] The use of PMMA is now uncommon, personal communication, Graham Howie, reviewer.

good result in the discectomy-alone group: 82% in the Smith-Robinson group, and 73% in the Caspar plating group. Prolonged severe iliac crest pain was observed in a total of five patients in the fusion groups.

With fusion rates varying between 28% and 63% and clinical outcomes of between 67%-82% none of the reported techniques had a clear advantage in terms out radiographic and clinical outcomes.

Author's conclusion

From this systematic literature review, a gold standard for the treatment of degenerative disc disease could not be identified.

Comment

The conclusions of this systematic review were based on a small number of studies one of which was published in 1976. Otherwise, with an Oxman score of 5/7 for internal validity this review was considered to be a "higher quality" review with less potential for bias and a higher likely hood of valid results than those with lower scores.

Dvorak 2007 "The Surgical Approach to Subaxial [375]Cervical Spine Injuries"

Dvorak et al (2007) carried out a systematic review of the literature on surgical approaches to subaxial cervical spine *injuries* in order to produce an evidence based algorithm for the management of these conditions. They noted a lack of consensus on the best surgical approach which they attributed, in part, to the lack of a clinically relevant system for classifying these injuries.

The authors developed an evidence based treatment algorithm based upon a newly developed Subaxial Injury Classification (SIC) scoring system which categorized injury morphology into 3 broad groups (a) cervical subaxial burst fractures, (b) distraction injuries, and (c) translation or rotation injuries.

The main characteristics and author's conclusions from this systematic review are summarised in Table 6.2.2.

[375] Subaxial = below C2.

Table 6.2.2. Key features and findings from Dvorak et al (2007): The Surgical Approach to Subaxial Cervical Spine Injuries.

Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [376]	Conclusions
Subaxial (below C2) cervical spine injury				
Dvorack et al (2007) 3/7	26 articles (level I =1, level II=3, level III=7, Level IV= 15)	Anterior fusion Posterior fusion Circumferential fusion Comparator(s) Anterior fusion Posterior fusion Circumferential fusion	Not specified	Burst or compression injuries and distraction injuries were more likely to be treated with a single anterior approach, whereas the more severe translation or rotation injuries were more commonly approached from the posterior or with combined anterior and posterior surgery. 1 high quality RCT, 1 low quality RCT, 2 higher quality comparative studies, 7 lower quality comparative studies.

Treatment algorithms were developed based on a systematic literature search which identified a total of 26 articles meeting the author's inclusion criteria. One article presented level I evidence (an appropriately powered RCT), three presented level II articles (non-randomised studies or RCT not appropriately powered), 7 were level III articles (retrospective comparative studies) a further 15 articles were considered as level IV evidence (cohort studies).

Author's conclusion

Burst or compression injuries and distraction injuries were more likely to be treated with a single anterior approach, whereas the more severe translation or rotation injuries were more commonly approached from the posterior or with a combined anterior and posterior approach. Treatment algorithms for each of these groups are shown in Appendix II.

Comment

This study included both anterior and posterior injuries of varying severity. The clinical outcomes upon which these choices were made were not reported. The final algorithms were based not only on the scientific evidence but also on expert opinion and anticipated patient preferences and were designed to offer the best standard of care to eligible patients. For the purposes of this review, the study differentiates cervical fusion approaches based on differential success in the treatment of different indications. With an Oxman score of 3/7 this review was considered to be of a "poorer quality" and its focus of marginal interest perhaps in the current review[377].

[376] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR

[377] Cervical spine fractures are very individual and varied and to get statistically meaningful data would require a much larger sample size. The data presented here may not be relevant to ACCs requirements/client population.

Cunningham 2010 "Systematic review of cohort studies comparing surgical treatments for cervical spondylotic myelopathy."

Cunningham et al (2010) reported on the findings of a systematic review of cohort studies to compare the results of major surgical treatments for moderate to severe or progressive cervical spondylotic myelopathy (CSM) (Cunningham et al., 2010).

The main purpose of the review was to assess the clinical and radiological results and complications relating to the various surgical approaches in order to guide clinical decision making and provide information which may be helpful in the design of an RCT. The aim of the review was to determine which surgical treatment was the most effective to prevent progression, aid in recovery and obtain the best clinical outcome.

The main characteristics and author's conclusions for this systematic review are summarised in Table 6.2.3.

Table 6.2.3. Key features and findings from Cunningham et al (2010): Systematic review of cohort studies comparing surgical treatments for cervical spondylotic myelopathy.

Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [378]	Conclusions
Cervical spondylotic myelopathy (CSM)				
Cunningham et al (2010) 3/7	11 retrospective cohort studies 3 case series with >10 years FU	ACDF (fusion) Comparator(s) Corpectomy+ fusion ACD + fusion Laminoplasty Laminectomy+ fusion	JOA score Nurick score recovery rate secondary spondylosis neck ROM axial neck pain sagittal alignment operative complications.	All of the surgical approaches reviewed yielded similar neurological recovery rates. Overall laminoplasty a treatment for CSM has fewer complications, possibly greater ROM and similar neurological recovery compared with ACDF, multilevel corpectomy and laminectomy but has a higher incidence of bothersome neck pain.

The authors compared studies in each group for a wide range of clinical outcomes which included:

- Japanese Orthopaedic Association (JOA) score
- Nurick score
- recovery rate
- secondary spondylosis

[378] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR

- neck range of motion (ROM)
- axial neck pain
- sagittal alignment
- operative complications.

The search yielded 7[379] separate cohorts/studies for review. These studies compared:

- corpectomy (CORP) with laminoplasty (LAMP) (n=4)
- anterior cervical discectomy and fusion (ACDF) with LAMP (n=2)
- laminectomy and fusion (LAMI) with LAMP (n=1

The findings of the comparisons are summarised in Table 6.2.4.

Table 6.2.4. Results of a review of cohort studies comparing surgical treatments for cervical spondylotic myelopathy.

Corpectomy vs laminoplasty (four studies)	ACDF with laminoplasty (n=2)	LAMI with LAMP (n=1)
No significant difference between groups in: • Nurick score • JOA score • Recovery rate • Significant differences for all patients from pre-operative status in: • Neurological recovery • No differences in rates between the groups in • Secondary spondyloptosis/spondylolisthesis • Change in sagittal alignment Two studies found significant changes in Cervical ROM Axial neck pain	No statistically significant differences in post-operative scores for: JOA Recovery rates There was a higher rate of secondary spondylolisthesis in patients who underwent ACDF In one study all levels fused.	• Both groups improved their Nurick scores. There were no statistical differences in the improvement. • LAMI had a statistically significant decrease in the ROM, but post op axial neck pain were the same in both groups. • LAMI had a higher rate of non-union • LAMP patients tended to lose on average 3° of lordosis.
• Complications Significantly increased rate of complications in the CORP group.	Complications No reported complications	Complications The LAMI group had 8 serious complications, LAMP had none.

CORP= corpectomy , LAMP = laminoplasty, ACDF = anterior cervical discectomy and fusion (ACDF), LAMI -laminectomy and fusion. JOA=Japanese Orthopaedic Association.

Three cases series with 10 year follow up were also reported.

All of these studies showed a statistically significant improvement in JOA scores up to the final follow-up, ROM of the neck was decreased after surgery in two studies. The study examining the effects of multi-level CORP reported a slight (6.5%) increase in axial neck pain.

[379] There were a number of statement giving conflicting numbers of included studies.

The authors of the review concluded that;

- all of the surgical approaches reviewed yielded similar neurological recovery rates
- laminoplasty had a significant incidence of neck pain compared with multilevel corpectomy
- anterior cervical discectomy and fusion increased the rate of adjacent secondary spondylosis compared with laminoplasty
- multilevel corpectomy and laminectomy with fusion had a significantly higher level of graft instrumentation and approach related complication
- multilevel corpectomy and laminectomy with fusion had a significantly higher rate of graft, instrumentation, and approach related complications significant decrease in range of motion of neck compared with laminoplasty.

Overall, laminoplasty as a treatment for CSM had fewer complications, possibly greater range of motion and similar neurological recovery compared with ACDF, multilevel corpectomy and laminectomy with fusion, but had a higher incidence of bothersome neck pain.

Comment

This review scored 3/7 for internal validity indicating that this was a "poorer quality" review. The wide variety of procedures reported and the spectrum of results obtained with retrospective cohort studies underpined the need for higher quality studies that can deliver reliable and valid evidence to inform clinical choices.

Jacobs 2011 "Single or double-level anterior interbody fusion techniques for cervical degenerative disc disease."

The most recent review identified was an updated Cochrane review(W. Jacobs et al., 2011). The objective of this review was to determine which technique of anterior interbody fusion (AIF) gave the best clinical and radiological outcomes in patients with single- or double-level degenerative disc disease of the cervical spine.

The search strategy identified 33 small RCTs (40 articles including 14 studies from an earlier version of the review (W. Jacobs et al., 2004). Where studies were judged to be sufficiently homogeneous, the results from individual studies were pooled. For dichotomous outcomes risk ratios (RR) were reported, for continuous outcomes a mean difference (MD) was calculated. For each outcome, a 95% confidence interval (95% CI) was computed and a random-effects model was used.

Clinical relevance was assessed by five questions recommended by Furlan 2009[380]. Clinically important change was evaluated using the guideline given by Ostelo 2008, where in a consensus, a minimal important change of 30% for the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Roland

[380] Furlan A, Pennick V, Bombardier C, van Tulder M. 2009 Updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine 2009; Vol. 34, issue 18:1929–41.

Morris Disability Questionnaire (RDQ), Oswestry Disability Index (ODI), and Quebec Back Pain Disability Questionnaire (QBPQ) was proposed.

Eleven treatment comparisons were reported. The main characteristics and author's conclusions for this systematic review are summarised in Table 6.2.5.

Table 6.2.5. Key features and findings from Jacobs et al (2011): Single or double-level anterior interbody fusion techniques for cervical degenerative disc disease.

Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [381]	Conclusions
Degenerative disc disease				
Jacobs 2011 (Cochrane review update) 6/7	33 RCTs With flaws (19 new studies)	AIF with Bone graft (allo/auto) Cage Cement Plate Comparator(s) Discectomy Discectomy	Complications Fusion rate VAS pain (arm, neck) Satisfaction SF 36 (physical and mental) Odom's criteria Recovery Return to work Muscle power JOA Headache	For reduction of pain in patients with cervical degenerative disc disease or disc herniation, the authors of this Cochrane review found no superior treatment. It was unclear what patients, if any, benefit from cervical fusion as opposed to discectomy alone. In most studies and for most outcomes, discectomy was not statistically different from fusion by any technique, and there are no clear differences among fusion techniques.

Details of the comparisons, outcome measures used and results are summarised below.

1. Discectomy alone versus human bone graft

Seven small studies (487 patients) provided low quality evidence that there was no significant difference in short-term pain relief [382], and very low quality evidence of no significant difference between the treatments in Odom's criteria[383]; short-term return-to-work (10 weeks) [384]; or intermediate-term return-to work[385]. There was moderate quality evidence that bone graft was more effective than discectomy alone in achieving fusion[386] and very low quality evidence that there was no significant difference in

[381] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR
[382] (1 RCT, 84 participants, RR 0.82; 95% CI 0.20 to 3.46)
[383] (2 RCTs, 149 participants, RR 0.95; 95% CI 0.82 to 1.10)
[384] (2 RCTs, 144 participants, RR 1.26; 95% CI 1.02 to 1.54)
[385] (2 RCTs, 70 participants, RR 1.44; 95% CI 0.77 to 2.69)
[386](5 RCTs, 303 participants, RR 0.22; 95% CI 0.17 to 0.48)

alignment[387]. There was moderate quality evidence that there was no significant difference in complication rates[388].

2. Discectomy alone versus cages or cement

Four small studies compared discectomy alone with a cage or with intervertebral cement. Two studies used a cage, one used cement, and one used both. Between those who received discectomy alone and those who received a cage, there was no evidence for pain relief, and very low quality evidence that there was no significant difference in recovery[389], or preventing non-fusion[390]. There was moderate quality evidence that there were no significant differences in complication rates (3 RCTs, 260 participants).

3. Discectomy alone versus iliac crest autograft with plates

Between those who received discectomy alone and those who received anterior plating, there was very low quality evidence from three small studies that there was no significant difference for:

- VAS arm pain391
- Odom's criteria 392
- achieving fusion393

There was very low level evidence that bone graft with anterior plating resulted in better neck pain relief than discectomy alone[394]. Complications were reported in all three studies. Two studies reported no serious complications; one study reported five complications in each group. The conclusion was that the difference in complication rate between the two groups was not clinically significant.

4. Iliac crest autograft versus human allograft or bone substitute

Four small studies with 220 patients compared fusion with autograft (N = 96) versus any kind of allograft (N = 124). The treatments examined in this comparison were too clinically heterogeneous to combine any of the results in a meta-analysis. Primary outcomes of the two studies with low risk of bias were pain (total, arm and neck) in one study and SF-36 and fusion in the other. The latter did not report any usable information the former only reported change scores for arm pain and neck pain, so these also could not be analysed.

[387] (2 RCTs, 75 participants, RR 0.34; 95% CI 0.07 to 1.56).
[388] (7 RCTs, 487 participants, OR 1.56; 95% CI 0.71 to 3.43)
[389] (1 RCT, 64 participants, RR 1.12; 95% CI 0.91 to 1.38)
[390] (3 RCTs, 250 participants, RR 0.65; 95% CI 0.09 to 4.42).
[391] (1 trial, 2 participants, MD -0.16; 95% CI -0.85 to 0.53)
[392] (1 RCT, 61 participants, RR 0.96; 95% CI 0.71 to 1.28)
[393] (2 RCT, 91 participants, RR 1.10; 95% CI 0.96 to 1.27)
[394] (1 trial, 20 participants, MD0.81 favouring plating 95% CI 0.20 to 1.42).

5. Iliac crest autograft versus cages

Seven small studies with 889 patients compared iliac crest autograft (N = 355) versus a cage (N = 534). One study also compared iliac crest autograft with polymethylmethacrylate (PMMA) spacer. Generally, the cages were either not filled or were filled with local autograft or bone substitute, all autograft groups received iliac crest autograft. Between those who received iliac crest autograft and those who received a cage, there was;

- very low quality evidence that the difference in VAS arm pain was not statistically significant[395]
- moderate quality evidence that the difference in Odom's criteria was not statistically significant[396]
- low quality evidence that iliac crest autograft was more effective in achieving fusion than a cage[397]
- low quality evidence that cages were more effective in preventing complications than iliac crest autograft 398.

6. Iliac crest autograft versus iliac crest autograft with plates

Three small studies (N = 136) compared autograft (N = 67) with autograft and anterior plating (N = 69). Between those who received iliac crest autograft and those who received iliac crest autograft with a plate, there was;

- very low quality evidence that the difference in clinical outcomes was not statistically significant[399]
- low quality evidence that the difference in fusion rate was not statistically significant[400]
- moderate quality evidence that the difference in complication rate is not statistically significant (3 RCT, 136 participants).

7. Different types of autograft

One small study with 46 patients and a high risk of bias evaluated different types of autograft. This study concluded that vertebral body graft was not superior to iliac crest autograft. This comparison could not be included in the quantitative analysis.

8. Allograft versus cages

[395] (2 RCT, 180 participants, MD -0.29; 95% CI -0.90 to 0.33)
[396] (6 RCT, 412 participants, RR 1.11; 95% CI 0.99 to 1.24)
[397] (5 RCT, 424 participants, OR 1.87; 95% CI 1.10 to 3.17)
[398] (7 RCT, 889 participants, OR 0.32; 95% CI 0.11 to 0.92).
[399] (2 RCT, 106 participants, RR 1.14; 95% CI 0.91 to 1.41)
[400] (2 RCT, 90 participants, RR 0.99; 95% CI 0.92 to 1.07)

One small study with a high risk of bias compared cylindrical allograft bone (N = 22) with a titanium cage implant (BAK-C®). This study concluded that there were no clinical differences between titanium cage and cylindrical bone, but that the cylindrical titanium cage provided better interspace height, interspace angulation and fusion rate. This comparison could not be included in a quantitative analysis.

9. Comparisons between different types of instrumentation. Six small studies compared different types of instrumentation:

9.a Allograft with plate vs. cage

Two small studies with high risk of bias compared allograft with plate (N = 53) versus cage (N = 48).There were no clinical differences between the different instrumentation techniques in either study, but the cage prevented donor site harvesting and plate complications. There were no differences between allograph or cage with regard to complications. Due to study flaws no quantitative analysis was carried out.

9.b PMMA cement vs. cage

Between those who received PMMA cement (polymethylmethacrylate) and those who received a cage, there was low quality evidence that the difference in improving Odom's criteria was not statistically significant (2 RCT, 169 participants, RR 1.00; 95% CI 0.85 to 1.19).

9.c Cage vs. cage + anterior plate

Between those who received a cage and those who received a cage with additional anterior plate, there was very low quality evidence that there was no statistically significant difference in post-operative Japanese Orthpaedic Association score (1 RCT, 62 participants, MD 0.50; 95% CI -0.65 to 1.65) or segmental lordosis (1 RCT, 62 participants, MD -0.60; 95% CI -2.95 to 1.75; P = 0.62).

Summary

In 2011 Jacobs et al published an update of two earlier versions (W. Jacobs et al., 2004; van Limbeek et al., 2000) of a Cochrane review of anterior interbody fusion techniques for cervical degenerative disc disease. In the update, the literature search was extended to capture RCTs published up to 2009 and included 19 new studies (W. Jacobs et al., 2011).

Interestingly, all of the new studies evaluated the use of instrumentation such as anterior plates for fusion. Overall, 33[401] small RCTs comprising 2267 patients and comparing different fusion techniques were reviewed. The major treatments were discectomy alone, addition of an interbody fusion procedure (autograft, allograft[402], cement, or cage), and addition of anterior plates.

[401] 14 studies form the original review and 19 new studies identified by the updated search
[402] Allograft is not commonly used in New Zealand, personal communication, Gordon Howie, reviewer.

The choice for a specific anterior interbody technique could not be made on the most important and primary outcome, *pain relief*.

In terms of other clinical outcomes, discectomy was more effective than human bone graft in improving return-to-work at five weeks, but the *effect was small and unstable* and at 10 weeks the difference was not statistically significant. For all other clinical outcomes, none of the evidence examined indicated that there was a statistical difference between any of the techniques.

Fusion rate, which was considered the key in the working mechanism of many of the surgical techniques, appeared to be the highest when the iliac crest autograft treatment was employed; it performed better (clinically and statistically) than discectomy alone and cages. There was no difference in fusion rates between discectomy plus cages or PMMA, discectomy alone, iliac crest autograft plus an anterior plate or iliac crest autograft [403].

In terms of complications, cages performed better than iliac crest autografts and the difference was clinically significant. Other comparisons between complication rates did not show statistically significant differences. However the trials that were reviewed *were not powered* to identify a difference in the occurrence of complication rates, which had a low incidence.

For discectomy, since the intended working mechanism does not involve fusion of the motion segment and the objective is the relief of pain not fusion lower fusion rates[404] compared to iliac crest autograft may have no clinical implications and fusion may be considered to be an irrelevant criterion.

When the working mechanism for pain relief and functional improvement was fusion of the motion segment, there was low quality evidence that iliac crest autograft was the better technique. When ignoring fusion rates and looking at complication rates, a cage has a weak evidence base over iliac crest autograft, but not over discectomy alone.

Authors' conclusions

For reduction of pain in patients with cervical degenerative disc disease or disc herniation, the authors of this Cochrane review found *no superior treatment.* It was unclear which patients, if any, benefit from cervical fusion as opposed to discectomy alone. In most studies, and for most outcomes, discectomy was not statistically different from fusion by any technique, and there were no clear differences among fusion techniques.

This review determined that the only evidence-based choice was between iliac crest autograft and cages for chronic cervical degenerative disc disease. The technique chosen depended on balancing the importance of improved fusion rates with autograft, versus improved complication rate with cages. As the relationship between clinical parameters and fusion rates was weak, cages were considered to be a

[403] The authors noted that this was in contradiction to the meta-analysis by Fraser 2007, who found better fusion rates for anterior plates. However, the meta-analysis included retrospective, noncontrolled, studies, which may be prone to bias.
[404] Although rarely mentioned in the literature reviewed, spontaneous fusion has been reported following discectomy.

valid alternative for iliac crest autograft, although the working mechanism of fusion might not apply for isolated nerve root compression.

The authors considered that (a) more methodologically rigorous studies were needed in the field of surgical treatment of cervical degenerative disc disease before evidence-based recommendations on the topic could be made and (b) the methodological quality of the design of the studies could be improved by standardizing the outcome parameters and follow-up time-points and presenting more long-term outcome data (i.e. 10 years). It was also suggested that future research should compare additional instrumentation such as screws, plates, and cages against discectomy with or without autograft, before any other comparisons are undertaken.

Comment

With an Oxman score of 6/7 this was considered to be a "higher quality" systematic review and the highest quality systematic review found.

Systematic reviews incorporating recommendations for surgical management.

In March 2006, the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons and Congress of Neurological Surgeons (AANS/CNS) gathered an expert group to perform an evidence-based review of the clinical literature on the management of cervical degenerative spine disease. In 2009 the Journal of Neurosurgery: Spine (volume 11(2)) devoted a whole issue to reporting the results of this effort[405].

Four systematic reviews published in this issue incorporated management recommendations (P. A. Anderson, 2009; Matz et al., 2009; Mummaneni et al., 2009; Ryken, 2009). Their recommendations were designed to inform clinical management BUT fell short of guidelines and standards for clinical practice.

All of these reviews had a common methodology. A 3-class system was used to report the quality of individual primary studies:

- Class I evidence from well-designed RCTs.
- Class II evidence from RCTs with design problems or well-designed cohort studies.
- Class III evidence from case series or poorly designed cohort studies.

Recommendations were formulated based on the evidence *and expert consensus.*

Each recommendation was given a grade for strength based on the quality of the underlying studies. Grading was based on the methods of the Scottish Intercollegiate Guidelines Network (SIGN) and the Oxford Centre for Evidence-Based Medicine (www.cebm.net).

[405] This was not called a guideline it was referred to as a critical summary and synthesis of the current evidence.

In brief, a recommendation based on;

- consistent Class I studies was graded “A”
- a single Class I study or consistent Class II studies was graded “B”
- a single Class II study was graded “C”
- Class III or weaker data, or based on inconsistent data were graded “D.”

The main characteristics of the four systematic reviews and their recommendations relating to specific indication/diagnoses are summarised in Tables 6-10. Each table is followed by a more detailed account in which results and recommendations for specific techniques are included

Anderson 2009 “Laminectomy and fusion for the treatment of cervical degenerative myelopathy”.

Anderson et al (2009) carried out a systematic review[406] to determine the efficacy of cervical laminectomy or laminoplasty (for spinal canal decompression) and posterior fusion for the treatment of cervical spondylotic myelopathy (CSM) and ossification of the posterior longitudinal ligament (OPLL). Practice recommendations were made based on the review evidence (P. A. Anderson, 2009). Table 6.2.6.

Table 6.2.6. Systematic review of fusion or fusion related techniques incorporating recommendations for cervical myelopathy (P. A. Anderson, 2009).

Study Oxman score Included studies	Fusion technique/ Comparator(s	Outcomes [407] measured	Recommendations
Cervical myelopathy			
Anderson et al (2009) 4/7 11 studies (8 case series and 3 comparative studies)	Posterior fusion Anterior fusion Comparator(s) No comparator (8 caser series) Laminectomy Laminoplasty	Nurick scale JOA scale, % recovery subjective symptom reporting gait.	Cervical laminectomy with arthrodesis is recommended in the treatment of patients with cervical spondylotic myelopathy and ossification of the posterior longitudinal ligament. Quality of evidence, Class III; strength of recommendation, D

Eleven studies were identified that reported on outcomes related to cervical laminectomy and fusion; eight were case series and three compared this treatment with other treatment modalities. There was no Class I or II evidence, all studies reviewed provided Class III evidence.

[406] Supported by the AANS/CNS
[407] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR

The three comparative studies reported on the relative effectiveness of laminectomy, laminoplasty compared to various types of fusions techniques. Outcome measures included the Nurick scale (difficulty of walking), the JOA scale (an objective assessment scale quantitating the severity of the spondylotic myelopathy), % recovery, pain and daily activity, subjective symptom reporting and gait. In one study laminectomy and fusion *was superior* to the other techniques, another study reported that fusion did *not add* significantly to neurological outcome[408], in the third study there was *no significant differences* in outcome in patients treated with laminoplasty or laminectomy with lateral mass plate fixation and autogenous grafting. All of these studies had serious flaws.

Eight case series reported on laminectomy and a wide range of fusion[409] techniques and outcome measures[410]. Overall, all eight studies reported positively results for fusion.

This systematic review provided low level evidence that;

- laminectomy and fusion resulted in adequate decompression of both ventral and dorsal aspects of the spinal cord as defined by MRI imaging
- fusion techniques were evolving but that there was inadequate reporting of fusion success in all studies and that there appeared to be high rates of failure.
- follow-up was generally too short
- t**here was no Class I or Class II evidence for any of the indications or techniques examined by this review.**

Authors' conclusion

In conclusion the authors of the review reported that there was consistent Class III evidence that 70–95% of patients show postoperative neurological improvement with an overall recovery ~ 50% of the JOA score deficit. Laminectomy and fusion consistently resulted in ventral and dorsal spinal cord decompression. Insufficient data were available to adequately assess whether fusion occurred, where data were available, radiographic results did not correlate with neurological outcome. Complications related to fixation included hardware failure with loss of alignment, radiculopathy, screw malposition, and the need for a repeated operation. The author's recommendations are given in Table 6.2.7.

[408] There was bias against fusion in this study because of dissimilarity in the treatment groups at baseline.
[409] Including: laminectomy & either wire facet fusion or spinous process plate, French door technique w/onlay bone graft, posterior laminectomy& luque rectangle fixation/fusion., laminectomy & fusion/fixation, laminectomy & wiring/facet fusion, French door laminoplasty & onlay posterior lateral fusion, laminectomy & lateral mass plating, laminectomy & lateral mass fusion/fixation.
[410] Including: Nurick scale, JOA scale, radiography, Harsch scale, Cooper scale.

Table 6.2.7. Practice recommendations arising from a systematic review[411] to determine the efficacy of cervical laminectomy or laminoplasty (for spinal canal decompression) and posterior fusion for the treatment of cervical spondylotic myelopathy and ossification of the posterior longitudinal ligament.

Subject	Recommendation
Indication	Cervical laminectomy with arthrodesis is recommended in the treatment of patients with CSM and OPLL (quality of evidence, **Class III; strength of recommendation, D**).
Technique	Cervical laminectomy with arthrodesis is recommended as an equivalent strategy to laminectomy or laminoplasty for functional improvement in the treatment of patients with CSM and OPLL. There is conflicting data as to whether fusion improves functional outcome relative to laminectomy, with one study showing arthrodesis superior and one showing equivalency (quality of evidence, **Class III; strength of recommendation, D).**
Technique	There is insufficient evidence to indicate whether the addition of cervical fixation improves functional outcome
Timing	There is insufficient evidence to make a recommendation regarding timing of surgery

Comment

This review scored 4/7 (modified Oxman criteria) suggesting that there was a potentially a high risk of bias, putting this review in the lower quality category.

Mummaneni 2009 "Cervical surgical techniques for the treatment of cervical spondylotic myelopathy."

Mummaneni et al (2009) used a systematic review of the literature to compare the efficacy, in terms of patient outcome, of different surgical techniques for the treatment of cervical spondylotic myelopathy (CSM) and to make practice recommendations, Table 6.2.8.

[411] Supported by the AANS/CNS

Table 6.2.8. Systematic review of fusion or fusion related techniques incorporating recommendations for cervical myelopathy (Mummaneni et al., 2009).

Study Oxman score Included studies	Fusion technique/ Comparator(s	Outcomes [412] measured	Recommendations
Cervical myelopathy			
Mummaneni 2009 5/7 33 Class III studies	Anterior cervical discectomy with fusion (ACDF) Anterior cervical corpectomy413 with fusion (ACCF) <u>Comparators</u> Laminoplasty Laminectomy	Odom's criteria Clinical NOS Radiological Functional Patient outcome NOS Fusion rate Nurick scale Pain Daily activity	It is recommended that a variety of techniques be considered in the surgical treatment of CSM including ACDF, ACCF, laminoplasty, laminectomy, and laminectomy with fusion <u>Quality of evidence, Class III; strength of recommendation, D</u>

The techniques assessed included anterior cervical discectomy with fusion (ACDF), anterior cervical corpectomy[414] with fusion (ACCF), laminectomy with and without fusion, and laminectomy. A search identified 33 eligible publications; 8 reporting on the efficacy of multilevel ACDF versus ACCF, 14 reporting on laminectomy compared to anterior surgery, 10 assessing laminoplasty or laminectomy with arthrodesis as compared to anterior surgery, 7 assessed laminectomy versus laminoplasty or laminectomy and arthrodesis. All studies were assessed as Class III evidence.

The review of the evidence suggested that:

- Multilevel anterior cervical discectomy with fusion and anterior cervical corpectomy with fusion offered equivalent treatment strategies and outcomes in the anterior surgical treatment of cervical spondylotic myelopathy.
- If fixation is not used anteriorly, anterior cervical corpectomy with fusion may offer better fusion rates.
- In comparison with laminectomy, 4 of 8 studies indicated better improvement with anterior cervical fusion.
- While three studies showed equivalency, one study showed better improvement with laminectomy.
- Only 1 study compared laminectomy with fusion to anterior cervical fusion in a multi-group comparison. In this study, laminectomy with fusion appeared to provide better results.

[412] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR
[413] Corpectomy is a surgical procedure that involves removing part of the vertebral body
[414] Corpectomy is a surgical procedure that involves removing part of the vertebral body

- Evidence showed equivalency in functional improvement between laminoplasty and anterior cervical fusion.
- The evidence was unclear regarding differences in complication rates between these techniques.
- In comparing posterior techniques, Class III evidence has shown equivalency between laminoplasty and laminectomy/ arthrodesis; however, laminoplasty appears to better preserve range of motion.
- Comparing laminectomy to laminectomy/arthrodesis, both treatment strategies had similar outcomes, but laminectomy was associated with a higher rate of kyphosis.
- Although there was no Class I or II evidence to suggest that anterior cervical fusion , laminoplasty, or laminectomy and arthrodesis are superior to laminectomy alone for cervical spondylotic myelopathy, there was Level III evidence indicating that laminectomy may be associated with late deterioration. Although this may not argue against laminectomy as a means of treatment, especially if there are technical issues in utilizing other techniques, it does argue for consideration of other techniques in younger patients in whom late deterioration may be more likely to develop.

The author's recommendations are summarised in Table 6.2.9.

Table 6.2.9. Recommendations arising from a review of cervical surgical techniques for the treatment of cervical spondylotic myelopathy (Mummaneni et al., 2009).

Indication/technique	Recommendation
Indication Cervical spondylotic myelopathy (CSM)	It is recommended that a variety of techniques be considered in the surgical treatment of cervical spondylotic myelopathy including anterior cervical discectomy with fusion, anterior cervical corpectomy with fusion laminoplasty, laminectomy, and laminectomy with fusion (quality of evidence, Class III; strength of recommendation, D).
Technique Anterior cervical discectomy with fusion/anterior cervical corpectomy with fusion (ACDF/ACCF)	It is recommended that anterior cervical discectomy with fusion or anterior cervical corpectomy with fusion (ACDF or ACCF) be used in patients undergoing multilevel anterior cervical spine decompression for lesions located at the disc level. The use of anterior plate fixation allows for equivalent fusion rates between these techniques (quality of evidence, Class III; strength of recommendation, D)
Technique	If anterior fixation is not used, it is recommended that anterior cervical corpectomy with fusion (ACCF) be considered before anterior cervical discectomy with fusion,(ACDF) because it may provide a higher fusion rate than multilevel anterior cervical discectomy with fusion . It should be understood that the use of ACCF is associated with higher graft failure rates than multilevel anterior cervical discectomy with fusion (quality of evidence, Class III; strength of recommendation, D).
Technique: Anterior cervical discectomy with fusion or anterior cervical discectomy vs. Laminectomy.	There is insufficient evidence to recommend anterior cervical discectomy or anterior cervical discectomy and fusion over laminectomy in the near term because both approaches have produced comparable improvements in the surgical treatment of CSM; however, because of the association of laminectomy with late deterioration, anterior cervical discectomy with fusion or anterior cervical discectomy should be considered for short segment decompression for CSM when technically feasible (quality of evidence, Class III; strength of recommendation, D).
Technique: Anterior cervical discectomy with fusion vs. laminectomy/arthrodesis	There is insufficient evidence to recommend anterior cervical discectomy with fusion over laminectomy/arthrodesis because both approaches have produced comparable improvement in the surgical treatment of CSM (quality of evidence,Class III; strength of recommendation, D)
Technique: Anterior cervical discectomy with fusion and anterior cervical corpectomy with fusion vs. laminoplasty	There is insufficient evidence to make a recommendation of anterior cervical discectomy with fusion or anterior cervical corpectomy with fusion over laminoplasty because both approaches have produced comparable improvement in the surgical treatment of CSM (quality of evidence, Class III; strength of recommendation, D).
Technique: Laminoplasty vs. Laminectomy/Arthrodesis.	There is insufficient evidence to recommend laminoplasty over laminectomy with arthrodesis because both approaches have produced comparable improvement in the surgical treatment of CSM (quality of evidence, Class III; strength of recommendation, D).

In summary, there was no strong evidence (Class I or Class II) to recommend any specific surgical technique (including fusion) for the treatment of cervical spondylotic myelopathy

Authors' conclusions

Overall the authors concluded that:

"A variety of techniques improved [near-term] functional outcome after surgical treatment for CSM, including anterior cervical discectomy with fusion (ACDF), anterior cervical corpectomy with fusion (ACCF), laminoplasty, laminectomy, and laminectomy with fusion (Class III)."

"Multiple approaches exist with similar near-term improvements; however, laminectomy appears to have a late deterioration rate that may need to be considered when appropriate."

Comment

With an Oxman score of 5/7 this was one of the higher quality reviews.

Ryken 2009 "Techniques for cervical interbody grafting."

Ryken et al (2009) reviewed the efficacy of techniques for cervical interbody grafting for cervical degenerative disease. Forty three studies were reviewed. In general, these studies addressed different types of grafting media including autograft, allograft, and xenograft, and a multitude of different interbody prostheses. Articles primarily included data on anterior approaches with a paucity of studies examining posterior fusion[415].

Four systematic reviews were identified for inclusion, two of which have been reported individually earlier in this report (W. Jacobs et al., 2004; van Limbeek et al., 2000). The remainder of the studies selected for inclusion were randomized trials, prospective cohort studies, or large case series reports. Given a large overlap between studies and techniques assessed in this systematic review and other systematic reviews reported in this document the results and recommendations of the review by Ryken at al (2009) are only reported briefly below.

The authors reported Class II evidence indicating that either autograft bone harvested from iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute were excellent interbody treatment options for obtaining cervical fusion.Expected autograft fusion rates are shown in Table 6.2.10.

[415] The lack of studies was no accident or omission, posterior fusion in the neck, because of its movement, was very unreliable.

Table 6.2.10. Expected autograft fusion rates

Technique	fusion rate
Autograft: non-instrumented	
1-level fusion	>80%
2-level fusion	>70%
Allograph: non-instrumented	
1-level fusion	>80%
2-level fusion	>50%
Titanium cage	>70% and often >90% With avoidance of donor site morbidity

If alternatives to autograft and allograft are preferred, therapeutic options were as follows:

- PEEK may be considered with or without the use of hydroxyapatite after anterior cervical discectomy with fusion with an expectation of fusion rates > 90% and with fewer complications due to the absence of graft harvesting (Class III).
- Carbon fibre cages may be considered as well with fusion rates ranging from 55 to 62% in the larger studies (Class III).
- Polymethyl-methylmethacrylate may be considered to preserve intervertebral distraction after discectomy, but is a poor fusion substrate (Class II).

All of the above options appeared to have similar clinical outcomes equivalent to the use of bone.

Recommendations

The evidence based recommendations are given in Table 6.2.11.

Table 6.2.11. Evidence based techniques for cervical interbody grafting: recommendations (Ryken, 2009).

Indication/technique	Recommendation
1- or 2-Level Cervical Discectomy	Autograft bone harvested from iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute, are recommended for use in creating an arthrodesis after 1- or 2-level anterior cervical discectomy with fusion (quality of evidence **Class II; strength of recommendation, C**
Technique: Autograft, Allograft, or Titanium Cage.	Autograft bone harvested from the iliac crest, allograft bone from either cadaveric iliac crest or fibula, or titanium cages and rectangular fusion devices, with or without autologous graft or substitute, are recommended for creating an arthrodesis after 1- or 2-level anterior cervical discectomy with fusion (quality of evidence, **Class II; strength of recommendation, C**
	If alternatives to autograft, allograft, or titanium cages are preferred, several options are recommended including Polyetheretherketone (PEEK) cages, carbon fibre cages, polymethylmethacryate (PMMA), and rhBMP-2. cages may be considered with or without the use of hydroxyapatite for anterior cervical discectomy with fusion . Using hydroxyapatite alone may result in more settling and fragmentation (quality of evidence. **Class III; strength of recommendation, D** Carbon fibre cages are recommended for arthrodesis after anterior cervical discectomy with fusion with fusion rates > 50% (quality of evidence **Class III; strength of recommendation, D**
	The use of PMMA is not recommended as a means to preserve interspace height after anterior discectomy. Although short-term results are similar to those obtained with bone grafts, fusion generally does not occur when PMMA is used as a spacer, and the long-term consequences have not been described (quality of evidence. **Class II; strength of recommendation, B**
	Although rh-BMP-2 promotes fusion with rates equivalent to autograft, its use in the cervical spine carries a complication rate of up to 23–27% (especially for local oedema) compared with 3% for a standard approach. This significant difference prompted a public health notification by the Food and Drug Administration (http://www.fda.gov/cdrh/safety/070108-rhbmp.html). Current evidence does not support the routine use of rh-BMP-2 for cervical arthrodesis. However, the use of rh-BMP-2 may have utility in the context of future studies in patients in whom cervical fusion poses a great technical challenge **Quality of evidence, Class II; strength of recommendation C**

Authors' conclusions

The authors concluded that there were generally high rates of improved clinical outcome with anterior cervical discectomy and fusion, regardless of methodology. However, current evidence did not support the *routine use* of interbody grafting for cervical arthrodesis. Multiple strategies for interbody grafting have been successful with Class II evidence supporting the use of autograft, allograft, and titanium cages.

Comment

There was only one reasonably strong recommendation made following an examination of the evidence reviewed i.e. that relating to the use of PMMA (polymethylmethacryate) which was not recommended as a means to preserve inter-space height after anterior discectomy. Class II; strength of

recommendation, B. This review scored 5/7 using the Oxman criteria for study validity placing it in the higher quality category.

Matz 2009 "Techniques for anterior cervical decompression for radiculopathy."[416]

Matz et al (2009) employed a systematic review to identify the best techniques for anterior cervical nerve root decompression (Matz et al., 2009). The authors noted that during the 1990s[417] there had been a paradigm shift toward inclusion of fusion in the treatment of cervical disc disease and more recently cervical disc replacement (arthroplasty) had been developed as an alternative to fusion.

The authors evaluated (through comparative studies) the performance of anterior cervical discectomy (ACD), anterior cervical discectomy and fusion (ACDF), ACDF and anterior cervical discectomy and anterior cervical plating (ACDFI), dynamic versus static plates, and ACDF versus arthroplasty, Table 6.2.12.

[416] A further study - Matz 2009 "Anterior cervical surgery for the treatment of cervical degenerative myelopathy" failed to report on specifically on fusion.
[417] Cervical fusion has been quite widely performed in NZ since the 80s, personal communication, Gordon Howie, reviewer.

Table 6.2.12. Characteristics and recommendations for evidence based techniques for anterior cervical decompression for radiculopathy (Matz et al., 2009).

Study Oxman score Included studies	Fusion technique/ Comparator(s	Outcomes [418] measured	Recommendations
Matz et al (2009) 5/7 30 studies (RCTs, SRs, studies containing prospective data)	Anterior cervical discectomy and fusion (ACDF) Anterior cervical discectomy and fusion instrumented (ACDFI), Dynamic plates <u>Comparators</u> Anterior cervical discectomy (ACD) Anterior cervical discectomy and fusion (ACDF) Static plates Arthroplasty	Clinical outcomes-VAS pain score, Odum's criteria, McGill Pain Questionnaire, SF-36 and arm pain.	**1-Level Cervical Disc Degeneration.** Both anterior cervical discectomy and anterior cervical discectomy with fusion are recommended as equivalent treatment strategies for 1-level cervical disc degeneration with respect to clinical outcome measures such as VAS pain score, Odom's criteria, the McGill Pain Questionnaire, SF-36, and arm pain. <u>Quality of evidence, Class II, strength of recommendation, C</u> There is conflicting Class II evidence as to whether anterior cervical discectomy with fusion relieves overall neck pain associated with 1-level cervical disc degeneration better than anterior cervical discectomy. **2-Level Cervical Disc Degeneration.** Anterior cervical plating is recommended over anterior cervical discectomy with fusion, to improve arm pain in the treatment of 2-level cervical disc degeneration <u>Quality of evidence, Class II strength of recommendation, C.</u> Plating does not improve other clinical outcome parameters with respect to 2-level disease. **1-Level Cervical Disc Degeneration.** With respect to 1-level cervical disc degeneration, the addition of a cervical plate is recommended if the goal is to reduce the risk of pseudarthrosis and graft problems. <u>Quality of evidence, Class III; strength of recommendation, D</u> and to maintain lordosis <u>Quality of evidence, Class II; strength of recommendation, C</u> but not necessarily to improve clinical outcome alone <u>Quality of evidence, Class II; strength of recommendation, B.</u> Cervical arthroplasty is recommended as an alternative to ACDF in selected patients for control of neck and arm pain. <u>Quality of evidence, Class II; strength of recommendation, B.</u>

Thirty studies met the authors inclusion criteria; ten primary studies and one systematic review examined ACD compared with ACDF, sixteen primary studies and two systematic reviews addressed ACDFI (plating) versus ACDF without plating, and four studies examined the effectiveness of dynamic versus static plating.

The authors of the review found that despite an abundance of studies there was no Class I evidence to assess the efficacy of adding fusion or plate fixation to anterior cervical discectomy. Furthermore, there

[418] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR

was no Class I evidence indicating that arthroplasty[419] was superior to anterior cervical discectomy and fusion.

Class II evidence indicated that anterior cervical discectomy and anterior cervical discectomy and fusion were equivalent treatment strategies for cervical disc degeneration with regard to the clinical outcomes as measured by the VAS, McGill Questionnaire, and Odom's criteria. Two Class II studies demonstrated equivalency for arm pain, and conflicting evidence was demonstrated for neck pain. One Class II study showed equivalence and another Class II study showing anterior cervical discectomy and fusion to be superior.

The time to relief of neck or arm pain was shorter after anterior cervical discectomy and fusion (Class III evidence). The ACDF technique was associated with better fusion (Class II evidence) and avoidance of postoperative kyphosis (Class II evidence).

Class II evidence indicated that plate fixation did not improve long-term outcome in patients with 1-level cervical disc degeneration but did improve arm pain associated with 2-level disc degeneration (Class II evidence).

The results of two Class II and six Class III studies indicated equivalent clinical and functional outcome with or without plate fixation. The use of a cervical plate improved cervical lordosis (Class II), reduces the risk of pseudoarthrosis (Class III), and reduced the incidence of graft-related complications (Class III), but increases surgical blood loss (Class III). Dynamic plate fixation was not shown to increase fusion rates compared to rigid plates (Class III).

The recommendations arising from the review are summarised below by indication.

One-level Cervical Disc Degeneration:

- Anterior cervical discectomy and anterior cervical discectomy and fusion were recommended as equivalent treatment strategies for 1-level cervical disc degeneration with respect to clinical outcome measures such as VAS pain score, Odom's criteria, the McGill Pain Questionnaire, SF-36, and arm pain (quality of evidence, Class II, strength of recommendation, C).
- There was conflicting Class II evidence as to whether ACDF relieved overall neck pain associated with 1-level cervical disc degeneration better than anterior cervical discectomy.
- Anterior cervical discectomy and fusion was recommended over anterior cervical discectomy for a more rapid reduction of neck and arm pain (quality of evidence, Class III; strength of recommendation, D), although functional outcomes may be similar.
- Anterior cervical discectomy and fusion was also recommended over anterior cervical discectomy as a means to reduce the risk of kyphosis and increase fusion rate (quality of evidence, Class II; strength of recommendation, C)

[419] Many of the arthroplasty studies have industry support but still not proven to be better. However, any advantage of arthroplasty over fusion may take ten years to show, by which time the arthroplasties may be disintegrating. Personal communication, Gordon Howie, reviewer.

- Anterior cervical discectomy and fusion was not recommended as a lasting means of increasing foraminal or disc height compared to anterior cervical discectomy (quality of evidence, Class II; strength of recommendation, C).
- Addition of a cervical plate is recommended if the goal was to reduce the risk of pseudarthrosis and graft problems (quality of evidence, Class III; strength of recommendation, D) and to maintain lordosis (quality of evidence, Class II; strength of recommendation, C) but not necessarily to improve clinical outcome alone (quality of evidence, Class II; strength of recommendation, B).

Two-level Cervical Disc Degeneration:

- Anterior cervical discectomy and instrumented fusion was recommended over anterior cervical discectomy and fusion to improve arm pain in the treatment of 2-level cervical disc degeneration (quality of evidence, Class II; strength of recommendation, C).
- Plating did not improve other clinical outcome parameters with respect to 2-level disease.
- Anterior cervical discectomy and instrumented fusion was recommended over ACDF to improve arm pain in the treatment of 2-level cervical disc degeneration (quality of evidence, Class II; strength of recommendation, C).
- Plating did not improve other clinical outcome parameters with respect to 2-level disease.

Author's conclusions

The authors of the systematic review concluded that despite an abundance of studies there were no Class I studies to assess key questions regarding the efficacy of adding fusion or plate fixation to anterior cervical discectomy, and that because there was a substantial number of these procedures performed each year, there was a need for more methodologically rigorous studies with more uniform outcome parameters, standardized follow-up methods and outcome measures which included activity restriction and return-to-work.

Comment

This review scored 5/7 using the Oxman criteria for study validity placing it in the higher quality category.

Evidence Assessment : Guidelines

Two guidelines were identified (Bono et al., 2010; Work Loss Data Institute, 2008b)

The objective of the North American Spine Society (NASS) Clinical Guideline (Bono et al., 2010) was to provide evidence-based recommendations to address key clinical questions surrounding the diagnosis and treatment of cervical radiculopathy from degenerative disorders[420]. Expert consensus was incorporated only where Level I-IV evidence was insufficient and the work group deemed that a recommendation was warranted.

The guideline was intended to reflect contemporary treatment concepts for cervical radiculopathy arising from degenerative disorders as reflected in the highest quality clinical literature available on this subject as of May 2009. The guideline addressed a number of clinical questions relating to the effectiveness of anterior cervical discectomy with fusion and the value of adding instrumentation, and the comparative effectiveness of posterior approaches.

The recommendations were graded as shown below:

A= Good evidence: Level I studies[421] with consistent findings

B= Fair evidence: Level II[422] or III studies[423] with consistent findings

C= Poor quality evidence Level IV[424] or V[425] studies

I= Insufficient or conflicting evidence not allowing a recommendation for or against intervention

A summary of the North American Spine Society (NASS) Clinical Guideline is given below, Table 6.2.13.

[420] Defined as pain in a radicular pattern in one or both upper extremities related to compression and/or irritation of one or more cervical nerve roots.
[421] High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals. Systematic review of Level I RCTs (and study results were homogenous)
[422] Level II: lesser quality RCT (e.g., <80% follow-up, no blinding, or improper randomization), Prospective comparative study. Systematic review of Level II studies or Level 1 studies with inconsistent results. Retrospective study Untreated controls from an RCT. Lesser quality prospective study (e.g.,. patients enrolled at different points in their disease or <80% follow-up).Systematic review of Level II studies. Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard). Systematic review of Level II studies. Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses . Systematic review of Level II studies
[423] Level III • Case control study. Retrospective comparative study. Systematic review of Level III studies
[424] Case series
[425] Expert consensus

Table 6.2.13. Summary of the North American Spine Society (NASS) Clinical Guideline (Bono et al., 2010) questions and recommendations in relation to degenerative cervical radiculopathy.

Question	Evidence	Recommendation	Grade
Does anterior cervical discectomy and fusion (ACDF) result in better outcomes (clinical or radiographic) than anterior cervical discectomy (ACD) alone?	Six RCTs	Both anterior cervical discectomy and anterior cervical discectomy with fusion are suggested as comparable treatment strategies, producing similar clinical outcomes, in the treatment of single level cervical radiculopathy from degenerative disorders	B
	Two RCTs	The addition of an interbody graft for fusion is suggested to improve sagittal alignment following anterior cervical discectomy.	B
Does anterior cervical discectomy and fusion (ACDF) with instrumentation result in better outcomes (clinical or radiographic) than ACDF without instrumentation?	Two RCTs and one retrospective comparative study	Both anterior cervical discectomy with fusion with and without a plate are suggested as comparable treatment strategies, producing similar clinical outcomes and fusion rates, in the treatment of single level cervical radiculopathy from degenerative disorders.	B
	Two RCTs and one retrospective comparative study	The addition of a cervical plate is suggested to improve sagittal alignment following anterior cervical discectomy with fusion.	B
	A review of the literature yielded no studies to adequately compare outcomes for ACDF with and without a plate for multilevel surgeries.	While plate stabilization may be indicated in some patients undergoing multilevel anterior cervical discectomy with fusion, there is insufficient evidence that this practice results in significant improvement in clinical outcomes for degenerative cervical radiculopathy	Work Group Consensus Statement
Does anterior surgery result in better outcomes (clinical or radiographic) than posterior surgery in the treatment of cervical radiculopathy from degenerative disorders?	Two RCTs and one retrospective comparative study	Either anterior cervical discectomy with fusion or posterior laminoforaminotomy are suggested for the treatment of single level degenerative cervical radiculopathy secondary to foraminal soft disc herniation to achieve comparably successful clinical outcomes.	B
		Compared to posterior laminoforaminotomy anterior cervical discectomy is suggested for the treatment of single level degenerative cervical radiculopathy from central and paracentral nerve root compression and spondylotic disease	Work Group Consensus Statement

Question	Evidence	Recommendation	Grade
Does posterior decompression with fusion result in better outcomes (clinical or radiographic) than posterior decompression alone in the treatment of cervical radiculopathy from degenerative disorders?	A systematic review of the literature yielded no studies to adequately compare the outcomes of posterior decompression with posterior decompression with fusion in the treatment of cervical radiculopathy from degenerative disorders. Most decompression and fusion appears to be indicated for multilevel stenosis resulting in myelopathy or for instability due to trauma, tumour, or inflammatory disease. Due to limited indications and thus limited sample size, there is likely little to gain and a low probability of generating meaningful data to compare effects of posterior decompression alone to posterior decompression and fusion for degenerative disease resulting in cervical radiculopathy. No recommendation		
How do long-term results of single level compare with multilevel surgical decompression for cervical radiculopathy from degenerative disorders?	A systematic review of the literature yielded no studies to adequately address the comparison of long term results of single-level compared with multilevel surgical decompression in the management of cervical radiculopathy from degenerative disorders. After this review, it is clear that most patients with true radiculopathy suffer from one level and occasionally two level disease. The incidence of multilevel disease without the additional presence of myelopathy is rare. Thus, there is likely little to gain and a low probability of generating meaningful data to answer this question. No recommendation		

Most of the evidence that was assessed was from RCTs and there were six grade B recommendations.

The addition of fusion to anterior cervical discectomy was not considered to add anything in terms of clinical outcomes (for single level conditions) although the addition of an interbody graft was considered to improve sagittal alignment as was the addition of a cervical plate; the latter was not considered to improve clinical outcomes of fusion.

When single level degenerative cervical radiculopathy was secondary to foraminal soft disc herniation anterior (ACDF) and posterior laminoforaminotomy surgical approaches were reported to have comparably successful clinical outcomes.

Comment

This was a generally well conducted guideline which fulfilled 70% of the AGREE criteria for guideline development and recording. The main shortcomings related to applicability criteria e.g. it was not made clear how the recommendations could be put into practice, resource implications and barriers to their implementation.

Work Data Institute 2008 "Guidelines for the treatment of work related disorders of the neck and upper back"

In 2008 The Work Loss Data Institute published and update of its 2007 guidelines for the treatment of work related disorders of the neck and upper back (Work Loss Data Institute, 2008b). Only a summary of its findings/recommendations was available to the authors of this ACC review.

The Guideline objective was to offer evidence-based step-by-step decision protocols for the assessment and treatment of workers' compensation conditions. The target population was workers with

occupational disorders of the neck and upper back. The major outcomes considered in the development of the guidelines were the effectiveness of treatments for relieving pain and restoring normal function. Preference was given to high quality systematic reviews, meta-analyses, and clinical trials published since 1993, plus existing nationally recognized treatment guidelines from the leading specialty societies.

Forty four interventions and practices were considered in the guideline which included *anterior cervical fusion*. Posterior cervical fusion was considered to be a procedure that was "under study" and was not specifically recommended/covered. Back bracing, post fusion surgery, was also considered to be "under study" and was not specifically recommended.

Comment

There was not enough information in the summary to assess the quality of the guideline.

Best evidence synthesis: systematic reviews and guidelines

Systematic reviews

The systematic reviews of RCTs carried out by a Dutch team (W. Jacobs et al., 2011; van Limbeek et al., 2000) presented the highest levels of evidence, analysis and reporting.

These studies concluded that none of the reported surgical techniques had a clear advantage/was superior to the other i.e. there was no evidence that fusion improved outcome.

It is perhaps worth nothing that this European study may be expected to be free of some of the biases that have been levelled at American studies in this area.

Guidelines

Only one of the two guidelines was reported in full (the North American Spine Society (NASS) Clinical Guideline (Bono et al., 2010)). This guideline provided evidence-based recommendations to address key clinical questions surrounding the diagnosis and treatment of cervical radiculopathy from degenerative disorders.

The best evidence presented and the highest recommendations (Recommendation Grade B i.e. Fair evidence from Level II[426] or level III studies[427] with consistent findings) supported the conclusions reached from an analysis of the evidence from systematic reviews alone.

It was advised that;

- anterior cervical discectomy (ACD) and anterior cervical discectomy with fusion (ACDF) produced similar clinical outcomes
- the addition of an interbody graft and/or a cervical plate could improve sagittal alignment in patients with single level cervical radiculopathy from degenerative disorders, though the clinical significance of the latter was not made clear
- fusion surgery with and without cervical plates produced similar results.

[426] Level II: lesser quality RCT (e.g., <80% follow-up, no blinding, or improper randomization), Prospective comparative study. Systematic review of Level II studies or Level 1 studies with inconsistent results. Retrospective study Untreated controls from an RCT. Lesser quality prospective study (e.g., patients enrolled at different points in their disease or <80% follow-up).Systematic review of Level II studies. Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard). Systematic review of Level II studies. Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses . Systematic review of Level II studies

[427] Level III • Case control study. Retrospective comparative study. Systematic review of Level III studies

Conclusions

A best evidence synthesis of the highest quality systematic review (W. Jacobs et al., 2011; van Limbeek et al., 2000) and the North American Spine Society (NASS) Clinical Guideline (Bono et al., 2010) concluded that there was no evidence that fusion improved outcome for cervical degenerative disc disease or cervical radiculopathy from degenerative disc disease.

Appendix I: comparative table of systematic reviews

Key features and findings of standard systematic reviews of surgical treatment/fusion surgery for degenerative cervical disease.

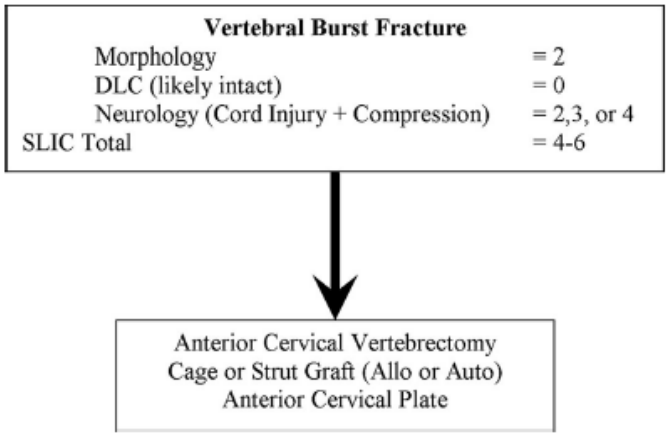
Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [428]	Conclusions
Degenerative disc disease				
Van Limbeek et al (2000) 5/7	3 good RCTs[429] Van den Bent et al (1996) Martins (1976) Savolainen et al (1998)	Anterior cervical interbody fusion with either polymethylmethacrylate, Clowerd fusion with an iliac crest graft, Smith-Robinson or Caspar plating Comparator Discectomy	Fusion (radiological) Kyposis (radiological) Clinical (questionnaires)	With fusion rates varying between 28% and 63% and clinical outcomes of between 67%-82% (which were not always in favour of fusion with instrumentation), none of the reported techniques had a clear advantage in terms out radiographic and clinical outcomes and the reviews authors concluded that none of the techniques provided a gold standard for treatment of degenerative disc disease.
Jacobs 2011 (Cochrane review update) 6/7	33 RCTs With flaws (19 new studies)	AIF with Bone graft (allo/auto) Cage Cement Plate Comparator(s) Discectomy Discectomy	Complications Fusion rate VAS pain (arm, neck) Satisfaction SF 36 (physical and mental) Odom's criteria Recovery Return to work Muscle power JOA Headache	For reduction of pain in patients with cervical degenerative disc disease or disc herniation, the authors of this Cochrane review found no superior treatment. It was unclear what patients, if any, benefit from cervical fusion as opposed to discectomy alone. In most studies and for most outcomes, discectomy was not statistically different from fusion by any technique, and there are no clear differences among fusion techniques.
Subaxial (below C2) cervical spine injury				
Dvorack et al (2007) 3/7	26 articles (level I =1, level II=3, level III=7, Level IV= 15)	Anterior fusion Posterior fusion Circumferential fusion Comparator(s) Anterior fusion Posterior fusion	Not specified	Burst or compression injuries and distraction injuries were more likely to be treated with a single anterior approach, whereas the more severe translation or rotation injuries were more commonly approached from the posterior or with combined anterior and posterior surgery. 1 high quality RCT, 1 low

[428] These are the outcomes reported in the individual studies, they were not necessarily detailed or reported in the SR
[429] There were eight eligible RCTs however five failed to meet strict the strict methodological requirements of the review.

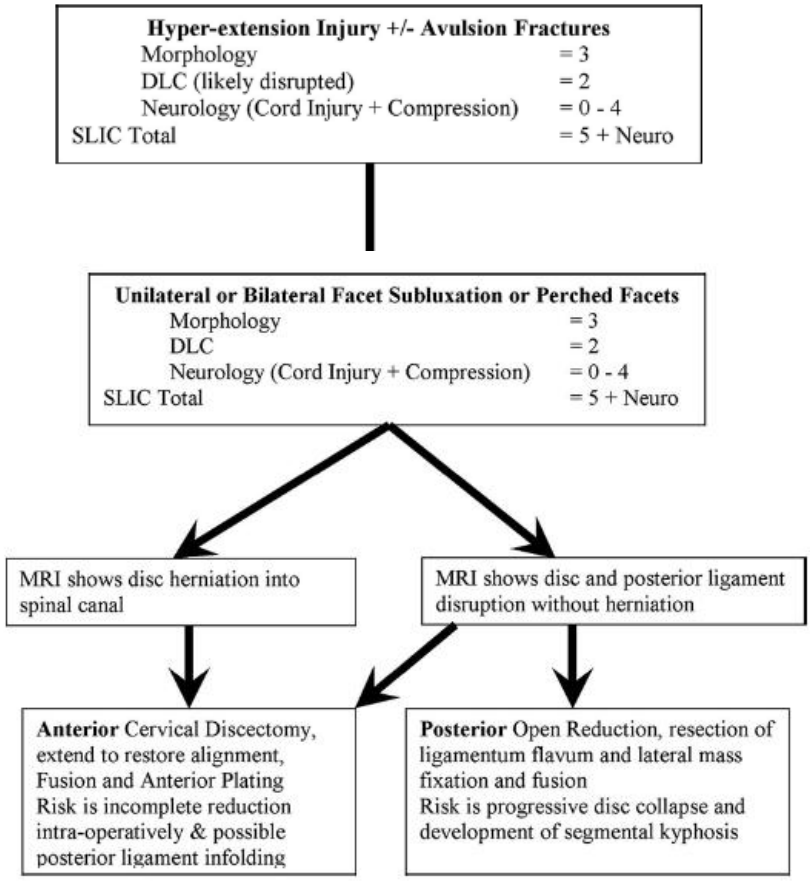
Study Quality/ Oxman score	Studies	Fusion technique Comparator(s)	Outcomes [428]	Conclusions
		Circumferential fusion		quality RCT, 2 higher quality comparative studies, 7 lower quality comparative studies.
Cervical spondylotic myelopathy				
Cunningham et al (2010) 3/7	11 retrospective cohort studies 3 case series with >10 years FU	ACDF (fusion) Comparator(s) Corpectomy+ fusion ACD + fusion Laminoplasty Laminectomy+ fusion	JOA score Nurick score recovery rate secondary spondylosis neck ROM axial neck pain sagittal alignment operative complications.	All of the surgical approaches reviewed yielded similar neurological recovery rates. Overall laminoplasty a treatment for CSM has fewer complications, possibly greater ROM and similar neurological recovery compared with ACDF, multilevel corpectomy and laminectomy but has a higher incidence of bothersome neck pain.

ACD= anterior cervical discectomy. ACDF= anterior cervical discectomy and fusion.. JOA=Japanese Orthopaedic society. ROM= range of motion.

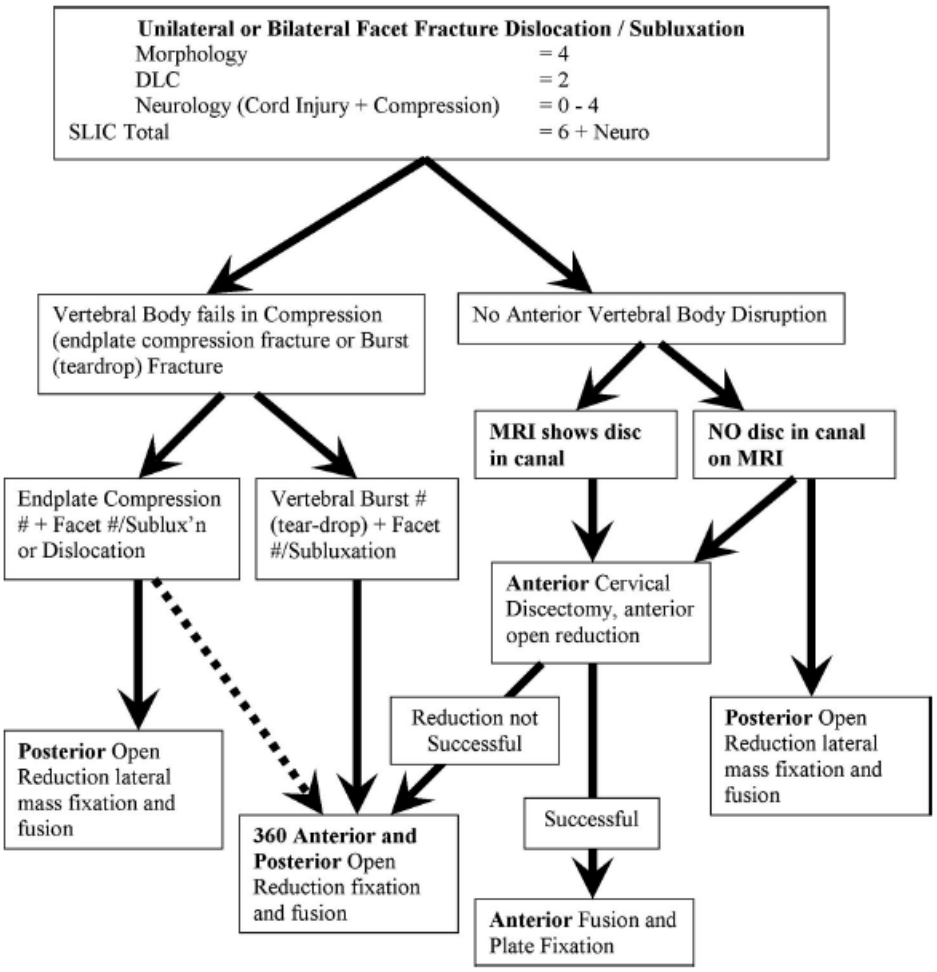
Appendix II : treatment algorithms for cervical injury



Distraction injuries



Translation/rotation injuries



Section 6.3: Adjacent segment disease

Background

This section focuses on the consequences of fusion surgery for adjacent spinal segments.

The degeneration that develops at mobile segments above or belowstrea fused segment is known as adjacent segment disease (ASD) (Auerbach & Balderston, 2005). Higher mechanical demands on the adjacent spinal segment following spinal fusion or arthrodesis are thought to lead to hypermobility and increased intra discal pressure in spinal units above and below the fused units. This is in turn is thought to lead to progressive, degenerative radiographic changes in the adjacent segments (Smith & Kang, 2004).

ASD was first noted over 50 years ago in case reports as a relatively unusual late complication of lumbar or lumbosacral fusions (C. E. Anderson, 1956). Since then, ASD has been found in many patients following fusion and is now considered a *potential long-term complication* of spinal arthrodesis (fusion). The significance of ASD is that it can necessitate further surgery and adversely affect functional outcomes of the original fusion; with the increasing number of spinal fusions being performed this is a real concern (P. Park, Garton, Gala, Hoff, & McGillicuddy, 2004).

The *belief* that ASD[430] is *causally* linked to the fusion treatment carried out in the adjacent vertebral segments has served as an impetus for the development and marketing of motion-preserving alternatives for the treatment of degenerative disc disease (DDD). The most noteworthy of these is total disc replacement (TDR) or arthroplasty which is a more recent and costly treatment for DDD (Auerbach & Balderston, 2005). The possibility that ASD is a long-term consequence of spinal fusion is also a major health concern in *young* patients undergoing surgical correction/treatment for a range of spinal conditions. Not surprisingly, adjacent segment disease is currently of great interest.

The existence of a causal link between ASD and vertebral fusion treatment has been questioned and hotly debated[431]. The question has arisen as to how much degenerative in a particular segment is intrinsic i.e. due to natural degeneration at that segment, and how much is extrinsic i.e. caused by fusion of an adjacent segment? Opponents of the latter argue that changes in segments adjacent to the fusion site reflect the *natural course* of an individual's spondylotic condition. Thus controversy exists in the literature as to whether adjacent segment degeneration (ASD) is a biomechanical by-product of the original fusion/arthodesis or represents the natural history of the ageing spine (Smith & Kang, 2004).

[430] ASD will be used when speaking generically,
[431]. A recent review of the content of Spine a foremost international journal, revealed 93 articles focussed on the topic.

Definitions

Adjacent segment disease is generally defined by a combination of clinical symptoms and morphologic findings.

A distinction has been made in the literature between adjacent segment *degeneration* (ASDeg) defined as *asymptomatic radiographic changes* of degeneration at levels adjacent to a spinal fusion, and adjacent segment *disease* (ASDis) defined as development of *new symptoms* correlating with adjacent segment degeneration (Cheng, Maiman, & Chambers, 2003; Harrop et al., 2008).

Not all studies make this distinction and it is often difficult to determine the clinical significance of their finding.

Occurrence and clinical consequences

Long term clinical outcome studies of patients undergoing anterior *cervical fusion* suggest that approximately 3% experience symptomatic ASD, and predict that 25% of patients undergoing fusion will experience new disease requiring further surgical intervention in adjacent segments within 10 years (Alan S. Hilibrand & Robbins, 2004).

Scott-Young et al (2006) reported that the incidence of ASDeg after lumbar fusion in Australian patients ranged between 5 and 100% and the incidence of lumbar ASDis ranged between 5 and 18% (Scott-Young, 2006). However, not all studies concur with these figures. Wai et al (2006) using MRI imaging performed 20 years after anterior lumbar instrumented fusion (ALIF) found that that the majority of degenerative changes occurred at levels distinct from the fusion (Wai, Santos, & Morcom, 2006). Furthermore, a *natural history analysis* of ASDeg in a *non-surgical population* carried out by Hassett et al (2003) found that ASDeg progressed naturally at an incidence of 3-4% per annum (Hassett, Hart, & Manck, 2003); a rate that is not too dissimilar to that reported for patients who have undergone fusion (Harrop et al., 2008).

Long-term follow up of cervical and lumbar and cervical fusions procedures have suggested that, whatever the aetiology, ASD is most common;

- above lumbar fusions
- below thoracolumbar scoliosis fusions
- above and below anterior cervical fusions: single level fusions with advanced degenerative changes at adjacent level appears to be at greatest risk [432]

Clinical problems/consequences of ADS as reported by Farcy (1999) include facet joint arthrosis, segmental instability, spinal stenosis, accelerated disc degeneration and spondylolysis acquisita. The definition of these abnormal processes often varied between studies. The frequency of these problems have been reported by Park (P. Park et al., 2004) with disc degeneration reported as the most frequent finding, Table 6.3.1.

[432] Instrumented Fusion for Idiopathic Scoliosis: Review of Current Trends and Controversies Ilharreborde, Brice MD* †; Morel, Etienne MD* †; Mazda, Keyvan MD, PhD†; Dekutoski, Mark B. MD*

Table 6.3.1. Abnormal processes observed at the adjacent segment after spinal fusion (P. Park et al., 2004).

Finding in adjacent disc	Frequency
Disc Degeneration (Loss of Disc Height, Disc Space Narrowing)	***
Listhesis (anterolisthesis,retrolisthesis)	**
Instability	**
Herniated nucleus pulposus	**
Stenosis	**
Hypertrophic facet arthritis	**
Osteophyte formation	*
Scoliosis	*

*** most commonly reported, ** commonly reported, * least commonly reported

Methods

For a comprehensive description of the searches carried out for this review and the reporting methods see the General Methods section. Briefly, a systematic search of the literature for high evidence level studies and overviews (systematic reviews, meta-analyses and clinical guidelines) reporting on the consequences for adjacent segments of spinal fusion surgery was carried out.

Eligible systematic reviews were required to have carried out (a) systematic searches of the relevant literature and (b) an explicit analysis of the quality of the reported evidence (or minimally reported of the level of evidence provided for each study). Guidelines were required to make treatment/management recommendations and be underpinned by systematic reviews.

In addition to searching bibliographic databases such as Medline and Embase for guidelines, the following sources/websites were searched for recent (2005 onwards) evidence based guidelines reporting substantially on fusion surgery:

American Academy of Orthopaedic Surgeons (AAOS)

American Society of Neuroradiology (ASN)

American Society of Spine Radiology

Guidelines International Network (GIN)

Institute for Clinical Systems improvement (ICSI)

Medical Services Advisory Committee

National Health and Medical Research Council (NHMRC)

National Institute for Health and Clinical Excellence (NICE)

New Zealand Guidelines Group (NZGG)

NHS Evidence

North American Spine Society (NASS)

Scottish Intercollegiate Guidelines Network (SIGN)

TRIP database

World Health Organisation (WHO)

Clinical guidelines were originally intended to be a key resource in the current overview undertaken for the ACC. However, as noted in the two related reports of the effectiveness of lumbar and cervical spinal fusion, critical reviews of American guidelines have claimed biased reporting due to conflicts of interest in some guidelines and in the current overview systematic reviews provide the primary evidence source.

Quality assessment

Systematic reviews identified for this report were also reported and assessed for quality in the recent 2009 APS guidelines. Given the volume of literature and the limited time and resources available for the current review, adoption of these APS quality scores (rather than a re-analysis of the reviews using the designated tool[433]) was felt to be prudent. Additional systematic reviews not covered by the APS guidelines were assessed using the same tools.

The internal validity (quality) of the systematic reviews underpinning the APS guideline was assessed using a checklist based on criteria developed by Oxman and Guyatt (Oxman & Guyatt, 1991). The concept behind the Oxman criteria is fairly simple – the greater the scientific quality (methodological rigour), the more likely an overview/systematic review is to avoid bias, and its finding reflect the truth regarding, for instance, the magnitude of the effect of a treatment.

Using the Oxman criteria each study was scored between 1 and 7 based on the comprehensiveness of the search strategy, application of pre-defined inclusion criteria to select studies, appropriate assessment of validity (quality) and use of appropriate methods to synthesize the evidence. Using this system, systematic reviews with a score of four or less were considered to have potential major flaws or biases (which are more likely to produce positive conclusions about effectiveness) and were classified as "lower quality" systematic reviews. Systematic reviews with scores of five or more were considered to be "higher quality" with less potential for bias and a higher likely hood of valid results.

The internal validity of RCTs was assessed using the SIGN 50 checklist 2 for randomised controlled trials[434].

[433] See protocol
[434] SIGN 50 A guideline developer's handbook - Annex C Methodology Checklist 2 Randomised Controlled Trials.

Search results

Forty one potentially eligible publications were identified. Following an examination of the titles and abstracts, 16 were eliminated as not relevant and the remaining 25 publications were examined in full.

One relevant systematic review (Harrop et al., 2008) and literature review using a systematic search strategy[435] (P. Park et al., 2004) was identified.

The ACC brief for this work required that the search procedure for the current review to identify scientific overviews such as systematic reviews and guidelines, rather than primary research studies. However, when examining the literature relating to adjacent segment disease (ASD) it became clear that the *first RCTs* addressing the problem of ASD were published shortly *after* the only eligible fully systematic review (Harrop et al., 2008) which only included/reviewed low level studies. These recent RCTs (Ekman, Möller, Shalabi, Yu, & Hedlund, 2009; Kelly, James, Frisch, & Tay, 2011; D. Park, Lin, & Phillips, 2010; Videbaek, Egund, Christensen, Grethe Jurik, & Bünger, 2010) were considered to be of particular importance and were reviewed.

No clinical guidelines were identified.

[435] It is not clear if this was a full systematic review , a quality assessment of individual studies does not appear to have been undertaken – however all studies were reported to be retrospective and the general of level of evidence that they offered was reported.

Systematic reviews

Two reviews were identified and assessed (Harrop et al., 2008; P. Park et al., 2004).

Park et al (2004) "Adjacent segment disease after lumbar or lumbosacral fusion: Review of the literature."

Park et al (2004) carried out the first comprehensive review[436] of the scientific literature relating to adjacent segment disease after *lumbar or lumbosacral fusion*.

In this publication the definition, aetiology, incidence, and potential risk factors contributing to ASD were reviewed following a systematic search of the literature. The quality of individual studies was not reported, though a general statement in the author's conclusion suggested that all of the reviewed studies were retrospective Class III studies (i.e. low level evidence regardless of quality).

Over 70% (16 of 22) of the studies reviewed by Park et al (2004) were also included in the systematic review by Harrop et al (2008). Given the methodological uncertainties[437] around the Park review, and a substantial study overlap with the later systematic review (Harrop et al., 2008), this study is reported only briefly for comparison and completeness.

In an examination of the published definitions of ASD, Park et al (2004) noted that the term had been used to describe almost *any* abnormal process that develops in the mobile segment next to a spinal fusion. Biomechanical stresses (particularly facet loading) and increased mobility of the adjacent segment were reported to play a key role in the development of ASD. Intradiscal pressure was also reported to increase in the disc immediately neighbouring a fused segment, and it was suggested that this could lead to disc degeneration/accelerated disc degeneration. The most commonly reported adjacent disc abnormalities were those relating to disc degeneration.

Few studies were found that evaluated the effect of biomechanical and pressure changes on the *development* of ASD. In vivo animal studies suggested that the fusion process was responsible for ASD, but clinical studies were contradictory. Some investigations concluded that ASD was a consequence of the normal aging process, noting that, spinal fusion was usually indicated for patients with *severe degenerative disease that was unlikely to be restricted to the fused segments*.

A number of comparative studies with age and gender matched controls were reported that showed no significantly higher ASD at follow-up[438] in the group undergoing fusion surgery; one case control study reported significantly high rates of ASD in segments adjacent to fused segments. These studies were not assessed for quality and there was considerable between-study-heterogeneity in terms of surgical techniques, patient population and other key variables which makes comparisons difficult.

[436] This was a review based on a systematic search of the literature rather than a systematic review. EX = exercise group.
[437] Lack of overt quality assessment of the included studies.
[438] The significance of this will depend on the length of the follow-up.

The incidence of ASD was calculated from data provided by 22 studies. The incidence of *asymptomatic* ASD (based on radiographic findings) varied from 8-100%, the incidence of *symptomatic* ASD ranged from 5.2-18.5%. Age was the most reported risk factor for ASD.

Author's conclusions

Biomechanical alterations are likely play a primary role in causing adjacent segment disease. Radiographically apparent, asymptomatic adjacent segment disease is common but does not correlate with functional outcomes. Potentially *modifiable* risk factors for the development of adjacent segment disease include fusion without instrumentation, protecting the facet joint of the adjacent segment during placement of pedicle screws, fusion length, and sagittal balance. Surgical management when indicated consists of decompression of neural elements and extension of fusion. Outcomes after surgery, however, are modest.

Comment

This was a low quality review of low quality studies susceptible to biased outcomes with variable definitions of instability. Some of the fusion techniques used were out-of-date and thus combining the evidence from these studies with those reporting more recent techniques throws doubt on the overall validity of the author's conclusions.

Harrop et al 2008 "Lumbar adjacent segment degeneration and disease after arthrodesis and total disc arthroplasty".

Harrop et al (2008) carried out a systematic review of the published incidence of adjacent segment degeneration (ASDeg) and adjacent segment disease (ASDis) after lumbar segment fusion or lumbar disc replacement. The purpose of the review was to assess the impact of surgery method and other factors on the incidence of ASDeg and ASDis.

No randomised controlled trials were identified at this time. Twenty seven non-randomised comparative studies were identified and assessed, 17 studies had contemporaneous controls (Grade III [439] evidence), and 10 had historical controls (Grade IV evidence)[440].

Nineteen of the 27 studies (70%) reported on the incidence of ASDeg, 16 of the 27 studies (59%) reported on the incidence of ASDis. The most recent studies were published in 2006. Twenty studies reported primarily on lumbar fusion using a *variety of surgical techniques*.

Thirty four percent (314 of 926) of patients undergoing fusion developed **ASDeg** compared to 9% (31 of 313) of patients undergoing disc replacement (P<0.001). Fourteen percent (173 of 1216) of patients undergoing fusion developed **ASDis** compared to 1% (7 of 595) of patients undergoing disc replacement

[439] Sackett 1986: Level I: Large randomized trials with clear cut results (and low risk of error). Level II : Small randomized trials with uncertain results (and moderate to high risk of error). Level III: Nonrandomized, contemporaneous controls Level IV: Nonrandomized, historical controls. Level V: No controls, case-series

[440] Sackett 1986: Level I: Large randomized trials with clear cut results (and low risk of error). Level II : Small randomized trials with uncertain results (and moderate to high risk of error). Level III: Nonrandomized, contemporaneous controls Level IV: Nonrandomized, historical controls. Level V: No controls, case-series

(P<0.0001). The results of an analysis[441] to determine the predictors of ASD are shown in Table 2, which gives the ratio of the odds of an event occurring in one group to the odds of it occurring in another group (odds ratio). The odds ratio is a useful measure of effect size and describes the strength of association between adjacent segment degeneration or disease and a variable such as surgical technique. An odds ratio of 1.0 indicates that the condition or event under study is equally likely in both groups, an odds ratio greater than 1 indicates that the condition or event is more likely in the first group, an odds ratio less than 1 indicates that the condition or event is less likely in the first group.

Table 6.3.2. Predictors of adjacent segment degeneration and disease.

Variable	Odds Ratio for ASDeg (95% CI)	P	Odds Ratio for ASDis (95% CI	P
Surgical technique (total disc replacement vs spinal fusion)	2.55 (1.50-4.51)	0.0008	17.69 (8.12-44.19)	0.0000
Gender (% male)	1.20 (0.49-2.88)	0.6771	3.07 (1.63-6.33)	0.0019
Older mean age	20.45 (7.62-55.65)	<0.0001	0.47 (0.11-1.66)	0.2621
Longer follow-up	2.98 (1.46-6.08)	0.0025	0.25 (0.05-0.85)	0.0453

The authors concluded that higher odds of ASDeg were associated with;

- older patients442
- fusion surgery
- longer follow-up.

Higher odds of ASDis were associated with;

- fusion
- higher % of male patients
- shorter follow-up[443].

The type of surgery had the greatest impact on the incidence of ASDis; disc replacement appeared to have the greatest impact on reducing the incidence of ASDis. The length of follow-up had a significant effect on the incidence of ASDis; the longer the follow-up the greater the chance of developing ASDis (P=0.0453).

[441] Multivariate logistic regression.
[442] In one study (Borden et al 1990) an increased risk of ASDeg was reported in the age range 50-55 years.
[443] I do not think this follows fro m the data – have I lost the plot?

It is interesting to note that the authors of the systematic review found a trend towards the development of ASDeg ($p<0.08$) as the quality of the studies *worsened* from level III to level IV and a significant trend in the opposite direction for ASDis ($P<0.0001$).

Authors conclusions

Analysis of the literature suggests a correlation between fusion and the development of ASDeg compared to arthroplasty, but this association is dampened by the influence of patient age. There is a stronger correlation between fusion and ASDis compared to arthroplasty. The data supports only class C recommendation (lowest tier) for the use of arthroplasty rather than arthrodesis to reduce ASDis and disc degeneration.

Comment

This systematic review was methodologically weak (Oxman score of 4/7). As reported, the study appeared to have the potential for selection bias due to a weak search strategy and unclear inclusion criteria. Most of the included studies provided a *low level of evidence by design* and had relatively short follow-up. The combining of a large number of very heterogeneous studies with a multiplicity of fusion techniques is also a weakness of the review. It is not clear, if fusion patients were older or had more advanced disease than the comparison populations (disc replacement patients).

Recent randomised controlled trials (2009-20011)

The preceding methodologically weak systematic review of low level studies does not provide convincing evidence one way or another regarding the relationship between fusion surgery and ASD. Higher quality studies are required.

In 2009 the *first study of randomised patients* to examine the relationship between fusion (lumbar fusion) and degenerative changes was published.

At least three other studies focussing on ASD in patients participating in RCTs were published in 2010-2011 (Kelly et al., 2011; D. Park et al., 2010; Videbaek et al., 2010). The main characteristics of each of these RCTs are summarised in Table 6.3.3.

Table 6.3.3. The main characteristics of randomised studies of adjacent segment disease following fusion.

RCT SIGN internal Validity score	Primary aim	Assessment method	Surgical methods Comparator(s)	Indication(s)	Mean FU
Ekman 2009 N= 111 **LUMBAR** 5/10	To compare the rates of ASD in fused and non-fused patients (natural history)	Standard A-P and lateral radiographs.	Posterolateral fusion with autologous bone grafts (iliac crest harvest) Comparator Exercise	Isthmic spondylolisthesis	12.6 years Min=10 years
Videbaek 2010 N=148 **LUMBAR** 4/10	To analyze long-term adjacent segment degeneration (ASD)	Radiographs and MRI	Anterior lumbar interbody fusion combined with posterolateral lumbar fusion (ALIF +PLF) Comparator Posterolateral fusion (PLF)	Disc degeneration (73%) Spondylolisthesis	Median 9.8 (8.1–13.0)
Kelly 2011† N=209 **CERVICAL** 6/10	To compare the effect of fusion and investigator Arthroplasty on post-operative adjacent level ROM	Flexion and extension radiographs	Anterior cervical discectomy and fusion Comparator Arthroplasty (single level total disc replacement)	Single level cervical degenerative disc disease	2 years
Park 2010† N=454 **CERVICAL** 5/10	To assess the in vivo kinematics of the cervical spine after fusion and arthroplasty	Neutral, flexion and extension radiographs	Anterior cervical discectomy and fusion Comparator Arthroplasty (single level total disc replacement)	Single level cervical radiculopathy or myelopathy	1 year

† Post-hoc analysis of the FDA trial (IDE #G030059). ACDF = anterior cervical discectomy and fusion, ALIF= anterior lumbar interbody fusion, PLF= posterior lumbar fusion, A-P anterior-posterior, ROM=range of motion, ASD=adjacent segment disease.

These studies examined the effect of fusion in patients with lumbar and cervical indications separately. All studies were all carried out as follow-up studies in patient who participated in trials designed for other purposes, mostly treatment comparison trials. One of the biggest problems with these studies was the high number of patients lost to follow-up from the original trial population thus compromising the initial randomisation and increasing substantially the risk of selection bias. Another difficulty with these studies was the lack of blinding which necessarily accompanies most surgical studies. As a consequence, these studies generally scored poorly for internal validity (range 4/10 to 6/10). The recently published trial reported by Kelly et al (2011) had the highest score of 60% for internal validity.

Lumbar fusion

Ekman 2009 "A prospective randomised study on the long-term effect of lumbar fusion on adjacent disc degeneration."

Ekman et al 2009 set out to determine whether fusion compared with natural history resulted in accelerated degenerative changes at the adjacent segment in patients with *isthmic spondylolisthesis*. Other aims were to determine (a) the long-term prevalence of ASD, (b) the clinical significance of ASD, and (c) the effect of instrumentation in instrument aided fusion.

Patients with *isthmic spondylolisthesis* were randomised to exercise (N=34), or posterolateral fusion (PLF, N=77), with (N=37) or without (N=40) pedicel screw instrumentation. The minimum 10 year follow-up rate was 72% and the mean follow-up time was 12.6 years (range 10-17 years).

Outcome measures included questionnaires concerning functional disability (Disability Rating Index (DRI) and the Oswald Disability Index (ODI)), pain (VAS) and global outcome compared with pre-treatment situation (much better, better, unchanged, worse).

ASD at long-term follow-up was determined by disc height reduction, worsening of the University of California Los Angeles (UCLA) grading score for disc degeneration and totally reduced posterior disc height (0 mm). Subgroup analyses were carried out of (a) patients who received instrumentation versus those who did not, and (b) patients who underwent laminectomy versus those who did not.

Adjacent segment disease was measured/determined/defined in a variety of ways, Table 6.3.4.

Table 6.3.4. The determination/measurement of adjacent segment disease

ASD determined as	Prevalence in the control group	Prevalence in the Fusion group
Posterior disc height reduction more than 2 standard deviations below the mean, as observed in the exercise (control) group	6% (1/17)	14% (9/63)
Remaining mean disc height less than 20% of anterior vertebral height	6% (1/17)	11% (7/63)
Any deterioration of the UCLA grading scale	0%	38% (24/63)

Instrumentation did not appear to affect the prevalence of ASD using any of the study definitions of ASD. Patients with sciatica underwent PLF with laminectomy and decompression. Prior to surgery there were no differences in disc height between the laminectomy and non-laminectomy groups. Following surgery with posterior lumber fusion and laminectomy 22/47 patients developed ASD (defined by UCLA criteria grade 2-4), only 2/6 patients who did not have a laminectomy developed ASD (p=0.015). Measurements of pain, disability and global outcome were insignificantly worse for patients who had ASD (by any of the study definitions).

Authors' conclusion

The authors concluded that fusion, particularly when combined with laminectomy, accelerated ASD (as measured). They also concluded that clinical importance of ASD was limited, with only the more severe forms affecting the outcome.

Comment

This single centre RCT was not of the highest quality, although some of the flaws were unavoidable e.g. lack of blinding, only 72% of the original randomised patients were available for follow-up (mean follow-up time 12.6 years). The most significant weakness was the small number of patients in the sub-group analysis which contributed most to the association of fusion with ASD

Videbaek 2010 "Adjacent Segment Degeneration After Lumbar Spinal Fusion: The Impact of Anterior Column Support: A Randomized Clinical Trial With an Eight- to Thirteen-Year Magnetic Resonance Imaging Follow-up."

Videbaeck et al 2010 reported the results of a second follow-up study of randomised patients which was designed to;

- analyse long-term adjacent segment disease (ASD) after lumbar fusion and compare randomised groups treated with anterior column support combined with posterolateral lumbar fusion (ALIF+PLF) and without anterior column support (PLF),
- study a possible correlation between ASD and clinical outcome.

The original RCT of 148 patients with severe chronic low back pain demonstrated that anterior lumbar interbody fusion combined with posterolateral lumbar fusion (ALIF +PLF) was superior to posterolateral fusion (PLF) alone in terms of both outcomes and cost.

Ninety-five patients (64%) participated in the follow-up study (Videbaek et al., 2010). The presence of ASD was determined using magnetic resonance imaging for signs of disc degeneration, disc herniation, stenosis, and endplate changes. Disc heights on radiographs taken at index surgery and at long-term follow-up were compared. Outcome was assessed by validated questionnaires. The follow-up rate was 76%.

Table 6.3.5. Radiological and clinical outcomes for patient randomised to exercise or fusion surgery for isthmic spondylolisthesis (Videbaek et al., 2010)

Group	Radiological outcome measures				Clinical outcome measures		
	ASD[444] a,b,c,d	RDM 1-4‡ EX vs PLF	QMA 1-4¶	UCLA Grade 1=normal *P=0.026	Global Outcome and disc degeneration	Pain Index (VAS)	Functional Disability (DRI, ODI)
Randomised treatment groups							
Exercise for 1 year	6%, 6%, 0%, 0%	Between group P RDM1= 0.0098 RDM2= 0.0079 RDM3=0.0016 RDM4=0.64	Between group P QMA1=ns QMA1=ns QMA1=ns QMA1=ns	Grade 1= 17*	ns †	ns†	ns†
PLF lumbar brace for 6 months	14%, 11%, 38%, 6%†			Grade 1= 39* Grade 2= 11 Grade 3= 12 Grade 4= 1			
PLF + pedical screw instrumentation							
PLF (± instrumentation)‡							
Sub-set treatment group							
Laminectomy and decompression (sciatica pts)	(c) 47%	P=0.015§					
No laminectomy no decompression (remaining pts)	(c) 12.5%						

NSD=no significant difference. † Instrumentation did not affect the prevalence of ASD using any definition of ASD. ‡ as there were no difference between the instrumented and non-instrumented PLF groups they were combined to improve statistical power.§ using other measures of ASD (a,b,d) differences between these groups were not significantly different.‡ RDM1= radiological digital method anterior disc height, RDM2= radiological digital method posterior disc height, .‡ RDM3= radiological digital method mean disc height, .‡ RDM4= radiological digital method sagittal translation. ¶QMQ1= anterior disc height, QMA2= posterior disc height, QMA3 =disc angle, QMA4-sagittal translation. †insignificantly worse for patients with ASD

Eighty-nine percent of all participants had some sort of MRI evidence of ASD, primarily disc degeneration and herniation. Both randomized groups (ALIF + PLF and PLF alone) were similar with

[444] Defined as a) posterior disc height reduction more than 2 SD below the mean as observed in the exercise group, b) a remaining mean disc height less than 20% of anterior vertebral height c) any deterioration in the UCLA scale, d) totally reduced posterior disc height.

regards to ASD. A sub-group analysis of patients according to diagnosis (disc degeneration (n =69) or spondylolisthesis (n =26)) did not demonstrate any significant difference in MRI parameters between the groups at any level.

Because of the lack of MRI at the time of index surgery, the *best estimate of degeneration* at trial entrance was a subjective evaluation of the disc height observed on radiographs. This was compared with MRI at the time of the follow-up. Normal disc height, at all of the levels evaluated, was found at index surgery *and* follow-up in 39 patients. Normal disc height, at all levels evaluated, at index surgery *but reduced height at follow*-up was seen in 37 patients. Reduced height at index surgery with further progression at follow-up was found in 9 patients.

Overall, 39 (46%) patients had no disc height reduction over time. Comparing patients with no disc height reduction at any level and patients with disc height reduction at a minimum of 1 level (n = 46, 54%), the authors found the group with no disc height reduction to be significantly younger (mean age, 55 years (28–69 years) *vs.* 59 years (43–77 years)). The significantly younger mean age in patients with no disc height reduction supported the claim that age is a risk factor for ASD.

Authors' conclusions

The authors concluded that the degree of ASD at long-term follow-up was similar in the randomization groups. Without a control group it could not be determined if ASD was accelerated in the randomised study groups (exercise versus fusion) in comparison with the expected *natural degenerative process*. However, following a review of the literature, the authors suggested that *it was possible* that the degenerative changes found at the adjacent levels were *in concordance with the expected degenerative changes in a non-operated symptomatic population of the same age as the group studied*. As a consequence, alternative surgical treatments (e.g. disc prosthesis and semi-rigid devices) should not be chosen rather than fusion only because of concern for accelerated ASD.

Comment

This was a well conducted randomised trial follow-up study that had some quality issues (SIGN quality score of 40%). The study did not find significant differences in the occurrence of ASD between the two treatment groups (exercise vs. fusion) on long term follow-up as measured by differences in disc height between surgery and follow-up. The authors concluded (though did not actually demonstrate) that compared with the findings reported in the literature, the prevalence of ASD was likely to be in accordance with the expected changes in a non-operated symptomatic population and therefore not accelerated by fusion.

Randomised trials of ASD and lumbar fusion: summary

- These two RCT follow-up studies (Ekman et al., 2009; Videbaek et al., 2010) came to opposite conclusions about a possible relationship between ASD and fusion in the lumbar spine. However, the two studies had different study definitions of ASD and the patient populations in these two trials;

- underwent different surgical procedures (with a subgroup in the Ekman study undergoing laminectomy),
- had predominantly different diagnoses

If these factors were significant, it is possible that ASD may be causally related to fusion in patients with isthmic spondylolisthesis undergoing posterolateral fusion with autologous bone transplantation (iliac crest harvest) but not in patients with predominantly disc degeneration undergoing ALIF +PLF[445]. Other explanations (such as age difference in the two study populations) however, cannot be ruled out in either study. It is also worth noting that a group of patients in the Ekman study underwent posterior lumbar fusion with laminectomy and that nearly half of these patients (47%) developed ASD compared to 12.5% in those that underwent PLF without laminectomy. Ekman also concluded that clinical importance of ASD was limited, with only the more severe forms affecting outcome.

Cervical fusion

Two studies (Kelly et al., 2011; D. Park et al., 2010) reported analyses of data from two FDA Investigation Device Exemption (IDE)[446] trials of artificial discs. The trials compared adjacent segment motion and kinetics following cervical disc replacement[447] and cervical fusion.

Park 2010 "Index and Adjacent Level Kinematics after Cervical Disc Replacement and Anterior Fusion in Vivo Quantitative Radiographic Analysis."

Park et al (2010) carried out a study to assess the in vivo kinematics of the cervical spine after anterior cervical discectomy and fusion (ACDF) and total disc replacement (TDR) with the new artificial disc. This analysis was part of a multicentre prospective randomised clinical evaluation[448] of the porous coated motion (PCM) artificial cervical disc[449].

Patients with cervical radiculopathy or myelopathy were randomised to receive either a single-level total disc replacement (272 patients) or anterior cervical discectomy and fusion (182 patients). Neutral, flexion, and extension *radiographs* of the cervical spine obtained before surgery, and at 3, 6, and 12 months after surgery were assessed. Quantitative assessments and comparisons of motion patterns were produced using validated computer-assisted methods. Kinematic parameters, including segmental rotation, translation, centre of rotation (COR), disc height, and disc angle were calculated. The results are presented in Table 6.3.6 below.

[445] This however may be biomechanically unlikely.
[446] An Investigational Device Exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to Food and Drug Administration (FDA).
[447] With two artificial discs, Pro-Disc® -C447 and a porous coated motion (PCM) disc.
[448] http://clinicaltrials.gov/ct2/show/NCT00578812
[449] NuVasive, LA Jolla, CA

Table 6.3.6. Outcomes for fusion and disc replacement patients (D. Park et al., 2010).

Variable measured	Fusion (ACDF)			Disc replacement (porous coated motion disc)		
	Before surgery	12 months post surgery	P	Before fusion	12 months post surgery	P
Angular rotation	9.6° ± 5.1°	11.0° ± 5.5°	<0.003*	9.8° ± 5.2°	10.8° ± 5.5°	0.43*
Translation	1.3± 0.8 mm	1.5 ± 0.9mm	0.09	Unaltered		
Horizontal COR	No significant change		>0.1	No significant change		>0.1
Disc angle†	5.0° ± 3.8°	2.7°± 4.2°	< 0.001**	4.3° ± 3.8°	2.8° ± 4.0°	0.04***
*superior adjacent level, ** inferior adjacent level (lordosis at the superior level remain the same) *** inferior, the superior angle remained the same.						

†A positive disc angle represents lordosis at that level. COR= centre of rotation.

At 12 months the combined angle of lordosis *was restored for both disc replacement (TDR) and fusion (ACDF)* patients.

The results of this study suggested that after surgery the spine rebalanced itself to achieve similar overall motion and alignment to preoperative levels. Thus after fusion, compensatory motion developed superior to the fused level in response to the lost motion at the treated level.

Similarly, the increased lordosis (forward curve of the lower back) across the treated level achieved with either fusion or TDR appeared to be accompanied by a compensatory decreased lordosis at the inferior adjacent level. These findings suggest the possibility of some type of soft tissue "memory" whereby the spine appears to rebalance itself to achieve similar overall motion and alignment to preoperative levels.

Author's conclusions

The authors concluded that total disc replacement was able to restore and maintain lordic alignment and disc height and maintain angular motion, while after anterior cervical discectomy and fusion the superior adjacent level developed increased angular motion. The clinical significance of the changes was not reported.

Comment

This RCT received a modest quality score (5/10). The purpose of the trial was to establish equivalence between fusion and disc replacement, *the effectiveness of fusion was not the focus*. The primary outcomes were biomechanical rather than clinical. Thus in the current context this trial is of marginal relevance except for the observation that the spine may be able to rebalance itself after surgery. The follow-up was very short (mean of 1 year) and not long enough to allow any credible clinical conslusions.

Kelly 2011 "Adjacent segment motion following anterior cervical discectomy and fusion versus ProDisc-C cervical disc arthropody: analysis from a randomized controlled trial."

Kelly et al (2011) compared adjacent segment range of motion (ROM) following anterior cervical discectomy and fusion (ACDF)[450] and cervical total disc arthroplasty (TDA) in 209 patients who took part in a multicentre (13 sites) prospective RCT. Patients were assessed at two years post surgery. The authors conducted a post-hoc analysis of radiographic data collected during this FDA[451] investigation device trial (IDE) trial[452]. All patients had single-level symptomatic cervical disc disease.

Radiographic evaluation was performed pre-operatively and post-operatively at 6 weeks and 3, 6, 12, 18, and 24 months. Three cervical spine plain radiograph lateral views in neutral, maximum active flexion, and maximum active extension were obtained at each time point.

Linear regression was used to model postoperative range of motion (ROM) at the index (treatment), cranial adjacent, and caudal adjacent levels. Variables (main effects) included in the model were: treatment (ACDF or TDA), index level (spinal surgery level), and time.

For *adjacent cranial segments* the main findings were;

- combining all cranial levels for each group (i.e. ACDF, TDA), regression analyses indicated no significant differences in change of range of motion between anterior cervical discectomy and fusion and total disc replacement at any time point
- a comparison of the pre-surgical and 24 month post surgical range of motions (ROMs) at the adjacent cranial segment (all levels) for the anterior cervical discectomy and fusion and total disc replacement patients showed a significant increase in ROM in the anterior cervical discectomy and fusion group453 .
- time from surgery was significantly associated with post-operative ROM ($p<0.0001$)
- there was no significant association between the treatment chosen (ACDF or TDA) and change in ROM.

For *adjacent caudal segments* the main findings were;

- there was no statistically significant difference between the anterior cervical discectomy and fusion and total disc replacement groups in pre-operative ROM values at the adjacent caudal segment454
- a comparison of the pre-surgical and 24 month post surgical ROMs at the adjacent caudal segment (C4-C6) for the anterior cervical discectomy and fusion and total disc replacement

[450] The authors considered this to be the standard of care for the surgical treatment of cervical myelopathy or radiculopathy with degenerative disc disease (ref = rao 2007).

[451] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm

[452] http://clinicaltrials.gov/ct2/show/NCT00291018?term=ProDisc&rank=1

[453] There was no statistically significant difference between the ACDF and TDA groups in pre-operative ROM values at the adjacent cranial segment, however post treatment ACDF: +1.4 degrees (0.4, 2.4), p = 0.01; TDA: +0.8 degrees, (-0.1, +1.7), p = 0.166.

[454] ROM at the caudal levels was 8.1 + 5.3 degrees for the ACDF group (N= 60) and 8.7 + 4.9 degrees for the TDA group (N = 63),p =0.51

patients showed a significant increase in ROM[455] in the ACDF group only; the ROM was not significantly different between treatment groups.

- combining all caudal levels for each group (i.e. ACDF, TDA), regression analyses indicated that there were no significant differences in change of ROM between the two groups at any follow-up time point.
- time from surgery was significantly associated with post-operative ROM ($p<0.0001$)
- there was no significant association between the treatment chosen (ACDF or TDA) and change in ROM.

Author's conclusions

The authors concluded that adjacent segment kinetics may be altered after both anterior cervical discectomy and fusion and total disc replacement surgery. No association between the treatment chosen (ACDF vs. TDA) and adjacent segment range of motion (ROM) was observed and time rather than treatment had a larger effect on adjacent ROM. The clinical importance of these findings was not clear and further follow-up with clinical correlation was advised.

Comment

This trial achieved the highest quality score of the four trials reviewed, however it was not clear if a truely random allocation was achieved and if the analysis kept to the randomisation scheme (intention to treat analysis). The findings were not related to clinical outcomes and the follow-up was relative short (2 years).

Randomised trials of ASD and cervical fusion: summary

Neither of these studies (Kelly et al., 2011; D. Park et al., 2010) of cervical surgery indicated the clinical significant of their results. Both trials focussed on biomechanical parameters of the cervical spine (and thus are of marginal interest), and both had relatively short follow-up periods (1-2 years). One trial failed to demonstrate sustained biomechanical changes in either surgical group, the other one failed to demonstrate an association between treatment and biomechanical changes in the segments adjacent to fusion. Results from both trials added information of interest; one suggested that after surgery the spine rebalanced itself to achieve similar overall motion and alignment to its preoperative level, the other demonstrated that time from surgery was an important predictor of post surgical range of motion in adjacent segments.

[455] a significant change in ROM was observed at 24 months in the ACDF group at the C4-C5 level (+3.9 degrees, (0.8, 7.0), p = 0.046) and C5-C6 level (+2.4 degrees (1.0, 3.8), p = 0.002).

Overall summary

One of the major arguments made against spinal fusion has been that spinal fusion accelerates the development of the adjacent segment degeneration. This argument has been based largely on the findings of studies of low scientific validity (case series reports), reporting what appeared to be an increased incidence of adjacent segment degeneration after arthrodesis.

The most widely quoted data came from a study by Hilibrand et al (2004) which was a case series of 374 patients treated with anterior cervical fusion for the treatment of cervical spondylosis with radiculopathy or myelopathy or both. Hilibrand et al (2004) observed the occurrence of symptomatic adjacent segment disease at a relatively constant incidence rate of 2.9% per year during the 10 year-post operation follow-up. Using survival analysis methods, the authors predicted that 25.6% of the patients who had an anterior cervical arthrodesis would have new disease at an adjacent level within 10 years after the operation.

In a recent follow-up, Hilibrand et al (2004) concluded that the results of their studies suggested that adjacent segment disease was indeed a common problem, but that it may reflect the natural history of the underlying cervical spondylosis rather than the effect of the cervical fusion.

The current overview examined evidence from two low quality systematic reviews and four higher quality follow-up studies of randomised patients. The working definitions of ASD varied considerably between studies and overall these studies failed to demonstrate convincingly an association between fusion surgery and clinically important adjacent segment disease. A recurring finding was an association between age and/or length of follow up and adjacent segment disease.

Conclusion

On balance it is considered that there is insufficient evidence to conclude that fusion results in accelerated spinal segment disease or degeneration, compared to natural processes.

Section 7: Spinal fusion and disc replacement - return to work outcomes

An evidence-based review of the effectiveness of spinal fusion and disc replacement surgery with 'return to work' as the outcome.

Executive summary

There appears to be a general agreement that work-related outcomes from surgery are an important consideration, however, when reviewing the effectiveness of surgical treatment for spinal conditions, data from primary research sources remains limited. In the current overview, 12 relatively recent (2005 onwards) systematic reviews, one technology overview and seven guidelines were identified that reported return-to work data of one sort or another.

The reported results for return-to-work outcomes were *inconsistent* when lumbar fusion was compared to conventional non-surgical intervention or disc replacement surgery for low back pain. Mixed results were reported when fusion was compared to disc replacement surgery for degenerative disc disease and when fusion and discectomy were compared for the treatment of lumbar disc herniation. For cervical conditions there were conflicting results from studies comparing discectomy and anterior fusion.

Comparisons between different techniques of fusion and between fusion and disc replacement and between surgical and non-surgical interventions generally yielded non-significant or very small differences in return to work outcomes particularly when comparison were made within randomised controlled trials. These general conclusions appeared to hold over different patient groups

In summary, it would appear that there is no consistent or strong evidence to suggest that any of the reported interventions significantly improve return to work rates more than their comparators.

There were a number of limitations that must be borne in mind when interpreting these results. The proportion of primary studies reporting return-to-work outcomes in these reviews was generally low and the volume of evidence relatively small and heterogeneous. In general, the effect size appeared to be small and the global importance of the differences observed in the return-to-work measures between different interventions was difficult to determine. The quality of the evidence was generally regarded as poor and follow-up was generally short (1-2 years).

There was some evidence to suggest that outcome differences between techniques reduced with longer follow-up. Different studies favoured different work related outcome measures, and no study compared different return-to work measures.

Background

The ACC has requested an evidence based overview of return-to-work outcomes following *spinal fusion and disc replacement surgery* for a range of spinal conditions. This report focuses on the evidence relating to these outcomes as presented in systematic reviews and clinical guidelines pertaining to the relative effectiveness of these two therapies.

The economic consequences of low back pain have provided keen incentives to determine predictors of non-return and return-to-work for these conditions following therapy. A number of systematic reviews have assessed the findings of the resulting large volume of studies. Non- return-to-work has been shown to be a strong predictor for persistent low back pain, while receipt of benefits or worker's compensation has been associated with poorer outcomes. Higher scores on the Vermont disability prediction questionnaire (>0.48) have been associated with a positive likelihood ratio for an early (3 months) return-to-work (Pengal 2003).

Predictors of the speed of return-to-work have also been investigated and the following determined to be predictors of slower return-to-work (Crook 2002);

- psychological distress
- older age and/or female gender
- functional disabilities
- job problems or problems with colleagues
- previous hospitalization and previous episode of back pain.

Predictors of faster return-to-work have included;

- availability of modified jobs
- light mobilization
- more than 2 years on the job or referral to occupational injury
- less than 30 days from injury to treatment
- no pain or sprain,
- good flexion,
- absence of neurological signs.

More recently, *patient expectations* of recovery have also been reported as a predictor for return-to-work (Kuijer 2006).

For chronic low back pain, intensive interdisciplinary rehabilitation with functional restoration has been shown to be moderately more effective than usual care or non-interdisciplinary rehabilitation for reducing pain and improving function, though effects on work-related outcomes are inconsistent (Chou, Atlas, Stanos, & Rosenquist, 2009; Chou & Huffman, 2007). The role of surgical treatment and in particular fusion and disc replacement in efforts to return chronic spinal pain sufferers to work has been less well reported. Many of the earlier studies of effectiveness of these modalities highlighted the need for information relating to patients return-to-work to aid clinical decision making (Memmo, Nadler, & Malanga, 2000).

The aim of the current report is to identify and assess evidence relating to return-to-work outcomes for fusion and disc replacement surgery. The purpose of the report is to aid ACC determine the role of fusion surgery and total disc replacement in returning patients suffering from painful lumbar or cervical spine conditions to work following treatment.

Surgical techniques: arthroplasty

Fusion surgery (arthrodesis) for lumbar and cervical spinal conditions has been described in previous sections of this overview, the description below relates only to disc replacement surgery (arthroplasty).

In spinal fusion surgery, vertebrae are fused together so that they heal into a single, solid bone. Motion of the functional spinal unit is forfeited in order to eliminate pain caused by abnormal painful motion of the vertebrae. A number of other procedures, each targeting different areas of the functional spinal unit, have been developed to *preserve the motion of the functional spinal unit*. These include;

- reconstruction or augmentation of the posterior ligaments
- insertion of interspinous spacers
- replacement or regeneration of the nucleus pulposus
- total disc replacement.

The most common technique in routine use today is *total disc replacement*, which is generally presented as an alternative to surgical fusion and involves the complete removal of the intervertebral disc are replacement with a prosthetic disc (Fekete & Porchet, 2010) .

Disc replacement devices developed in parallel with fusion techniques in the 1950s. Numerous arthroplasty devices were patented and/or described in the literature and over 100 devices were listed in a historical review by Szpalski et al. (2002); most of these devices never reached the clinical implementation phase (Szpalski, Gunzburg, & Mayer, 2002). The majority of these devices were designed for the lumbar spine and only a few for the cervical spine. A number of artificial discs have US FDA Investigational Device Exemption having demonstrated equivalence to fusion in multicentre randomised controlled trials.

Disc arthroplasty devices

These devices may be grouped according to either their articulating surfaces;

- metal-on -metal discs
- metal-on-plastic discs

Artificial discs can also be grouped according to their biomechanical properties as;

- constrained: a device allowing mechanical restrictions in motion within the physiological range
- semi-constrained: a device that allows motion in the physiological range
- non-constrained: a device that allows hypermobility in comparison to the physiological range.

The normal healthy three-joint complex comprising the intervertebral disc and the two facet joints, is a semi-constrained system that allows physiological motion and prevents abnormal or excessive motion. Total disc replacement devices currently in clinical use are all *constrained* in axial compression (Fekete & Porchet, 2010). These discs are thus not necessarily technically ideal.

Methods

For a comprehensive description of the searches carried out for this review and the reporting methods see the General Methods section.

Briefly, a systematic search of the literature was carried out for high-level studies and overviews (systematic reviews, metaanalyses and clinical guidelines) reporting return-to-work outcomes following spinal fusion or disc replacement. Eligible studies were required to have carried out systematic searches of the literature and an explicit analysis of the quality of the reported evidence or minimally a grading of the level of the evidence provided.

For continuity, in addition to publications identified by the search, the full text all of the systematic reviews included in the sections on the effectiveness of fusion surgery for spinal conditions (Question 6) were examined for outcomes relating to return-to-work.

Because of the potentially large volume of literature involved and time and other resource limitations, return-to-work outcomes following disc replacement therapy were only considered where they were reported as part of an assessment that compared outcomes for surgical fusion and total disc replacement. Only a limited search of the "grey material" was carried out for the same reasons.

Publications identified in the search procedure for the current review together with significant publications identified through pearling references from retrieved articles are cited the bibliography at the end of this report. Other relevant references quoted to support particular statement in the reviewed studies are referenced in footnotes.

Quality assessment

The quality of individual systematic reviews or guidelines was only assessed if a substantial part of the review or guideline reported on return-to-work outcomes.

Reporting of lumbar and cervical interventions

Cervical discs must move well whereas lumbar discs must bear weight and move a little. These functional features of the cervical and lumbar spine affect treatment choices and in particular decisions relating to vertebral fusion and disc replacement. Studies assessing the effect of cervical and lumbar surgery on return-to work outcomes are therefore reported separately.

Search results

The literature search for the current review and systematic reviews and guidelines included in the previous reports to the ACC in this series together yielded a total of 123 publications for consideration; 27 of these purported to be systematic reviews, a further 24 were guidelines or reports of guidelines; three publications were evidence-based technical reviews. Thus 54 publications were examined for evidence or recommendations relating to return-to-work outcomes following spinal fusion or disc replacement.

Twelve systematic reviews, one technology overview and seven guidelines reported on return-to work outcomes somewhere in their text. The evidence provided by these publications is summarised below. At the request of one of the ACC reviewers two recent BMJ publications[456] were also considered.

Overall, there was not enough information/data on individual return-to-work outcomes to evaluate the various systematic reviews and guidelines for these outcomes and individual quality assessments were not carried out.

[456] (Fairbank, 2011; Hellum et al., 2011)

Systematic reviews

Return-to-work is not a standard outcome of surgical intervention for disc related pain. Thus no systematic reviews were identified that *focussed* on return-to-work[457] after fusion surgery or disc replacement therapy for spinal conditions. However, return-to-work is considered to be an important goal and was found to be listed as an eligibility factor and/or secondary outcome in a large number of reviews.

Twelve systematic reviews (Chou, Baisden et al., 2009; Gibson & Waddell, 2005; W. Jacobs et al., 2011; Resnick et al., 2005d, 2005e, 2005g, 2005h; van den Eerenbeemt, Ostelo, van Royen, Peul, & van Tulder, 2010; Yajun, Yue, Xiuxin, & Cui, 2010; Zechmeister, Winkler, & Mad, 2010) included "return-to work" or its equivalent as one of the outcomes upon which study eligibility was based. Between them these systematic reviews reported on return-to-work outcomes from 26 primary studies. The original text of the primary studies was not accessed; only information/data presented in the systematic reviews are reported here.

Within each systematic review, the reporting of levels of evidence and the quality of the primary studies varied. Where given, the definitions used in each study are indicated either in the text or in a footnote.

The studies reporting on return-to-work outcomes were also notably heterogeneous in design, surgical interventions and techniques and in the patient populations treated. A number of general points are worth noting;

- the systematic reviews were all published relatively recently i.e. 2005 and later
- the proportion of primary research studies reporting return-to-work outcomes in each systematic review was generally small
- the majority of the primary studies reporting return-to-work outcomes were low quality RCTs comparing outcomes for different fusion techniques and/or disc replacement surgery
- most of the primary studies comparing outcomes for disc replacement and fusion surgery were FDA IDE trials seeking to establish equivalency between these surgical techniques
- all but three of the systematic reviews focussed on lumbar conditions
- six different disc replacement devices were reported and anterior, posterior and circumferential fusions techniques with and without additional instrumentation were the comparators
- reported return-to-work rates varied considerably between studies
- follow-up was generally short (1-2 years)
- return-to work measures varied and included return-to work-rate, return –to-similar-work-rate and time to return-to-work.

[457] This includes "return-to-play" outcomes for injured athletes/sports persons

Studies reporting on return-to-work for patients undergoing lumbar interventions

Lumber back pain studies

Nine systematic reviews reported return-to-work data in patients undergoing surgery for painful lumbar conditions. Two reported on the outcomes of treatment for low back pain (Resnick et al., 2005c), Table 7.1.

Table 7.1. Summary of studies reporting on return-to-work outcomes following treatment for low back pain (various diagnoses).

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
Chou (2009) **"Surgery for low back pain" (APS)** 4/20 RCTs reported "return-to-work " outcomes	• Fusion • PILF ± instrumentation • Circumferential fusion • Non-surgical therapy (intensive and non-intensive) • Disc replacement	**Fusion vs. non-surgical therapy:** The Swedish Lumbar Spine Study (P. Fritzell et al., 2001) found that patients undergoing surgery had a higher proportion of patients return-to-work (36% vs.13%, p =0.002) than those undergoing *conventional (non-intensive*) non-surgical therapy†. Two Norwegian trials (Brox et al., 2006; Brox et al., 2003) compared posterolateral fusion with transpedicular screws and postoperative physiotherapy versus a *modern "rehabilitation"* type of program, consisting of an educational intervention and a 3-week course of intensive exercise sessions, based on cognitive-behavioural principles. There were no significant differences in any of the main outcomes which included return-to-work. **Fusion(ALF) vs. disc replacement (CHARITIE) (higher quality trial):** Blumenthal 2005 [458] (N=304). No difference in rates of employment at 2 years 9.25% vs. 7.4% (NS), but BAK interbody fusion was used which is known to have frequent poor outcomes. **Fusion (Circumferential) vs. disc replacement with Prodisc L (lower quality trial):** **Zigler 2007** [459](N=292) Employed 92% vs. 85% (p =0.048)
Resnick (2005) (AANS/CNS) Part 7 "Intractable low-back pain without stenosis or spondylolisthesis" 2/2 RCTs reported "return-to-work " outcomes	• Lumbar fusion • Instrumented lumbar fusion • Non surgical treatment – conservative care • Intensive rehabilitation	The same two fusion vs non-surgical therapy trials (Fritzell, et al., 2001 , Brox, et al., 2003)

ASPS = American Pain Society. AANS= American ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. Association of Neurological Surgeons. NASS North American Spine Society.

[458] Blumenthal S, Mc Afee PC, Guyer RD, et al. A prospective randomized multicentre Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITIE artificial disc versus lumbar fusion: Part 1: evaluation of clinical outcomes. Spine 2005;30:1565-75.

[459] Ziglar J, Delamarter R, Spivak JM, et al. Results of the prospective randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of level-1 degenerative disc disease. Spine 2007;32:1155-62; discussion 1163.

Four RCTs reported return-to-work outcomes for patients treated for *low back pain* arising from a number of different causes. Proportions of patients returning to work varied considerably between these trials and return-to-work outcomes were *inconsistent w*hen fusion was compared to non-surgical intervention and when disc replacement surgery was compared to fusion surgery. In both sets of comparisons there were differences between the comparators. For example, in one of the RCTs comparing fusion and disc replacement the Charitie III artificial disc was used, in the other Prodisc L was used. It is also worth noting that in each set of comparisons the higher quality trial resulted in non-significant differences between the techniques.

The Norwegian Spine Study Group trials (Brox et al., 2006; Brox et al., 2003) comparing instrumented *lumbar fusion* with cognitive intervention and supervised physical exercises were complemented recently by a randomised multicentre study of *lumbar disc replacement* with cognitive intervention and supervised physical exercises (Fairbank, 2011; Hellum et al., 2011). This was the first RCT to compare outcomes disc replacement and rehabilitation in patients with chronic low back pain and was independent of industry funding. At the start of the study, 28% of patients were in work full or part-time; at the two year follow-up, this had increased to 56% (n=74). There was a “net back to work” rate of 31% (n=21) in the surgical group and 23% (n=15) in the rehabilitation group (P=0.31).

Degenerative lumbar disc studies

Three systematic reviews reported on outcomes for patients with *degenerative lumbar disc* disease (Gibson & Waddell, 2005; van den Eerenbeemt et al., 2010; Yajun et al., 2010), Table 7.2. Between them these reviews reported on data from six RCTs and five prospective cohort studies.

Table 7.2. Summary of studies reporting on return-to-work outcomes following treatment for lumbar degenerative disc disease.

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
van den Eerenbeemt (2010) "Total disc replacement surgery for symptomatic degenerative lumbar disc disease" **5/16 prospective cohort studies and 3/3 RCTs (**conducted in the USA in order to get FDA approval) reported on return-to-work outcomes	• Disc replacement devices; Charite´, ProDisc and Flexicore. • Fusion; anterior interbody fusion with BAK cage, anterior lumbar circumferential fusion, +/- femoral ring allograft and posterolateral fusion with autogenous iliac crest bone graft in combination with pedicle screws	**RCTs** Zigler er al (2007) Return-to-work p = 0.0485 Blumenthal et al (2005) Return-to-work p = 0.6329 Guyer et al. (2009) Return-to-work p = 0.0403 **Prospective cohort studies (disc replacement)** **Charite III** Zeegers et al. (1999.) Return-to-work: 81% (35/43) Lemaire et al (2005) Return-to-work: 91.6% (87/95) **Prodisc** Bertagnoli et al (2002) Return-to-work: same level 64.8% (n = 35), lower level 31.5% (n = 17), unable 3.7% (n = 2) Tropiano et al. (2003) Return-to-work: ''normal'': 71.7%, ''slightly limited'': 28.3%, ''impossible'': 13.2% Bertagnoli et al (2005) Return-to-work: Full-time: threefold increase, Part-time: fourfold increase, not working: fivefold decrease
Yajun 2010 "A meta-analysis of artificial total disc replacement versus fusion for lumbar degenerative disc disease." 3/5 RCTs reported on return-to-work outcomes	• Artificial disc replacement with CHARITE´, or ProDisc-L, or Maverick, or Flexi- Core artificial disc. • Anterior lumbar interbody fusion + BAK cage packed with iliac crest autograft • ALIF with femoral ring allograft plus • instrumented PLF with autogenous iliac crest bone graft instrumented • PLIF with two carbon fibre cages and bone graft	Three RCTs (Blumenthal et al. (2005) , Zigler et al. (2007) and Berg et al. (2009)) reported work status . In a random effects meta-analysis, between study heterogeneity was observed in the proportion of patients returning to full-time/ part-time work (I2 = 29%, p = 0.24). There was no significant difference between disc replacement and fusion in the proportion of patients who returned to full-time/part-time work (OR 1.21; 95% CI [0.76,1.91]; p = 0.43) For meta-analysis see Appendix A.
Gibson (2005) "Surgery for degenerative lumbar spondylosis : updated Cochrane systematic review" 31 RCTs	• Anterior fusion • Posterior fusion • Circumferential fusion • Laminectomy • Laminotomy	Same studies reported as Chou 2009 above (Brox et al., 2003; P. Fritzell et al., 2001)

ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. ASPS = American Pain Society. AANS= American Association of Neurological Surgeons. NASS North American Spine Society.

These systematic reviews again reported mixed results. In one review (van den Eerenbeemt et al., 2010) two RCTs reported significant differences in return-to-work outcomes between fusion and disc

replacement while a third RCT reported no significant differences. In the same review return to work rates of 81%-92% were reported for patients treated with the Charitie III device and 65%-72% returning to normal or “same level” work for Prodisc; differences between the patient populations treated, which may have accounted for some of the different return-to-work rates, were not reported. A random effects metaanalysis pooling the results of the three RCTs reported in the van den Erenbeemt et al (2010) review found that there were no-significant differences in the proportion of patients who returned to full-time or part-time work following disc replacement or fusion.

Lumbar disc herniation

For patients with lumbar disc herniation one systematic review (Resnick et al., 2005d) of low level (Class III) studies reported on patients with disc herniation and radiculopathy, Table 7.3.

Table 7.3. Summary of studies reporting on return-to-work outcomes following treatment for disc herniation.

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
Resnick (2005) (AANS/CNS) Part 8 "Disc herniation and radiculopathy" 3/12 class III studies reported return-to-work outcomes.	• Discectomy + fusion • Posterior lumbar fusion • Discectomy	Donceel and Du Bois [460]described a series of 3956 patients treated for a lumbar disc herniation with either discectomy alone (3670 patients) or discectomy and fusion (286 patients). The authors used return-to-work 1 year following surgery as an outcome measure. They found that 70% of the discectomy-only group were able to resume their preoperative work level at the 1-year follow up compared with only 40% of the discectomy/fusion group. Poorest overall outcomes were in the fusion group which tended to have more complex histories & longer duration. Eie**, 1978**[461] Retrospective study of 259 patients: 119 discectomy only, 68 discectomy in situ non instrumented PLF. Seventy-nine percent of the discectomy patients and 86% of the discectomy/fusion patients maintained their preoperative work status at the 6-year follow up. No p values cited. Matsunaga, et al., 1993. Retrospective study of 82 manual labourers and athletes (micro-discectomy= 30, percutaneous discectomy = 51, fusion 29). Return-to-work at 1 yr (75% discectomy but 22% could not sustain work [53% in end], recovery after spinal fusion. 89% in spinal fusion group, 58% percutanous discectomy). Time to return-to-work (9 wks percutaneous discectomy, 15 wks micro-discectomy, 25 wks fusion). They found that although discectomy-treated patients returned to work earlier (12 weeks) than the discectomy/ fusion-treated group (25 weeks), 22% of the former could not maintain their previous activity level because of so-called lumbar fatigue. These authors concluded that the addition of fusion should be considered in manual labourers and active athletes because it appeared to provide a better chance of return to and maintenance of a preoperative level of function

ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. ASPS = American Pain Society. AANS= American Association of Neurological Surgeons. NASS North American Spine Society.

Two studies compared fusion and discectomy. In one study, after 1 year 70% of discectomy patients resumed their preoperative work level compared to 40% in the discectomy/fusion group; the later however, had more complex histories and longer disease duration. Following a six year follow-up, the other comparative study reported that a higher proportion of discectomy/fusion patients (86%) resumed their pre-operative work than discectomy alone patients (79%). A single retrospective study (Class III) of manual labourers and athletes with 1 year follow-up found that discectomy patients

[460] Donceel P, Du Bois M: Fitness for work after surgery for lumbar disc herniation: a retrospective study. Eur Spine J 7:29–35, 1998.
[461] Eie N: Comparison of the results in patients operated upon for ruptured lumbar discs with and without spinal fusion. Acta Neurochir 41:107–113, 1978

returned to work earlier (9-15 weeks) compared to fusion patients (25 weeks), however, 22% of the discectomy patients could not maintain their previous activity level because of lumbar fatigue.

Degenerative lumbar spondylisthesis studies

For patients with *degenerative lumbar spondylolisthesis* only one of two systematic reviews reported new information (Resnick et al., 2005e). In this review, one low level (Class III) non-comparative study of patients receiving circumferential fusion reported that 77% of patients returned to work (2 year follow-up), Table 7.4.

Table 7.4. Summary of studies reporting on return-to-work outcomes following treatment for lumbar stenosis and spondylolisthesis.

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
Resnick (2005) (AANS/CNS) Part 9 "Lumbar stenosis and spondylolisthesis" 1/32 class I-III studies reported return-to-work outcomes	• Circumferential fusion	Gertzbein, et al., 1996 (Class III) Circumferential fusion for various conditions. 67 patients available for 2-yr FU. 15.2% had degenerative spondylolisthesis w/ stenosis. 97% successful fusion. 77% were performing the same or lighter levels of activity & 23% were not working. In diagnostic categories, the nos. not working was as follows: degenerative disc disease, 25%; pseudoarthrosis, 33%; &, spondylitic spondylolisthesis 8%. In subgroup of patients w/ degenerative spondylolisthesis more return to work; more favourable subgroup in overall favourable study

ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. ASPS = American Pain Society. AANS= American Association of Neurological Surgeons. NASS North American Spine Society.

Different lumbar fusion techniques

With regard to *different* lumbar fusion techniques, two systematic reviews (Resnick et al., 2005g, 2005h) reported return-to-work outcomes for studies comparing a wide range of fusion techniques Table 7.5.

Table 7.5. Lumbar fusion techniques

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
Resnick (2005) (AANS/CNS) Part 11 "Interbody techniques for lumbar fusion" 2/17 class I-III studies reported return-to-work outcomes	PLF + instrumentation PLIF AILF with BAK cage	Vamvanij, et al. 462(1998) 56 consecutive patients, op w/ 1 of 4 lumbar fusion procedures. Simultaneous anterior interbody fusion by using BAK cage and posterior facet fixation provided the highest rate of fusion (88%) and clinical satisfaction (63%). Patients in whom successful lumbar fusion was achieved had better clinical outcomes and a better chance of work resumption Patients (Class II and III). Hacker 463and colleagues performed a retrospective review of 75 patients (Class III). Fifty-four of these patients were treated with stand-alone PLIF with BAK cages, and 21 patients were treated with ALIF with allograft spacers and PLF without screws. A minimum 2-year follow up was performed. There was a quicker return-to-work and closure of Workers' Compensation claims in the PLIF group.
Resnick (2005) (AANS/CNS) Part 12 "Pedicle screw fixation as an adjunct to posterolateral fusion for low-back pain". 2/15 studies reported return-to-work outcomes	PLF PLF+ instrumentation	Lorenz, et al.,464 1991 (Class II) Prospective randomized study of 68 patients w/ ≥ 6-month history of disabling back pain. Group I (29) PLF without instrumentation Group II (39) PLF + pedicle screw. All cases were one level. Mean FU 26 mos. Return to similar work was 31% in Group I & 72% Group II. This report is considered to provide Class II medical evidence in favour of pedicle screw fixation as a means to improve return-to-work rates Grubb and Lipscomb 465performed a retrospective cohort study of patients treated with either non instrumented PLF (49 patients) or PLF with a compression U-rod (52 patients), with a mean follow up of 30 months. In both groups of patients with chronic low-back pain secondary to DDD, solid lumbosacral fusion was associated with decreased pain and higher return-to-work rates (no probability values reported).

ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. ASPS = American Pain Society. AANS= American Association of Neurological Surgeons. NASS North American Spine Society.

In one review (Resnick et al., 2005g) of posterior and anterior lumbar fusion techniques with various types of aids and instrumentation conflicting results were reported in Class III studies. One study found that simultaneous *anterior interbody fusion by using a BAK cage and posterior facet fixation* provided the highest rate of fusion (88%) and had the best return-to-work outcomes (follow-up period not given). A second study stand-alone *posterior lumbar fusion with a BAK cag*e provided the fastest return to work (2 year follow-up).

In the other review (Resnick et al., 2005h) pedicle screw fixation as an adjunct to posterior lumbar fusion was assessed in two studies. The first study provided Class II evidence that PLF with pedicle screw fixation resulted in higher return-to- similar-work rates (72%) than PLF without instrumentation (32%), mean follow-up was 26 months. A second study with a mean follow-up of 30 months, in both groups of patients solid lumbosacral fusion was associated with *decreased pain and higher return-to-work rates* (no probability values were reported).

[462] Vamvanij V, Fredrickson BE, Thorpe JM, et al: Surgical treatment of internal disc disruption: an outcome study of four fusion techniques. J Spinal Disord 11:375–382, 1998
[463] Hacker RJ: Comparison of interbody fusion approaches for disabling low back pain. Spine 22:660–666, 1997
[464] Lorenz M, Zindrick MR, Schwaegler P, et al: A comparison of single level fusions with and without hardware. Spine 16: S455–S458, 1991
[465] Grubb SA, Lipscomb HJ: Results of lumbosacral fusion for degenerative disc disease with and without instrumentation. Two to five-year follow-up. Spine 17:349–355, 1992

Studies reporting on return-to-work for patients undergoing cervical interventions

Systematic Reviews

Three very recent systematic reviews reported on return-to-work outcomes for degenerative disc disease of the cervical spine (Bono et al., 2010; W. Jacobs et al., 2011; Zechmeister, Winkler, & Mad, 2011). Two compared anterior fusion and discectomy (Bono et al., 2010; W. Jacobs et al., 2011), one compared anterior discectomy and fusion with disc replacement (Zechmeister et al., 2011), Table 7.6.

Table 7.6. Cervical spinal conditions

Systematic review/ Title/ Studies reviewed	Fusion/disc replacement technique Comparator (s)	Studies reporting return-to-work outcomes
Jacobs 2011 "Single or double-level anterior interbody fusion techniques for cervical degenerative disc disease". (Cochrane review update) 3/33 RCTs reported :return-to-work" outcomes	• AIF with • Bone graft (allo/auto) • Cage • Cement • Plate • Discectomy	**Return-to-work at 5 weeks** There is very low quality evidence (high risk of bias, imprecise estimate, suspected publication bias) from two studies (Dowd 1999[466]; Rosenorn[467]; 1983; N = 144) that discectomy is more effective than autograft in improving return-to-work at five weeks (RR 1.26; 95% CI 1.02 to 1.54; p = 0.03). **Return-to-work at 10 weeks** There is very low quality evidence (high risk of bias, imprecise estimate, suspected publication bias) from two studies (Dowd 1999; Rosenorn 1983 N = 70) that there is no statistically significant difference in return-to-work at 10 weeks between discectomy and autograft (RR 1.44; 95% CI 0.77 to 2.69; p = 0.25). **Barlocher 2002**[468] concluded that the titanium or PEEK cage yielded a significantly better short and intermediate-term outcome than discectomy alone in terms of radicular pain, Odom's criteria; return-to-work, and earlier fusion.
Zechmeister 2011 "Artificial total disc replacement versus fusion for the cervical spine: a systematic review." 2/7 RCTs reported on return-to-work	• ProDisc-C • Bryan Cervical disc • Anterior cervical discectomy and fusion (with and without plate)	Murrey et al (2009) reported return-to-work times of 48 days/ 61 days, p = 0.004 Mummaneni et al (2007) reported return-to-work times of 45/61 days, p =0.022 Patients in the prosthesis group returned to work on average 15 days earlier than patients in the fusion group. However, while some studies demonstrated that patients after disc replacement return-to-work a few days earlier, the overall employment rate after 2 years did not differ between the groups.
Bono 2010 **NASS** "Diagnosis and treatment of cervical radiculopathy from degenerative disorders" Section D: Surgical treatment. 1/6 RCTs reported return-to - work outcomes	• ACD • ACDF	**Wirth et al**. (Level III evidence) conducted a prospective randomized controlled trial comparing clinical outcomes of ACD, ACDF and posterior cervical foraminotomy for single level HNP with radiculopathy. Of the 72 consecutively assigned patients included in the study, 22 were assigned to foraminotomy, 25 to ACD and 25 to ACDF. Return-to-work was 79% for the foraminotomy group, 92% for ACD and 81% for ACDF (not statistically significant).

ACD =anterior cervical discectomy/ decompression. ACDF= anterior cervical discectomy/ decompression and fusion. ACDFI = anterior cervical discectomy/decompression and instrumented fusion. HNP=herniated nucleus pulposus. PLF=posterior lumbar fusion.DDD = degenerative disc disease. FU=follow-up. ASPS = American Pain Society. AANS= American Association of Neurological Surgeons. NASS North American Spine Society.

[466] Dowd 1999 (published data only) Dowd GC, Wirth FP. Anterior cervical discectomy: Is fusion necessary?. Journal of Neurosurgery 1999;90(1):8–12.
[467] Rosenorn J, Hansen EB, Rosenorn MA. Anterior cervical discectomy with and without fusion: A prospective study. Journal of Neurosurgery 1983;59(2):252–5.
[468] Barlocher CB, Barth A, Krauss JK, Binggeli R, Seiler RW. Comparative evaluation of microdiscectomy only, autograft fusion, polymethyl-methacrylate interposition, and threaded titanium cage fusion for treatment of single-level cervical disc disease: a prospective randomized study in 125 patients. Neurosurgical Focus 2002;12(1):E4.

There were conflicting results from studies comparing discectomy and anterior fusion. Two studies reported low quality evidence to support better return-to-work rates for discectomy compared to fusion at five weeks (p =0.03) *but not at 10 weeks* (p =0.25). Another study reported that the addition of a titanium or PEEK cage yielded a significantly better short and intermediate-term return-to-work outcomes than discectomy alone (W. Jacobs et al., 2011). A further study found *no statistically different* differences in return-to-work proportions for anterior cervical discectomy (92%), anterior cervical discectomy plus fusion (81%) and posterior cervical foraminotomy (79%) (Bono et al., 2010).

Comparisons of anterior cervical discectomy and disc replacement reported statistically significant *shorter r*eturn-to-work times for patients undergoing disc replacement in two studies (48 days vs. 61 days, p = 0.004 and 45 vs. 61 days, p = 0.022). However, follow-up time appeared to be a crucial factor and in one study the overall employment rate at 2 years *did not differ* between fusion and disc replacement.

Health technology assessments

Cervical disc replacement

One relevant technology overview was identified (American Academy of Orthopaedic Surgeons (AAOS), 2010). The overview was prepared using systematic review methodology, and summarized the findings of studies published as of September 9, 2009 on cervical disc arthroplasty. The purpose of the overview was;

"to examine the best available evidence on cervical artificial disc replacement when compared to the current gold standard of anterior cervical fusion and plating."[469]

A systematic search of the literature identified 2054 potentially relevant citations. Seven publications matched the inclusion criteria set for the overview. Six of these studies compared the outcomes of patients treated with *single level cervical disc arthroplasty* to patients treated with single level fusion with adjunctive augmentation, one study compared the outcomes of patients treated with cervical disc arthroplasty (CDA) at *multiple levels* to patients treated with anterior cervical disc fusion (ACDF) at multiple levels.

Study quality was evaluated on a per-outcome basis rather than a per-study basis. A two-step process was used. First, a level of evidence was assigned to all results reported in a study based solely on that study's design. Data presented in randomized controlled trials were initially categorized as Level I evidence and data presented in non-randomized controlled trials and otherprospective comparative studies as Level II evidence. Each study outcome at each reported time point was then assessed using a quality questionnaire. When quality standards were not met, the level of evidence for the outcome at the time point was downgraded by one level. Bespoke quality assessment checklists were developed for RCTs, non-randomized controlled studies, retrospective comparative studies, case series, prognostic studies and joint registries.

Four questions were the focus of the overview. Evidence presented for *two* of the four questions was relevant to the current report, the relevant studies/data relating to these two questions are reported below.

Q. Do patients with herniated cervical disc who present with arm pain with or without neck pain [470]and are treated with a cervical disc arthroplasty have equal or better clinical outcomes than patients treated with anterior cervical discectomy and fusion?

Two flawed RCTs[471] reported no statistically significant difference in the *percentage* of patients who returned to work at 24 months following disc replacement or fusion surgery. Return-to-work rates

[469] In this publication the gold standard was assumed to be anterior cervical fusion and plating.
[470] The primary indication for cervical fusion is relief of radiculopathy by nerve decompression. Neck pain is a poor indication for cervical surgery (personal communication, Gordon Howie, reviewer).
[471] Murrey D, Janssen M, Delamarter R et al. Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. Spine J 2009;9(4):275-286. Heller JG, Sasso RC, Papadopoulos SM et al. Comparison of BRYAN cervical

varied between 77% and 74% in one study and 80% and 83% in the other. One study reported similar non-significant differences for patients returning to *heavy* work (48% vs. 45%), Table 7.7.

Table 7.7. Percentage of cervical fusion and disc replacement patients returned to work after 24 months.

Author	Level of evidence	Outcome	Duration	N CDA:ACDF	CDA %	ACDF %	p-value
Heller, et al. 2009	II	Return-to-work	24 months	301 (157:144)	76.8%	73.6%	p = .483
Murrey et al. 2009	II	Return-to-work	24 months	175 (87:88)	82.8%	80.0%	p = 0.71
Murrey et al. 2009	II	Return to heavy work	24 months	115 (54:61)	48.1%	44.7%	p = 0.75

CDA, cervical disc arthroplasty; ACDF, anterior cervical disc fusion a p-value reported from test of arcsine difference

Q. For patients, what is more economical, cervical disc arthroplasty or anterior cervical discectomy and fusion as defined by hospital (LOS) and length of time to return-to-work (RTW)?

Two flawed RCTs[472] reported on the *length of time* to return-to-work. These studies reported that patients treated undergoing cervical disk arthroplasty (CDA) returned to work in significantly *fewer days* (range 14-16 days) than patients treated with anterior cervical disc fusion (ACDF), Table 7.9.

Table 7.8. Length of time to return-to-work for cervical fusion and disc replacement patients

Author	Level of evidence	Outcome	Duration	N CDA:ACDF	CDA Median (variance)	ACDF Median (variance)	p-value
Heller, et al. 2009	II	Return-to-work (days)	24 months	301 (157:144)	48 (nr)	61 (nr)	p = 0.015
Mummaneni, et al 2007	II	Return-to-work (days)	24 months	350 (183:167)	45 (nr)	61 (nr)	p = 0.022

CDA, cervical disc arthroplasty; ACDF, anterior cervical disc fusion a p-value reported from test of arcsine difference. nr = not reported

disc arthroplasty with anterior cervical decompression and fusion: clinical and radiographic results of a randomized, controlled, clinical trial. Spine 2009;34(2):101-107.

[472] Heller JG, Sasso RC, Papadopoulos SM et al. Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion: clinical and radiographic results of a randomized, controlled, clinical trial. Spine 2009;34(2):101-107. Mummaneni PV, Burkus JK, Haid RW, Traynelis VC, Zdeblick TA. Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: a randomized controlled clinical trial. J Neurosurg Spine 2007;6(3):198-209.

Guidelines

Two US guidelines focussed on return-to work following *various interventions* which included spinal surgery. These guidelines were both published by the Work Loss Data Institute[473] and addressed questions relating to work-related acute and chronic low back conditions the other addressed questions relating to work-related acute and chronic neck and upper back conditions (Work Loss Data Institute, 2008a, 2008b).

The aim of these guidelines was to offer evidence-based step-by-step decision protocols for the assessment and treatment of workers' compensation conditions and to set out Official Disability Guidelines (ODG) Return-To-Work Pathways[474]. Spinal fusion but not disc replacement was a recommended option for the treatment of spinal fracture, dislocation, spondylolisthesis or frank neurogenic compromise. However, while the guidelines reported evidence based return-to-work pathways for disc disorders treated by discectomy and laminectomy (graded by work type from clerical to heavy manual) the current update did not incorporate a return-to-work pathway for patients treated with spinal fusion.

A number of guidelines reported data relating to return-to-work outcomes in their evidence bases but did not make any recommendations in this area.

- "American Association of Neurological Surgeons/Congress of Neurological Surgeons guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine." American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) (2005).
- "Evidence-based guidelines for multidisciplinary spine care. Diagnosis and treatment of cervical radiculopathy from degenerative disorders." North American Spine Society (2010).
- "Evidence-based clinical guidelines for multidisciplinary spine care. Diagnosis and treatment of degenerative lumbar spondylolisthesis." North American Spine Society (2008).
- “Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain. An evidence-based clinical practice guideline from the American Pain Society” (2009).
- “European guidelines for the management of chronic non-specific low back pain.” COST B13 Working Group (2004)[475]

[473] Work Loss Data Institute is an American independent database development company focused on workplace health and productivity. Products include Official Disability Guidelines which provides evidence-based disability duration guidelines and benchmarking data for every reportable condition. New medical treatment guidelines for work-related conditions are also available for those involved in workers' comp and non-occupational disability, including insurers, TPA's, health care providers, case managers, employers, benefits administrators, risk managers and claims attorneys in the management of return-to-work and utilization of medical services following illness and injury.
[474] These pathways give evidence based return-to-work days for specified treatments.
[475] This guideline Appendix A examined the same evidence as Chou 2009 and is not reported further here.

Summary and conclusions

It has been argued that the therapeutic aim of treatment for spinal conditions is to reduce pain and disability and to improve quality of life, patient satisfaction and *return-to-work* (Zechmeister et al., 2010). Thus in addition to outcomes measures to determine pain intensity and patient satisfaction, outcomes to measure functional ability and *work status* should be an integral part of spinal treatment trial designs (E. J. Carragee et al., 2008). In many instances, however, the reported focus of treatment is symptom reduction, rather than improving function with return-to-work as a goal. Thus while there appears to be a general agreement that work-related outcomes are an important consideration, when reviewing the effectiveness of surgical treatment for spinal conditions, data from primary research sources remains limited.

In the current overview, 12 systematic reviews, one technology overview and seven guidelines were identified that reported return-to work data of one sort or another. The results of the first RCT to compare disc replacement and a modern intensive rehabilitation regimen were also reported. The systematic reviews were all relatively recent (2005 and later)[476] and focussed on surgical interventions for low back pain, degenerative disc disease, disc herniation in the lumbar and cervical spine.

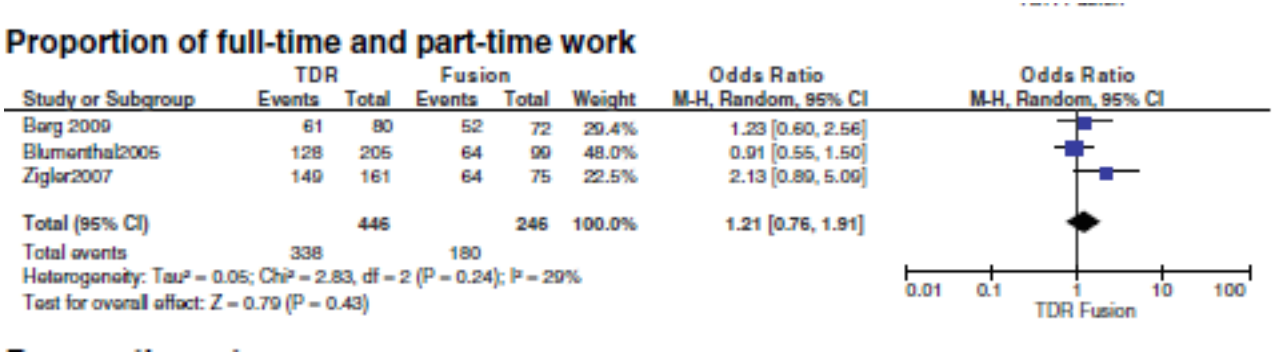
The reported results for return-to-work outcomes were *inconsistent w*hen lumbar fusion was compared to conventional non-surgical intervention or disc replacement surgery for low back pain. In the most recent independent trial comparing disc replacement surgery to modern rehabilitation at two years there was *no statistical difference* in net back-to -work rates. Mixed results were reported when fusion was compared to disc replacement surgery for degenerative disc disease and when fusion and discectomy were compared for the treatment of lumbar disc herniation. However, in a meta-analysis of three trials comparing disc replacement surgery and fusion in the treatment of degenerative disc, disease the *pooled results were not significantly different* for the two treatments. For cervical conditions there were *conflicting* results from studies comparing discectomy and anterior fusion. Two studies comparing anterior cervical discectomy and disc replacement reported statistically *significant shorter return to work times* for patients undergoing disc replacement. However, follow-up time was a crucial factor and in one of the studies the overall employment rate at the two-year follow-up did not differ.

In summary, it would appear that there is *no consistent or strong evidence* to suggest that any of the reported interventions significantly improved return to work rates more than their comparators. Comparisons between different techniques of fusion and between fusion and disc replacement and between surgical and non-surgical interventions generally yielded non-significant or very small differences in return to work outcomes particularly when comparison were made within randomised controlled trials. These general conclusions appeared to hold over different patient groups. However, it should be noted that because of the difficulty of obtaining reliable diagnoses in patients with spinal conditions it is likely that there was diagnostic overlap between the different groups.

[476] Possibly following calls in earlier reviews for working status post-surgery to be reported to aid clinical decision making.

There were a number of limitations that must be borne in mind when interpreting these results. The proportion of primary studies reporting return-to-work outcomes in these reviews was generally low and the volume of evidence relatively small and heterogeneous. In general, the effect size appeared to be small and the global importance of the differences observed in the return-to-work measures between different interventions was difficult to determine. The quality of the evidence was generally regarded as poor. Heterogeneity between studies in critical areas such as fusion techniques (posterior, anterior and circumferential fusion with and without a variety of adjuncts were reported), disc replacement devices (six different disc replacement devices were reported), patient diagnoses and outcome measures, made direct comparisons of results from different sources problematic. Systematic reviews reporting on surgical techniques for lumbar conditions were more common than those reporting on cervical conditions (nine versus three reviews) and reported *return-to-work rates varied considerably* between studies reported in these reviews. Follow-up was generally short (1-2 years). There was some evidence to suggest that outcome differences between techniques reduced with longer follow-up. Different studies favoured different work related outcome measures, and no study compared different return-to work measures. The most reported measure was the return-to work-rate. In some studies return-to-similar and return-to-lower level work rates were reported.

Appendix A: meta-analysis for 3 RCTs with return-to-work outcomes (Yajun et al., 2010)



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