REVIEW ARTICLE

Intervertebral Disc: Anatomy-Physiology-Pathophysiology-Treatment

P. Prithvi Raj, MD, FIPP, ABIPP

Department of Anesthesiology and Pain Management, Texas Tech University, Lubbock, Texas, U.S.A.

■ **Abstract:** This review article describes anatomy, physiology, pathophysiology and treatment of intervertebral disc. The intervertebral discs lie between the vertebral bodies, linking them together. The components of the disc are nucleus pulposus, annulus fibrosus and cartilagenous end-plates. The blood supply to the disc is only to the cartilagenous end-plates. The nerve supply is basically through the sinovertebral nerve. Biochemically, the important constituents of the disc are collagen fibers, elastin fibers and aggrecan. As the disc ages, degeneration occurs, osmotic pressure is lost in the nucleus, dehydration occurs, and the disc loses its height. During these changes, nociceptive nuclear material tracks and leaks through the outer rim of the annulus. This is the main source of discogenic pain. While this is occurring, the degenerative disc, having lost its height, effects the structures close by, such as ligamentum flavum, facet joints, and the shape of the neural foramina. This is the main cause of spinal stenosis and radicular pain due to the disc degeneration in the aged populations.

Diagnosis is done by a strict protocol and treatment options are described in this review. The rationale for new therapies are to substitute the biochemical constituents, or augment nucleus pulposus or regenerate cartilaginous endplate or finally artificial disc implantation. ■.

Key Words: Intervertebral disc, disc disease, Annuloplasty, disc decompression

Address correspondence and reprint requests to: P. Prithvi Raj, MD, FIPP, ABIPP, 1097 Cameron Glen, Cincinnati, OH 45245, U.S.A. E-mail: prithviraj@fuse.net.

Submitted: August 18, 2007; Revision accepted: October 23, 2007

© 2008 World Institute of Pain, 1530-7085/08/$15.00
Pain Practice, Volume 8, Issue 1, 2008 18–44

Back pain is a major public health problem in Western industrialized societies. The prevalence rates in a number of studies ranged from 12% to 35%,[1] with around 10% of patients becoming chronically disabled. It also places an enormous economic burden on society.

Back pain is strongly associated with degeneration of the intervertebral disc.[2] Disc degeneration, although in many cases asymptomatic,[3] is also associated with sciatica and disc herniation or prolapse. It alters disc height and the mechanics of the rest of the spinal column, possibly adversely affecting the behavior of other spinal structures such as muscles and ligaments. In the long term, it can lead to spinal stenosis, a major cause of pain and disability in the elderly; its incidence is rising exponentially with current demographic changes and an increased aged population.

Discs degenerate far earlier than do other musculoskeletal tissues; the first unequivocal findings of degeneration in the lumbar discs are seen in the age group 11 to 16 years.[4] About 20% of people in their teens have discs with mild signs of degeneration; degeneration increases steeply with age, particularly in males, so that around 10% of 50-year-old discs and 60% of 70-year-old discs are severely degenerate.[5]

ANATOMY

The Normal Disc

The intervertebral discs lie between the vertebral bodies, linking them together (Figure 1). They are the main

MEDTRONIC EXHIBIT 1020

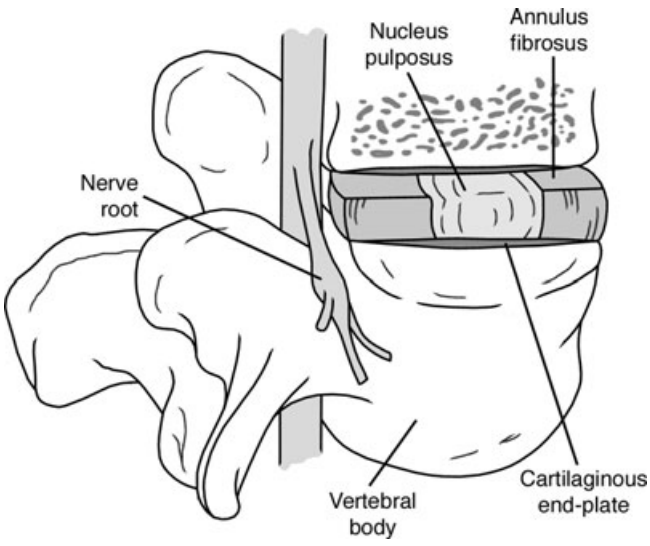


Figure 1. A line drawing of the spinal segment consisting of two vertebral bodies and a normal intervertebral disc sandwiched between them.

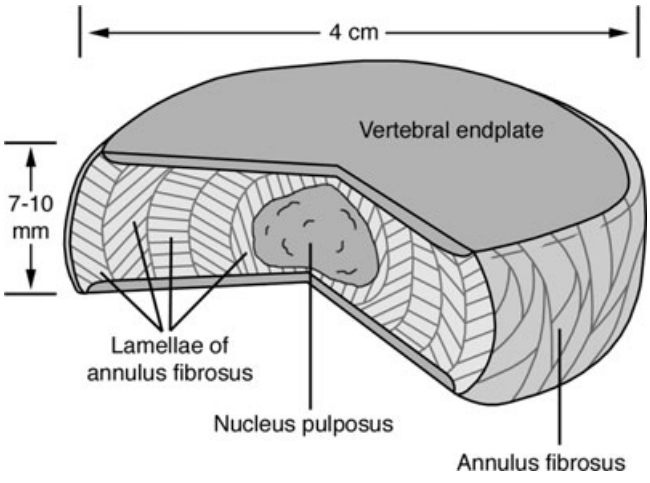


Figure 2. A cut out portion of a normal disc. Note the location of the Nucleus Pulposus, the vertebral end plate and the architecture of Annulus Fibrosis. The intervertebral disc is 4 cm wide and 7–10 mm thick.

joints of the spinal column and occupy one-third of its height. Their major role is mechanical, as they constantly transmit loads arising from body weight and muscle activity through the spinal column. They provide flexibility to this, allowing bending, flexion, and torsion. They are approximately 7 to 10 mm thick and 4 cm in diameter (Figure 2) (anterior–posterior plane) in the lumbar region of the spine.[6,7] The intervertebral discs are complex structures that consist of a thick outer ring of fibrous cartilage termed the annulus fibrosus, which

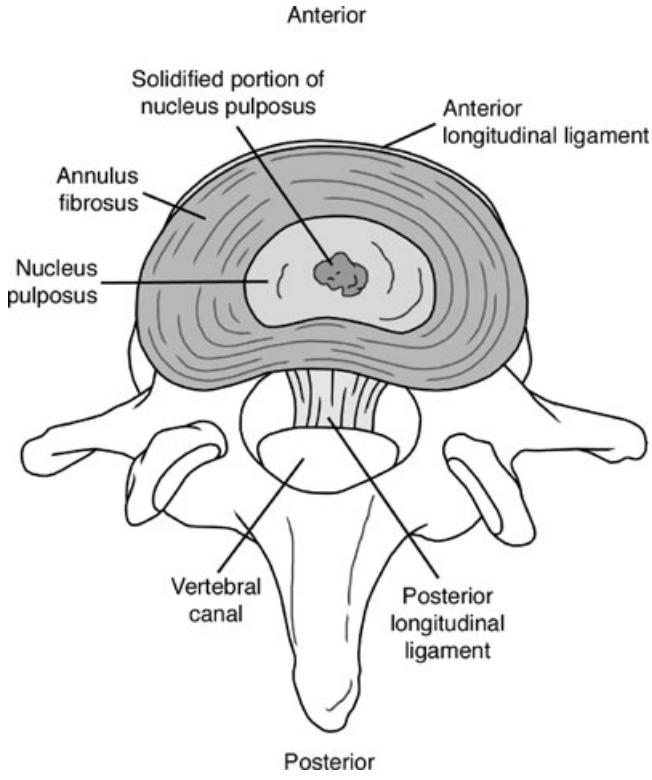


Figure 3. The central Nucleus Pulposus containing collagen fibers and elastin fibers. The solidified portion of the Nucleus Pulposus is surrounded by gel-like Nucleus Pulposus.

surrounds a more gelatinous core known as the nucleus pulposus; the nucleus pulposus is sandwiched inferiorly and superiorly by cartilage endplates.

Structure of the Nucleus Pulposus

The central nucleus pulposus contains collagen fibers, which are organized randomly,[8] and elastin fibers (sometimes up to 150 μm in length), which are arranged radially;[9] these fibers are embedded in a highly hydrated aggrecan-containing gel (Figure 3). Interspersed at a low density (approximately 5000/mm^3[3,10] are chondrocyte-like cells, sometimes sitting in a capsule within the matrix. Outside the nucleus is the annulus fibrosus, with the boundary between the two regions being very distinct in the young individual (<10 years).

Structure of the Annulus

This is made up of a series of 15 to 25 concentric rings, or lamellae,[11] with the collagen fibers lying parallel within each lamella. The fibers are oriented at approximately 60° to the vertical axis, alternating to the left and right of it in adjacent lamellae. Elastin fibers lie between the lamellae, possibly helping the disc to return to its

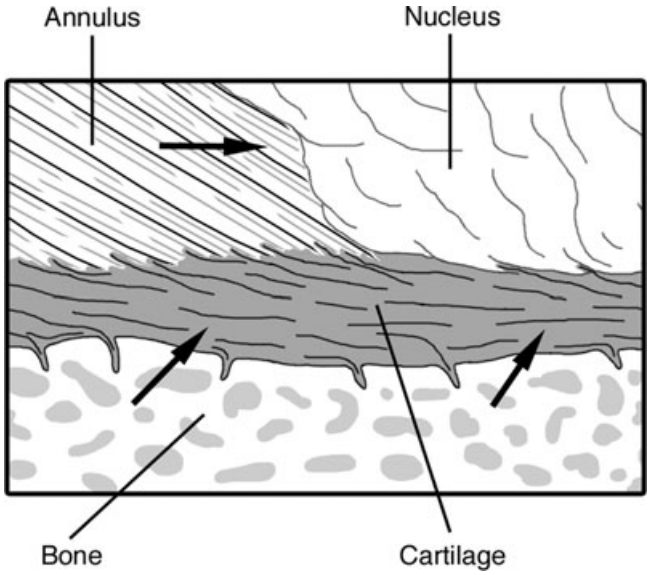


Figure 4. The organization of the vertebral endplate containing hyaline cartilage bonded to the perforated cortical bone of the vertebral body and collagen fibers of the annulus and the nucleus. Arrows indicate routes for nutrient transport from blood vessels into the central portion of the disc (Adapted from *J Orthop Res.* 1993;11:747–757).

original arrangement following bending, whether it is flexion or extension. They may also bind the lamellae together as elastin fibers pass radially from one lamella to the next.[9] The cells of the annulus, particularly in the outer region, tend to be fibroblast-like, elongated, thin, and aligned parallel to the collagen fibers. Toward the inner annulus the cells can be more oval. Cells of the disc, both in the annulus and nucleus, can have several long, thin cytoplasmic projections, which may be more than 30 µm long.[12,13] Such features are not seen in cells of articular cartilage.[12] Their function in disc is unknown but it has been suggested that they may act as sensors and communicators of mechanical strain within the tissue.[12]

The Structure of the Endplate

The third morphologically distinct region is the cartilage endplate, a thin horizontal layer, usually less than 1 mm thick, of hyaline cartilage (Figure 4). This interfaces the disc and the vertebral body. The collagen fibers within it run horizontal and parallel to the vertebral bodies, with the fibers continuing into the disc.[7] The appearance of the intervertebral disc at young (10 months old) and adult periods are shown in Figure 5A and B, respectively.

Blood Vessels and Nerve Supply of the Disc

The healthy adult disc has few (if any) blood vessels, but it has some nerves, mainly restricted to the outer lamellae (Figure 6), some of which terminate in proprioceptor.[14] The cartilaginous endplate, like other hyaline cartilages, is normally totally avascular and aneural in the healthy adult. Blood vessels present in the longitudinal ligaments adjacent to the disc and in young cartilage endplates (less than about 12 months old) are branches of the spinal artery.[15]

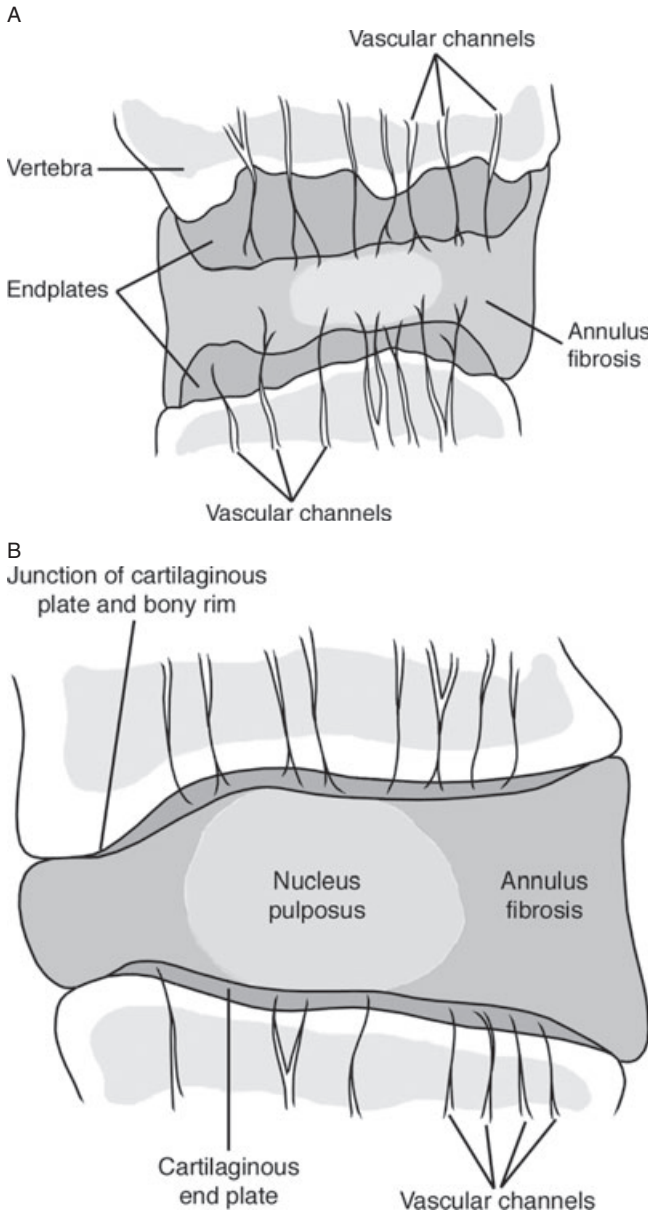


Figure 5. (A) An axial section of the intervertebral disc in a 10-month-old girl. Note the numerous vascular channels and wide cartilaginous endplates traversing to the annulus fibrosis and Nucleus Pulposus. The disc is more gel-like and highly hydrated. (B) An axial section of the intervertebral disc of a 50-year-old adult. Note the thin cartilaginous plate and lesser vascular channels traversing to less hydrated distinct Annulus Fibrosis and Nucleus Pulposus.

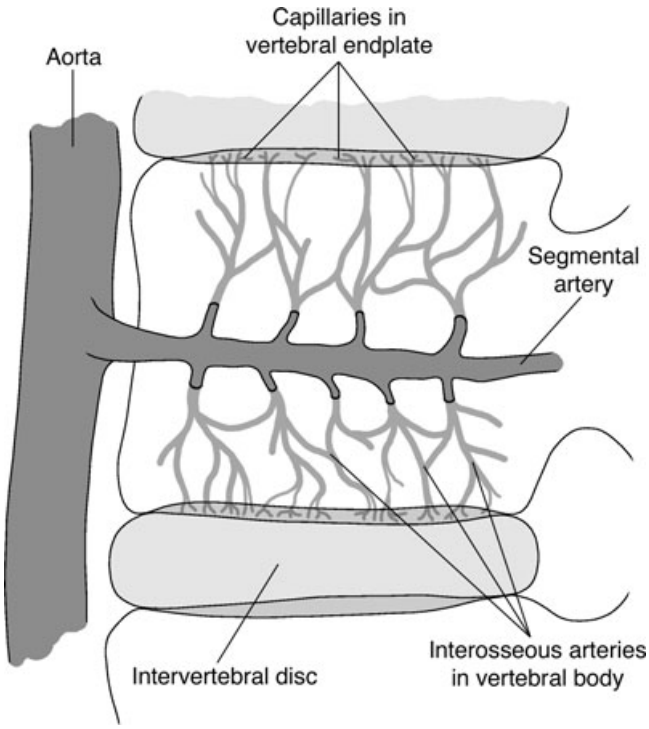


Figure 6. The organization of the blood vessels branching from the segmental artery entering the vertebral body and end as capillaries in the endplate (adapted from http://www.Medscape.com).

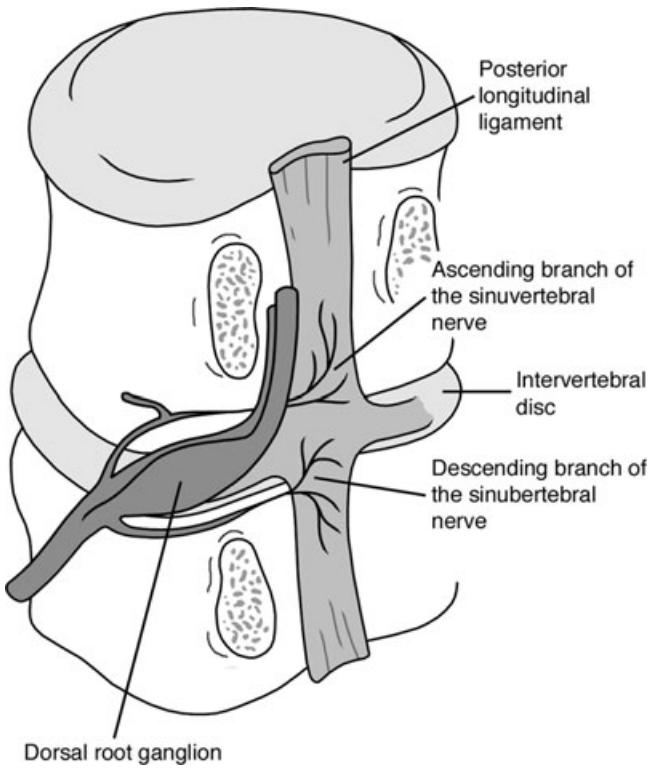


Figure 7. Innervation of the PLL and the disc annulus by the ascending branch of the Sino-vertebral nerve.

Nerves in the disc have been demonstrated, often accompanying these vessels, but they can also occur independently, being branches of the sinuvertebral nerve or derived from the ventral rami or gray rami communicantes. A meningeal branch of the spinal nerve, known as the recurrent sinovertebral nerve, originates near the disc space (Figure 7). This nerve exits from the dorsal root ganglion and enters the foramen, when it then divides into a major ascending and a lesser descending branch. It has been shown in animal studies that further afferent contributions to the sinovertebral nerve arises via the rami communicantes from multiple superior and inferior dorsal root ganglia (Figure 8). In addition, the anterior longitudinal ligament also receives afferent Innervation from branches that originate in the dorsal root ganglion. The posterior longitudinal ligament (PLL) is richly innervated by nociceptive fibers from the ascending branch of the sinovertebral nerve. These nerves also innervate the adjacent outer layers of the annulus fibrosis. Some of the nerves in discs also have glial support cells, or Schwann cells, alongside them.[16]

PATHOPHYSIOLOGY

Changes in the Disc due to Aging

During growth and skeletal maturation, the boundary between annulus and nucleus becomes less obvious, and with increasing age the nucleus generally becomes more fibrotic and less gel-like.[17] With increasing age and degeneration, the disc changes in morphology, becoming more and more disorganized. Often the annular lamellae become irregular, bifurcating, and interdigitating and the collagen and elastin networks also appear to become more disorganized. There is frequently cleft formation with fissures forming within the disc, particularly in the nucleus. Nerves and blood vessels are increasingly found with degeneration.[14] Cell proliferation occurs, leading to cluster formation (Figure 9), particularly in the nucleus.[18,19] Cell death also occurs, with the presence of cells with necrotic and apoptotic appearance.[20,21] It has been reported that more than 50% of cells in adult discs are necrotic.[20] With discs from individuals as young as 2 years of age having some very mild cleft formation and granular changes to the nucleus. With increasing age comes an increased incidence of degenerative changes, including cell death, cell prolif-

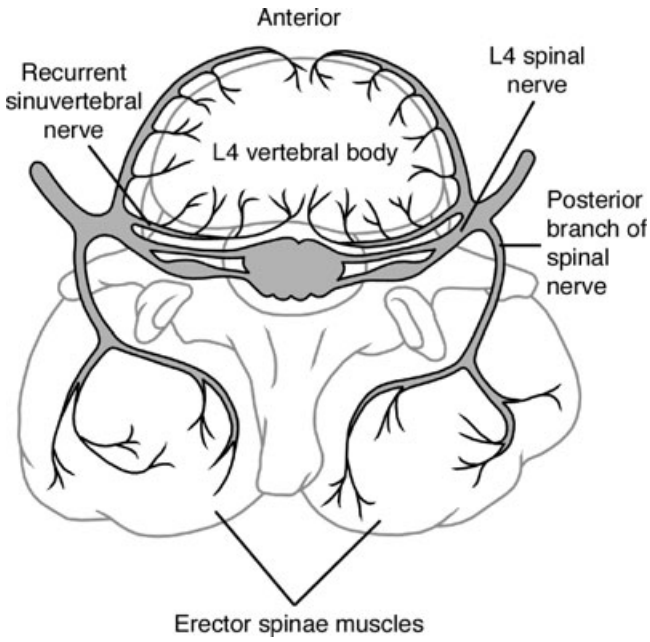


Figure 8. The course of the recurrent Sino-vertebral nerve, which innervates the Postero-lateral region of the disc. The nerve exits from the dorsal root ganglion and enters the vertebral foramen, where it divides into a major ascending and a lesser descending branch. The posterior longitudinal ligament is richly innervated by nociceptive fibers from the ascending branch of the Sino-vertebral nerve.



Figure 9. A nerve bundle in human intervertebral disc stained with an antibody to neurofilament (with permission from: Roberts S, Evans H, Menage J et al. *Eur Spine J.* 2005;14:36–42).

eration, mucous degeneration, granular change, and concentric tears. It is difficult to differentiate changes that occur solely due to aging from those that might be "pathological."

PHYSIOLOGY

Biochemistry of the Normal Disc

The mechanical functions of the disc are served by the extracellular matrix; its composition and organization govern the disc's mechanical responses. The main mechanical role is provided by the two major macromolecular components.

Collagen Fibers

The collagen network, formed mostly of type I and type II collagen fibrils and making up approximately 70% and 20% of the dry weight of the annulus and nucleus, respectively,[22] provides tensile strength to the disc and anchors the tissue to the bone (Figure 10A).

Aggrecan

Aggrecan, the major proteoglycan of the disc,[23] is responsible for maintaining tissue hydration through the osmotic pressure provided by its constituent chondroitin and keratan sulfate chains.[24] The proteoglycan and water content of the nucleus (around 15% and 80% of the wet weight, respectively) is greater than in the annulus (approximately 5% and 70% of the wet weight, respectively) (Figure 10B).

Matrix

The matrix is a dynamic structure. Its molecules are continually being broken down by proteiniases, such as the matrix metalloproteinase (MMPs) and aggrecanases, which are also synthesized by disc cells.[25–27] The balance between synthesis, breakdown, and accumulation of matrix macromolecules determines the quality and integrity of the matrix, and thus the mechanical behavior of the disc itself. The integrity of the matrix is also important for maintaining the relatively avascular and aneural nature of the healthy disc.

The intervertebral disc is often likened to articular cartilage. However, there are significant differences between the two tissues, one of these being the composition and structure of aggrecan. Disc aggrecan is more highly substituted with keratan sulfate than that found in the deep zone of articular cartilage. In addition, the aggrecan molecules are less aggregated (30%) and more heterogeneous, with smaller, more degraded fragments in the disc than in articular cartilage (80% aggregated) from the same individual.[28] Disc proteoglycans become increasingly difficult to extract from the matrix with increasing age.[23]

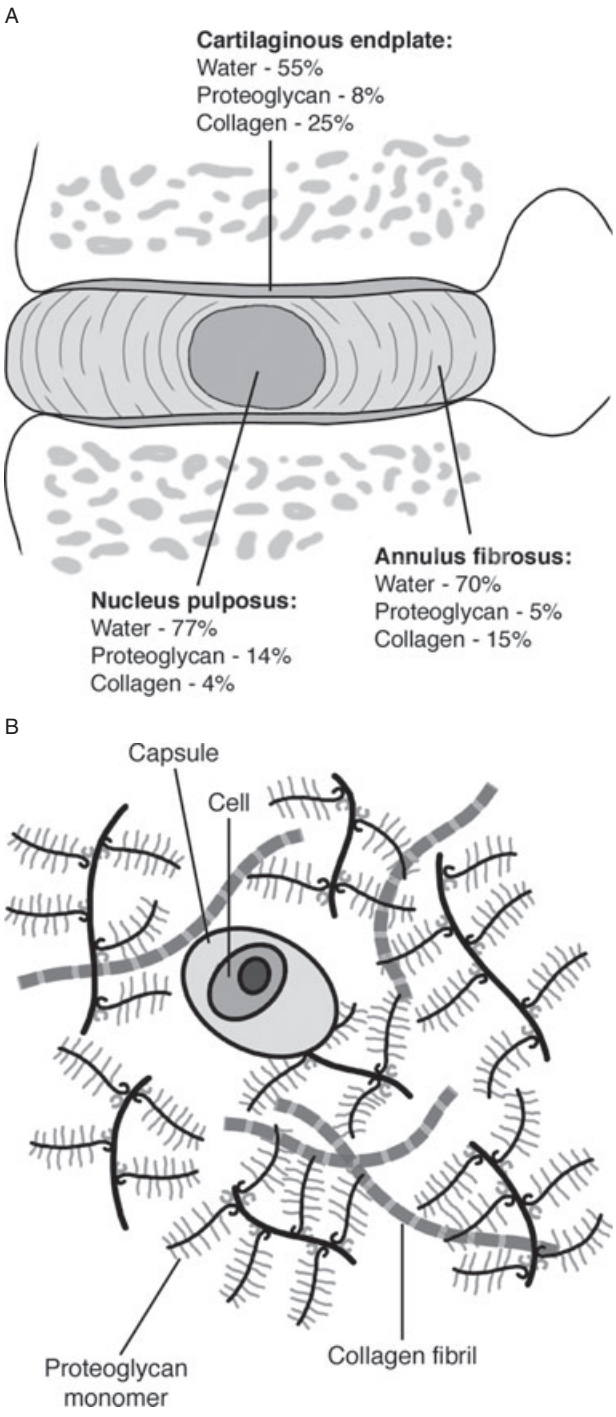


Figure 10. (A) A line drawing of the intervertebral disc structure. (B) A line drawing of a disc proteoglycan aggregate.

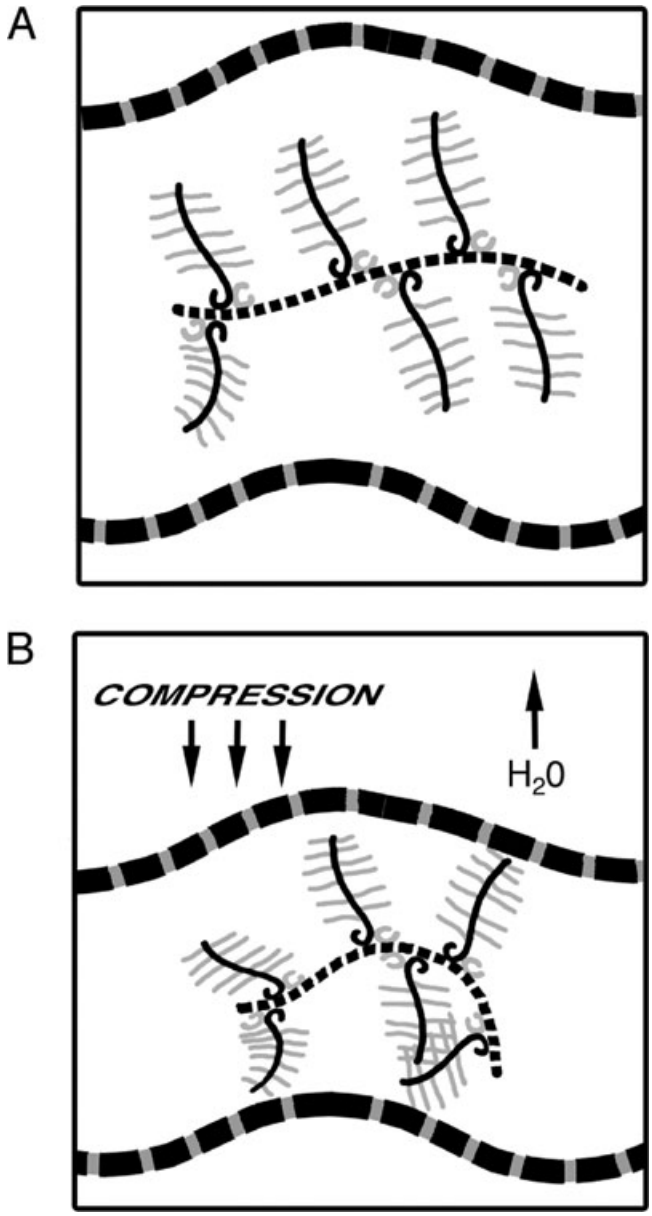


Figure 11. (A) The proteoglycan aggregates are depicted as the central hyaluronan molecule (dashed line) substituted with aggrecan molecules possessing a central core protein (open line) and sulfated glycosaminoglycan side chains (solid lines) The hydration properties of the glycosaminoglycan chains of aggrecan cause the tissue to swell until an equilibrium is reached, where the swelling potential is balanced by tensile forces in the collagen network. (B) Degradation of proteoglycan with the degeneration of the intervertebral disc. This results in loss of water pressure and disc dehydration.

PATHOPHYSIOLOGY

Loss of Proteoglycan

The most significant biochemical change to occur in disc degeneration is loss of proteoglycan (Figure 11A and B).[29] The aggrecan molecules become degraded, with smaller fragments being able to leach from the tissue more readily than larger portions. This results in loss of glycosaminoglycans; this loss is responsible for a fall in

the osmotic pressure of the disc matrix and therefore a loss of hydration.

Even in degenerate discs, however, the disc cells can retain the ability to synthesize large aggrecan molecules with intact hyaluronan-binding regions, which have the potential to form aggregates.[23] Less is known of how the small proteoglycan population changes with disc degeneration, although there is some evidence that the amount of decorin, and more particularly biglycan, is elevated in degenerate human discs as compared with normal ones.[30]

Loss of Collagen Fibers

Although the collagen population of the disc also changes with degeneration of the matrix, the changes are not as obvious as those of the proteoglycans. The absolute quantity of collagen changes little but the types and distribution of collagens can be altered. For example, there may be a shift in proportions of types of collagens found and in their apparent distribution within the matrix. In addition, the fibrillar collagens, such as type II collagen, become more denatured, apparently because of enzymic activity; the amount of denatured type II collagen increases with degeneration.[31,32] However, collagen cross-link studies indicate that, as with proteoglycans, new collagen molecules may be synthesized, at least early in disc degeneration, possibly in an attempt at repair.[33]

Increase in Fibronectin

Other components can change in disc degeneration and disease in either quantity or distribution. For example, fibronectin content increases with increasing degeneration and it becomes more fragmented.[34] These elevated levels of fibronectin could reflect the response of the cell to an altered environment. Whatever the cause, the formation of fibronectin fragments can then feed into the degenerative cascade because they have been shown to down-regulate aggrecan synthesis but to up-regulate the production of some MMPs in in vitro systems.

Enzymatic Activity

The biochemistry of disc degeneration indicates that enzymatic activity contributes to this disorder, with increased fragmentation of the collagen, proteoglycan, and fibronectin populations. Several families of enzymes are capable of breaking down the various matrix molecules of disc, including cathepsins, MMPs, and aggrecanases. Cathepsins have maximal activity in acid conditions. In contrast, MMPs and aggrecanases have an optimal pH that is approximately neutral. All of these enzymes have been identified in disc.

Functional Changes of the Disc due to Degeneration

The loss of proteoglycan in degenerate discs[29] has a major effect on the disc's load-bearing behavior. With loss of proteoglycan, the osmotic pressure of the disc falls[35] and the disc is less able to maintain hydration under load; degenerate discs have a lower water content than do normal age-matched discs,[29] and when loaded they lose height[36] and fluid more rapidly: the discs tend to bulge. Loss of proteoglycan and matrix disorganization has other important mechanical effects; because of the subsequent loss of hydration, degenerated discs no longer behave hydrostatically under load.[37] Loading may thus lead to inappropriate stress concentrations along the endplate or in the annulus; the stress concentrations seen in degenerate discs have also been associated with discogenic pain produced during discography.[38]

Such major changes in disc behavior have a strong influence on other spinal structures, and may affect their function and predispose them to injury. For instance, as a result of the rapid loss of disc height under load in degenerate discs, apophyseal joints adjacent to such disk may be subject to abnormal loads[39] and eventually develop osteoarthritic changes. Loss of disc height can also affect other structures. It reduces the tensional forces on the ligamentum flavum and hence may cause remodeling and thickening. With consequent loss of elasticity,[40] the ligament will tend to bulge into the spinal canal, leading to spinal stenosis—an increasing problem as the population ages.

Loss of proteoglycans also influences the movement of molecules into and out of the disc. Aggrecan, because of its high concentration and charge in the normal disc, prevents movement of large uncharged molecules such as serum proteins and cytokines into and through the matrix.[41] The fall in concentration of aggrecan in degeneration could thus facilitate loss of small, but osmotically active, aggrecan fragments from the disc, possibly accelerating a degenerative cascade. In addition, loss of aggrecan would allow increased penetration of large molecules such as growth factor complexes and cytokines into the disc, affecting cellular behavior and possibly the progression of degeneration. The increased vascular and neural ingrowth seen in degenerate discs and associated with chronic back pain[42] is also probably associated with proteoglycan loss because disc aggrecan has been shown to inhibit neural ingrowth.[43,44]

It is now clear that herniation-induced pressure on the nerve root cannot alone be the cause of pain because more than 70% of "normal," asymptomatic people have disc prolapses pressurizing the nerve roots but no pain.[3,45] A past and current hypothesis is that, in symptomatic individuals, the nerves are somehow sensitized to the pressure,[46] possibly by molecules arising from an inflammatory cascade from arachidonic acid through to prostaglandin E_2, thromboxane, phospholipase A_2, tumor necrosis factor-α,[47] the interleukins, and MMPs. These molecules can be produced by cells of herniated discs and because of the close physical contact between the nerve root and disc following herniation they may be able to sensitize the nerve root.[48,49] The exact sequence of events and specific molecules that are involved have not been identified.

Nutritional Pathways of Disc Degeneration

One of the primary causes of disc degeneration is thought to be failure of the nutrient supply to the disc cells.[50] Like all cell types, the cells of the disc require nutrients such as glucose and oxygen to remain alive and active. In vitro, the activity of disc cells is very sensitive to extracellular oxygen and pH, with matrix synthesis rates falling steeply at acidic pH and at low oxygen concentrations,[51,52] and the cells do not survive prolonged exposure to low pH or glucose concentrations.[53] A fall in nutrient supply that leads to a lowering of oxygen tension or of pH (arising from raised lactic acid concentrations) could thus affect the ability of disc cells to synthesize and maintain the disc's extracellular matrix and could ultimately lead to disc degeneration. The disc is large and avascular and the cells depend on blood vessels at their margins to supply nutrients and remove metabolic waste.[54] The pathway from the blood supply to the nucleus cells is precarious because these cells are supplied virtually entirely by capillaries that originate in the vertebral bodies, penetrating the subchondral plate and terminating just above the cartilaginous endplate.[15,55] Nutrients must then diffuse from the capillaries through the cartilaginous endplate and the dense extracellular matrix of the nucleus to the cells, which may be as far as 8 mm from the capillary bed (Figure 12).

The nutrient supply to the nucleus cells can be disturbed at several points. Factors that affect the blood supply to the vertebral body such as atherosclerosis,[56,57] sickle cell anemia, Caisson disease, and Gaucher's disease[58] all appear to lead to a significant increase in disc degeneration. Long-term exercise or lack of it appears to have an effect on movement of nutrients into the disc, and thus on their concentration in the tissue.[59,60]

The mechanism is not known but it has been suggested that exercise affects the architecture of the capillary bed at the disc–bone interface. Finally, even if the blood supply remains undisturbed, nutrients may not reach the disc cells if the cartilaginous endplate calcifies;[50,61] intense calcification of the endplate is seen in scoliotic discs.

Effect of Mechanical Load and Injury to the Disc

Abnormal mechanical loads are also thought to provide a pathway to disc degeneration. For many decades, it was suggested that a major cause of back problems is injury, often work-related, that causes structural damage. It is believed that such an injury initiates a pathway that leads to disc degeneration and finally to clinical symptoms and back pain.[62] Although intense exercise does not appear to affect discs adversely[63] and discs are reported to respond to some long-term loading regimens by increasing proteoglycan content,[64] experimental overloading[65] or injury to the disc[66,67] can induce degenerative changes.

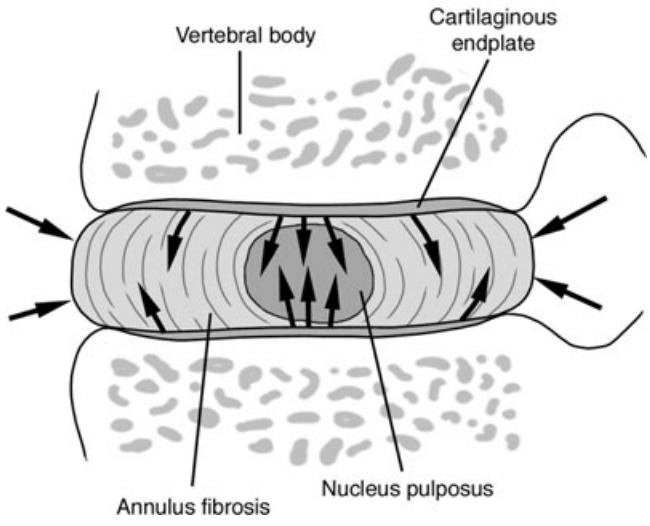


Figure 12. Nutritional pathways of the normal disc. The disc is large and avascular and depends on the blood supply at the margins to supply nutrients and remove metabolic waste. The pathway from the blood supply to the nucleus cells is precarious because these cells are supplied virtually, entirely by capillaries that originate in the vertebral bodies.

Genetic Factors in Disc Degeneration

More recent work suggests that the factors that lead to disc degeneration may have important genetic components. Several studies have reported a strong familial predisposition for disc degeneration and herniation.[68–70] Findings from two different twin studies conducted during the past decade showed heritability exceeding 60%.[71,72] Magnetic resonance images in identical twins were very similar with respect to the spinal columns and the patterns of disc degeneration.[73]

Genes associated with disc generation have been identified. Individuals with a polymorphism in the aggrecan gene were found to be at risk for early disc degeneration. Studies of transgenic mice have demonstrated that mutations in structural matrix molecules such as aggrecan,[74] collagen II,[75] and collagen IX[76] can lead to disc degeneration. Mutations in genes other than those of structural matrix macromolecules have also been associated with disc degeneration.[77–79]

CLASSIFICATION OF PATHOLOGY OF DISC DEGENERATION

The disc lesions can be classified as Contained or Herniated. The progression of disc degeneration can further be classified as follows:

Grade 0: Normal nonleaking nucleus.

Grade 1: Annular tearing confined to the inner region of the annulus fibrosis. In grade 1, a tear or fissure becomes visible. It extends from the nucleus radially into the inner one-third of the annulus fibrosus. This is described as a grade 1 Radial Annular Tear, or grade 1 internal disc disruption (IDD).

Grade 2: In this condition, annular tears have completely disrupted the disc architecture but do not affect the outer contour of the annulus. The entire anulus is disrupted. There is no leakage of injected dye on discography from the disc, nor bulging nor protrusion of the disc. This state of the disc is classified as grade 2 IDD or a grade 2 radial annular tear. There is no compressive effect on the corresponding nerve root. Many of these patients with (grade 2 IDD) complain of lower back pain, which may travel into the lower limb and even past the knee into the lower leg and foot.

Grade 3: In this situation, tears have completely disrupted the annulus and the PLL and deformed the contour of the posterior portion of the disc. There is a full thickness annular tear in which the outer annulus (Sharpey's Fibers) and PLL have been completely ruptured. During discography, contrast material leaks out of the back of the disc into the epidural space. The presence of a disc bulge and/or disc herniation is also included in this category. This condition is classified as grade 3 IDD, or grade 3 radial annular tear. This disc pathology produces the same incidence of patients having sciatica as the grade 2 IDD patients. This indicates the nerve fibers in the posterior annulus are a strong trigger for the of annular tears.[80] This classification has been modified by perception of sciatic pain in the lower limbs.

CT Classification of Annular Tears

The following classification was finalized in the 1990s and is the *gold standard* for the computerized tomography (CT) classification of annular tears.[80] This classification has been modified by Bogduk et al.[81] in 1992, and then further modified by Schellhas et al. in 1996.[82] There are five possible severities of the radial annular tear as seen on an axial CT image (Figure 13).

The grade 0 is a normal disc, where no contrast material injected in the center of the disc has leaked from the confines of the nucleus pulposus. The grade 1 tear has leaked contrast material but only into the inner one-third of the annulus. In the grade 2 tear, the contrast has leaked from the nucleus into the outer two-thirds of the annulus. The grade 3 tear has leaked contrast completely through all three zones of the annulus. This tear is believed to be painful since the outer one-third of the disc has many tiny nerve fibers that are irritated. The grade 4 tear is more serious form of the grade 3 tear, in that now the contrast has spread circumferentially around the disc, often resembling a ship's anchor. To qualify as a grade 4 tear, the spread must encompass greater than 30 degrees of the disc circumference. Pathologically, this represents the merging of a full thickness radial tear with a concentric annular tear. The grade 5 tear includes either a grade 3 or grade 4 radial tear that has completely ruptured the outer layers of disc and is leaking contrast material from the disc into the epidural space. This type of tear is thought to have the ability to induce a severe inflammatory reaction in the adjacent neural structures. In some patients, this inflammatory process is so severe that it causes a painful chemical radiculopathy and sciatica without the presence of nerve root compression.

MECHANISM OF DISCOGENIC PAIN

In 1979, Brodsky and Binder[83] characterized the mechanism for the provocation of pain with discography. Their findings included: (1) stretching of the fibers of an abnormal annulus, (2) extravasation of extradurally irritating substances such as glycosaminoglycans, lactic

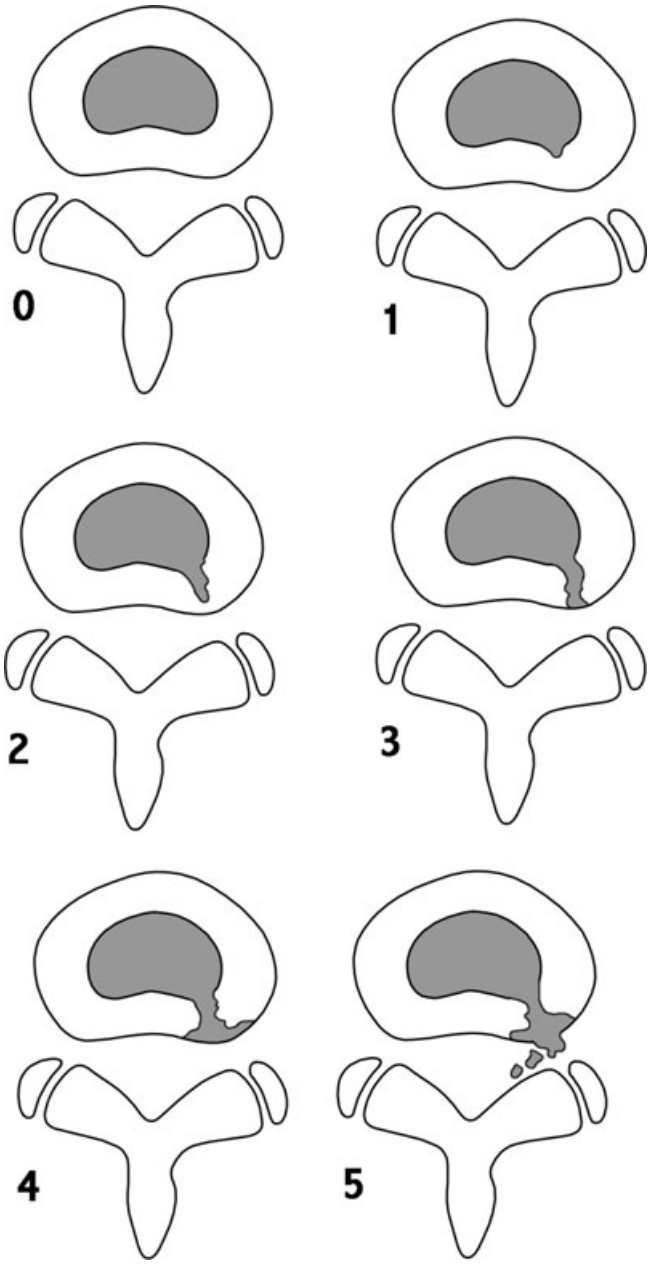


Figure 13. The classification of internal disc disruption from grade 0 to grade 5, based on the Modified Dallas Classification.

acid, and acidic media, (3) pressure on nerves posteriorly caused by bulging of the annulus, (4) hyperflexion of posterior joints on disc injection,[84] and (5) the presence of vascular granulation tissue, with pain caused by scar distension.[85] Another mechanism speculated was pain generators in the end plates that may be provoked by endplate deflection.[86]

Ohnmeiss et al.[86] studied the typical patterns of pain referral from different degrees of discogram-confirmed posterior annular tears (a.k.a. IDD, radial fissures/tears). Surprisingly, they discovered that the disc does not have to be completely torn for the patient to suffer from lower limb pain. In fact, discs did not even need to be completely ruptured or bulging.

Grade 2 (outer annulus nonruptured and nonleaking) were found to reproduce lower limb pain on discography just as often as grade 3 discs (bulging, herniated, completely ruptured, and leaking). About 60% of both types of IDD reproduced lower limb pains on provocative discography. This study supports the theory that nuclear material in the outer region of the posterior annulus may be a cause of sciatica on its own.

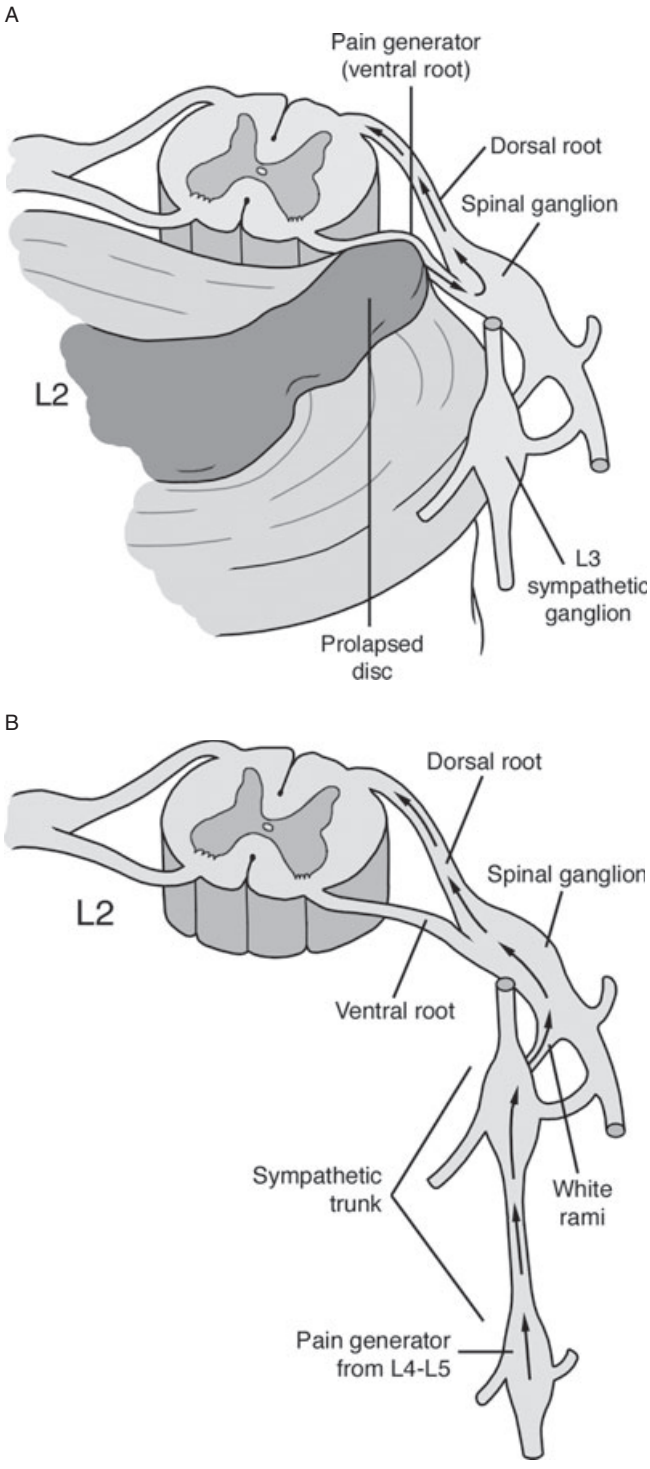
The pain pathways for discogenic pain are still very controversial. Traditionally, pain signals that originate in the nerve roots adjacent to the disc move from that root, into the corresponding dorsal root ganglion (DRG) and into the spinal cord (Figure 14A). However, recent new research suggests that pain signals from the lower lumbar discs (L4 and L5) are detoured up the sympathetic nerves (gray ramus communicans) and into the upper lumbar DRGs—especially at the L2 level (Figure 14B).[87–89] Clinically, in some patients it then would be possible for patients with L4 and L5 disc pathology to have L1 or L2 dermatomal pain (groin and anterior thigh pain).

DIAGNOSIS OF IDD

Provocative Discography

The gold standard in making the diagnosis of IDD is a very painful and invasive test called *provocation discography* with follow-up CT discogram. There are two components to provocation discography: the first is an attempt by the physician to provoke the patient to feel their usual pain (concordant pain) by pressurizing the disc with a contrast material. The second is a painless discogram in the adjacent discs.

The International Society for the Study of Pain, in its taxonomy,[90] has adapted the following set of criteria for diagnosing IDD: (1) no visible disc herniations seen on magnetic resonance imaging (MRI) or CT, (2) during provocation discography injection of the suspected disc, recreation of the patients' exact back, and/or leg pain must occur,[91,92] (3) injection of the disc above or below the suspect disc must be nonpainful, and this acts as a control disc or normal disc, and (4) a grade 3 or 4 radial annular fissure must be demonstrated on CT discography.[93–96]



Figures 14. Pain pathways for discogenic pain. (A) Pain signals that generate from the disc traverse pass into the corresponding 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.

Gadolinium-DTPA Enhanced MRI

Although provocation discography with CT discography is the "gold standard" to make the diagnosis of symptomatic IDD, the procedure itself can damage the disc and spread the degenerative disc disease.[97–102] As an alternative, the use of gadolinium (contrast) enhancement may be considered. Gadolinium-dimethoxypropane, when injected into the vein during the MRI, will "light up" the granulation tissue that forms within a healing/healed full thickness annular disc tear (Figure 15A and B).

Hyper Intensity Zone

A hyper intensity zone is a focal high intensity signal in the posterior annulus fibrosis distinct from the nucleus without disc protrusion. This phenomenon also gives another clue that IDD might be involved in the patient's pain syndrome, although this T2-weighted MRI finding is highly controversial (Figure 16).

OPTIONS FOR TREATMENT OF DISCOGENIC PAIN

The Pathological Basis for some Low Back Pain may be due to internally disrupted intervertebral discs and in particular, sensitized annular tears. Treatments described to manage IDD and discogenic pain include surgical intervention with total disc excision and arthrodesis or more conservative measures such as intradiscal steroids, chemonucleolysis, intradiscal decompression, annuloplasty, and the use of intradiscal laser devices.

Two minimally invasive procedures have been promoted as alternatives to major surgical interventions. Both involve the introduction of a flexible electrode into the painful disc, with the aim of coagulating the posterior annulus. In addition, new minimally invasive procedures have been introduced to decompress the disc with painful pathology. A classification of such percutaneous procedures is given below.

1. Annuloplasty
   A. Intradiscal electrothermal therapy (IDET)
   B. Radiofrequency posterior annuloplasty (RFA)
   C. Biacuplasty
2. Percutaneous disc decompression
   A. Laser discectomy
   B. Radiofrequency coblation (plasma discectomy)

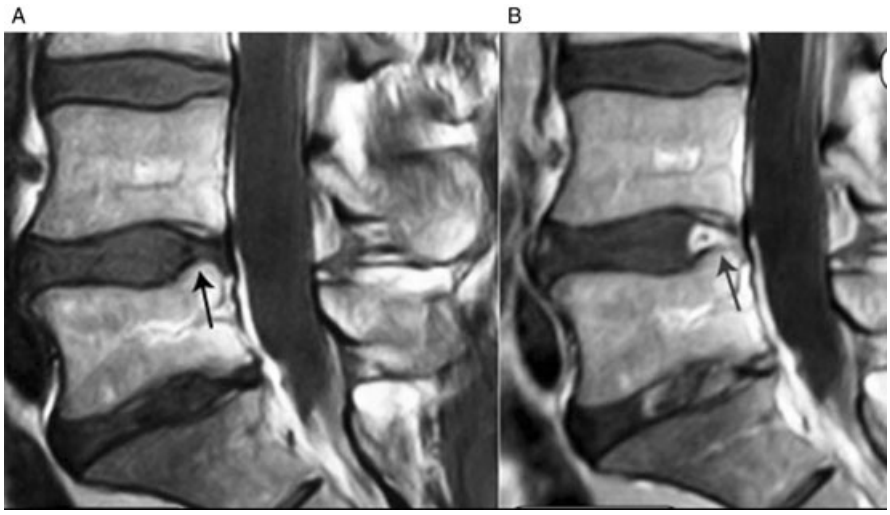


Figure 15. (A) MRI with a disc lesion. (B) Enhanced MRI with Gadolinium-DTPA. The enhanced MRI "lights up" the granulation tissue in the full thickness annular disc tear. MRI, magnetic resonance imaging; DTPA, dimethoxypropane.



Figure 16. T2-weighted MRI shows a hyper intensity zone (HIZ) in the posterior annular fibrosis, which is distinct from the signal from the nucleus. MRI, magnetic resonance imaging.

C. Mechanical disc decompression (dekompressor)
D. Manual percutaneous lumbar discectomy (PLD)

3. Endoscopic percutaneous discectomy

Conservative Management

Ninety percent of all IDD patients will obtain satisfactory pain relief by conservative measures. However, for the conservative treatment to be effective, it may take many months. Conservative treatment often takes the form of oral analgesics, gentle traction, and nondynamic spinal stabilization treatments and exercise.

1. Chemonucleolysis

In the early 1940s, chymopapain was derived from the papaya fruit by Jansen and Balls, as reported by Jaikumar, Kim, Kam, and Maroon.[103,104] By 1956, Thomas saw the potential for this enzymatic substance and began work on determining a clinical use. He injected the chymopapain intravenously into the ears of rabbits and noted that the ears became floppy.[105] Thomas confirmed the softening of the cartilaginous material in the ear due to the chymopapain. Smith et al. picked up the torch and hypothesized that chymopapain could be used to treat chondroblastic tumors, which it did not; however, they did find that when injected into the intradiscal space of rabbits, the nucleus pulposus disappeared but left the annulus intact.[104,105] In 1963, Smith injected the first human patient with chymopapain to treat sciatica. Chymopapain works by depolymerizing the proteoglycan and glycoprotein molecules in the nucleus pulposus.[104] These large molecules are responsible for water retention and turgidity. When exposed to chymopapain, the water content within the disc plummets; shrinkage follows and causes a reduction in disc height and girth. The bulging disc, therefore, shrinks.

Procedure

The patient is placed in either a lateral or a prone position. Under conscious sedation and guided by fluoroscopy, a 6-inch, 18-gauge needle is inserted posterolaterally and placed centrally within the disc. Discography, along with the pain provocation test, is performed for evaluation of the affected disc. Chymopapain is then

injected into the nucleus pulposus in amounts ranging from 1000 to 4000 U. The number of units injected decreases if more than one disc is to be treated.[104,105]

Chymopapain has been in use for more than 30 years. After approval by the U.S. Food and Drug Administration in 1982, early complications were reported even though studies had shown a very safe record.[105] Anaphylaxis, reported in 1% of cases, proved to be the most severe complication.[105] It became clear that good patient selection, proper surgical training and technique, preoperative hypersensitivity testing and antihistamine administration could greatly reduce the complication rate when using chymopapain. In fact, complications became almost nonexistent in the late 1980s and 1990s when utilizing the aforementioned criteria.

Indications for chymopapain include those patients who present with radicular pain as the chief complaint; confirmation of the disc herniation via MRI, CT, or myelogram; and patients having failed conservative treatment.[104–106] Kim et al. found that patients with moderate to severe positive straight leg raise had a significantly higher success rate as compared to those with no or mild straight leg raising pain.[106] The younger the patient, the better the outcome. Younger patients had a success rate ranging from 82.3% for those in their 30s to 94.6% for those in their teens. Patients 50 years and older had only a 71% success rate.[107] Those patients in whom the pain provocation test was positive had a 91.7% success rate compared to those who did not experience pain provocation at a 73.1% success rate.[106]

Chemonucleolysis has been fraught with controversy since FDA approval. There are those who want to dismiss the procedure as dead due to complications in earlier use (and lack of manufacture and distribution within the U.S.A. since 1999), but there are others who state that with the proper inclusion criteria, preprocedure testing, and good technique, chemonucleolysis has a significant place in the minimally invasive category.[104–106]

2. Ozone Chemonucleolysis

Another alternative therapy that has been receiving some interest in Europe is the use of medical ozone in the treatment of herniated intervertebral discs.[107] This therapy was developed by C. Verga in 1983. In the study of 15 years of treatment, Verga stated that the relapse of pain occurred in less than 2% of cases. The method involves the administration of 40/60 ml of ozone gas (O_2–O_3 mixture) at a concentration of 20/30 micrograms per ml, repeated eight to 14 times. The injection is generally made into the paravertebral musculature, and in the hernia zone. The injection itself, except for a slight sense of localized pain of short duration, is generally painless and well-tolerated. There is insufficient published data to conclude that this technique is a promising alternative method.

MINIMALLY INVASIVE PROCEDURES

1. Annuloplasty

1A. IDET. Intradiscal electrothermal therapy was developed and published by Saal and Saal in 2000 to serve as an alternative to fusion for patients with chronic discogenic low back pain.[108,109] There are several proposed causes for discogenic back pain. Some have stated that discogenic back pain is due to an IDD, most likely due to annular tears or fissures.[104] Others feel the discogenic pain may be a result of degenerative disc disease.[106] Even the developers of the current IDET procedure state that the pathophysiology of discogenic pain is complex and hard to pin down into one complete and true definition.[108] What is agreed upon is that the intervertebral disc, particularly the annulus, has nociceptive nerve receptors, which increase when the disk degenerates, is injured, or is exposed to a variety of inflammatory substances. This increase in neural pain receptors causes' increased and unremitting low back pain.[108,110,111] IDET was therefore developed to modify collagen, making collagen thicker and causing it to contract, decreasing the body's ability to revascularize.

Procedure. This procedure is performed with fluoroscopic guidance, while the patient is under conscious sedation lying prone. As with many intradiscal procedures, discography, along with the pain provocation test, ensues for evaluation of the affected disc. A 17-gauge needle is then inserted posterolaterally into the disc, generally from the patient's less painful side. A 30 cm catheter with a flexible 5 to 6 cm heating tip is threaded circumferentially into the disc through the nucleus pulposus to the pathologic area of the annulus (Figure 17). After fluoroscopic confirmation, the catheter tip is heated to 90°C over a 13-minute period. Once at 90°C, the temperature is maintained for an additional four minutes. The catheter and needle are then removed. The patient is then observed in a recovery area before being discharged home the same day.[108,110,111]

Indications for the IDET include long-term low back pain, failure of conservative therapy, normal neurologic exam, negative straight leg raise, MRI confirmation of no neural compressive lesion, and positive pain provo-

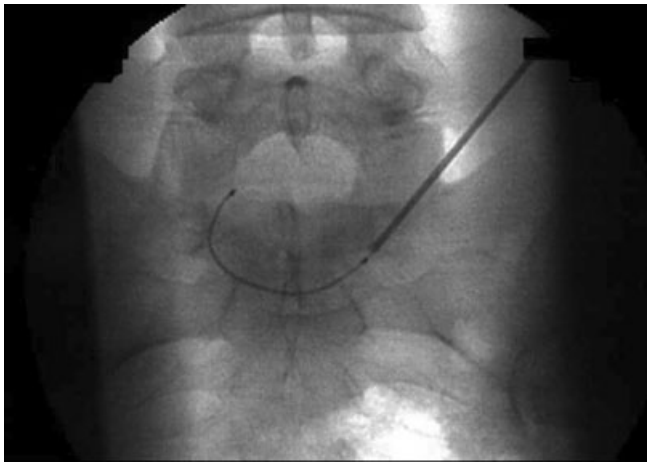


Figure 17. Cephalocaudal view of the Spine-CATH in the L4-L5, created by the curvature of the Lumbosacral spine in an anteroposterior radiographic image, showing the correct placement of the catheter for the IDET procedure. IDET, intradiscal electrothermal therapy.

cation test.[111] Exclusion criteria include inflammatory arthritis, nonspinal conditions that mimic lumbar pain, and any medical or metabolic condition that would preclude proper follow-up.[108,111,112] Much debate still centers on this technique, as there have been limited independent studies and studies reporting long-term follow-up of patients receiving IDET.[108,109,113] The collagen modification could also lead to a reduction in the size of annular fissures and increase the stability of the disc itself.[108,110] IDET also thermocoagulates the nociceptors within the annular walls, thus destroying the ability to transmit nociceptive input.[110,111]

Complications include catheter breakage, nerve root injuries, post-IDET disc herniation, cauda equina syndrome, infection, epidural abscess, and spinal cord damage.

The evidence for IDET is moderate in managing chronic discogenic low back pain.

1B. RFA. Radiofrequency annuloplasty is a minimally invasive method of delivering RF thermal energy to the disc to treat lower back pain. The discTRODE™ (Valleylab, Boulder, CO, U.S.A.) RF catheter electrode system uses heat to coagulate and decompress disc material, providing effective pain relief. Ideal candidates for a discTRODE™ procedure are patients with chronic low back pain that one has determined to be the result of an internally disrupted disc.

Procedure. The discTRODE™ procedure is typically performed on an outpatient basis in a clinical setting.

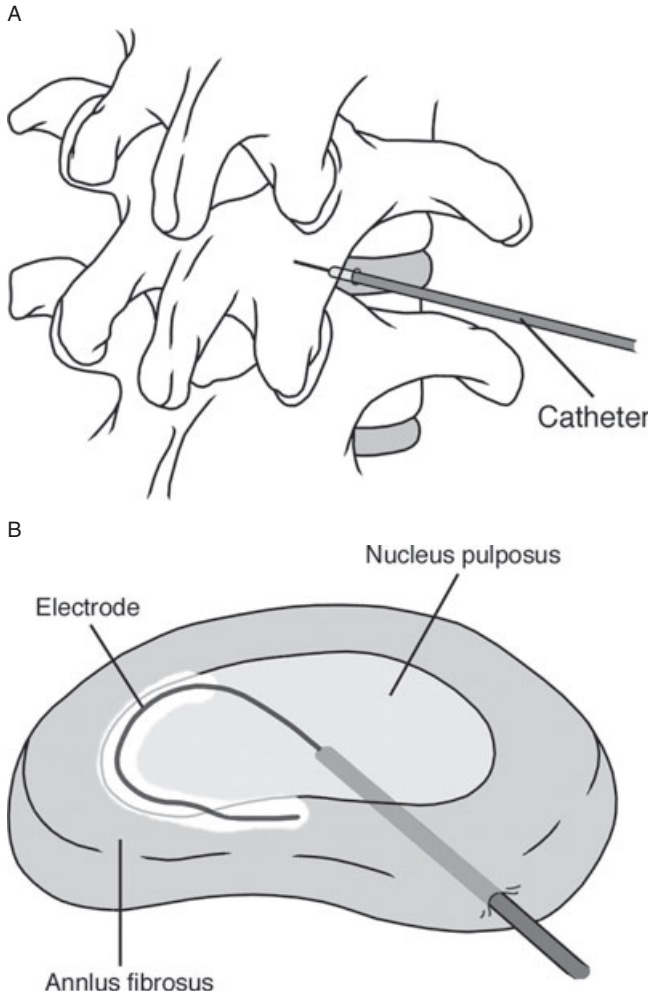


Figure 18. This figure illustrates the technique of Radiofrequency Annuloplasty. (A) The discTRODE™ (Valleylab, Boulder, Colorado) is inserted posterolaterally in the posterior annulus for this technique. (B) RF catheter electrode system uses heat to coagulate and decompress disc material (Courtesy of Valleylab, Boulder, Colorado).

Both a mild sedative and a local anesthetic may be used to reduce any discomfort the patient might experience.

Using X-ray guidance, the physician will insert the discTRODE™ cannula into an intervertebral disc (Figure 18A). The catheter electrode is passed through the cannula into the outer disc tissue (Figure 18B). RF current flows through the electrode, heating the tissue directly adjacent to the active tip of the electrode to a specific treatment temperature. An additional external temperature monitor allows the physician to continuously observe temperature changes in surrounding tissue throughout the procedure.

Complications are similar to IDET with catheter breakage, nerve root injuries, discitis, disc herniation,

cauda equina syndrome, infection, epidural abscess, and spinal cord damage.[114,115]

1C. Biacuplasty. The new annuloplasty procedure termed intradiscal biacuplasty (Baylis Medical Inc., Montreal, Canada) utilizes a bipolar system that includes two cooled, RF electrodes placed on the posterolateral sides of the intervertebral annulus fibrosus. Kapural and Mekhail reported on a young man with severe axial discogenic pain treated with this procedure.[116] The electrodes are placed fluoroscopically. Two 17-gauge transdiscal introducers were placed in the posterior annulus using posterolateral, oblique approach. Then, RF probes were positioned through each of the introducers bilaterally to create a bipolar configuration. There was a gradual increase of the temperature of the electrodes to 55°C over 11 minutes. There were no intraoperative complications. Following the completion of the procedure, the patient was monitored for 45 minutes then discharged home. The patient was followed over a period of 6 months. Outcome assessment included SF-36 and Oswestry questionnaires. Visual analog scale (VAS) pain scores changed from 5 (baseline) to 2 cm at 30 days and 1 cm at 6-month follow-up. Oswestry scale improvement was noted from 14 points prior to the procedure to 11 at 1-month follow-up and 6 points at 6 months.

This procedure warrants future studies to determine the efficacy, complication rates, and possible comparative advantages of this procedure with other minimally invasive procedures for disc lesions.

2. Percutaneous Disc Decompression

2A. Laser Discectomy (Figure 19). Medical lasers have been used since the early 1960s. Ascher, Choy et al. published their experiences with the use of a neodymium : yttrium-aluminum-garnet (Nd : YAG) laser on the lumbar spine for nucleolysis.[117] There are several types of lasers in use for the lumbar spine with the most common being the holmium : yttrium-aluminum-garnet (Ho : YAG) laser, the others are potassium-titanyl-phosphate, and the neodymium (Nd) : YAG laser. The Ho : YAG laser is most commonly paired with the endoscope for disc ablation and removal capabilities.[118,119] This laser-assisted technique combines two effective but limited approaches.

As the affected tissues absorb the laser, light is converted to heat. At 100°C, tissue vaporizes and ablation takes place. As a small amount of nucleus pulposus is vaporized, intradiscal pressure decreases, allowing the disc to return to its normal state.[119,120] If any disc material needs to be removed, endoscopic tools can be used to do so.

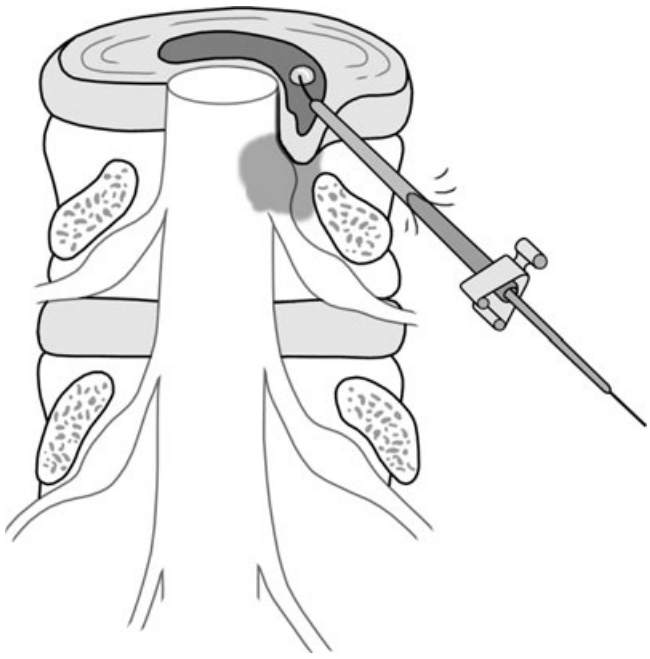


Figure 19. Device used for the LASE® procedure (Clarus Medical).

Procedure. The patient is placed in a prone or lateral position under conscious sedation. An 18-gauge 7-inch needle is introduced just anterior to the superior articular process and superior to the transverse process via a so-called "triangular safe zone." Using fluoroscopy, the needle is placed 1 cm beyond the annulus into the nucleus pulposus just parallel to the disc axis, preferably halfway between the superior and inferior endplates. If the procedure is endoscopically assisted, dilators are placed over the guide needle for visualization and the introduction of the endoscope. Irrigation with saline allows for better visualization of the spaces. Depending on the type, the laser is either fired as a pulse or continuously. The Ho:YAG laser is pulse-fired. Newer laser models offer side-firing capabilities. This advancement helps to provide more control of laser placement, better observation, and can help reduce the risk of injury to several areas, especially those anterior to the spinal column. Larger fragments, which are more difficult to remove through the endoscope, can be laser ablated. After firing the laser and adequate nucleus pulposus has been removed/ablated, the laser and dilators are

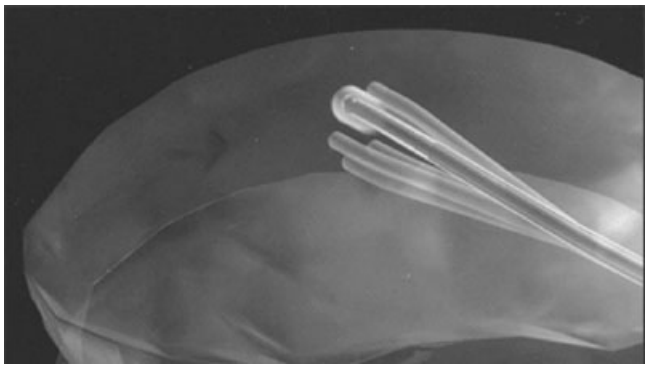


Figure 20. Radiofrequency Coblation (plasma discectomy) (ArthroCare, Sunnyvale, CA, U.S.A.) coagulation channels within the nucleus Pulposus after ablation.

removed. The incision can be closed with sutures or surgical adhesives. The patient is moved to recovery and sent home later in the day.

Indications for laser discectomy include those with back and leg pain with a confirmed disk herniation. A ruptured annulus and lateral recess stenosis are not contraindications. Newer Transforaminal procedures can treat those patients with fragments in the epidural space. In 2002, Tsou and Yeung reported the 9-year retrospective results of their percutaneous transforaminal approach, with an 88.1% excellent to good result.[120] Other studies report success rates from 78% to 85% in retrospective studies.[121] There is a scarcity of clinical trials regarding percutaneous lasers. Negative aspects of the laser include a steep learning curve for the physician. The use of lasers coupled with an endoscopic approach significantly increases the difficulty level for the surgeon.

2B. RF Coblation (Plasma Discectomy). Radiofrequency Coblation (plasma discectomy) (ArthroCare, Sunnyvale, CA, U.S.A.) is another procedure that has broken into the minimally invasive field in the 21st century. The first Nucleoplasty was performed in 2000.

Procedure. Radiofrequency Coblation combines disc removal and thermal coagulation to decompress a contained herniated disc. With the patient in a prone or lateral position under sedation, a posterolateral approach guided by fluoroscopy is made with a 17-gauge obturator stylet. A discogram may take place at this time to confirm location and for a positive provocation test. Taking care not to contact the anterior annulus, the nucleus pulposus is first ablated with RF waves as the wand (Figure 20) is advanced causing a molecular dissociation process converting tissue into gas, which is removed through the needle. As the wand is withdrawn, coagulation takes place thermally treating the channel, which leads to a denaturing of nerve fibers adjacent to the channel within the nucleus pulposus. This process is repeated up to six times within an individual disc. The patient is then sent to recovery and later sent home the same day.

Indications for this procedure include low back pain with or without radiculopathy, MRI confirmation of contained herniated disc, and failed conservative therapy. Patients who should be excluded from receiving this procedure include those with spinal stenosis, a loss of disc height of 50%, severe disc degeneration, spinal fracture or tumor.

2C. Mechanical Disc Decompression (Dekompressor). Few changes have been made in automated discectomy until recently with innovations in automation. The newest entry is the Dekompressor® (Stryker Corporation, Kalamazoo, MI, U.S.A.) introduced in 2002.[122] The Dekompressor® is a disposable, self-contained, battery-operated hand piece connected to a helical probe (Figure 21). The outer cannula measures 1.5 mm with an inner rotating probe. When activated, the probe rotates



Figure 21. Placement of the needle into the inflamed disc with the posterolateral approach for mechanical disc decompression in a model skeleton (with permission from Stryker Corp., Kalamazoo, MI, U.S.A.).

creating suction to pull milled nucleus pulposus from the disk up the cannula to a suction chamber at the base of the handheld unit. Approximately 0.5 to 2 cc of nucleus pulposus is removed. This efficient removal of disc material decreases surgical procedure times to approximately 30 minutes; with the actual time of use for the probe not exceeding 10 minutes. This procedure is performed under fluoroscopic guidance. The Dekompressor technique specifically has yet to be studied in a controlled clinical trial and results with this new automated technique are limited. Percutaneous discectomy generally has a reported success rate of 60% to 87% good outcomes.[123]

2D. Manual PLD. Percutaneous lumbar discectomies have been performed for more than 30 years with overall results ranging from disappointing to good results. The techniques and equipment used for percutaneous discectomy vary widely and have fallen in and out of favor. Hijikata et al. first reported performing a percutaneous *nucleotomy* in 1975.[124] The procedure included the use of 3 to 5 mm cannulas from the posterolateral approach, curettes, and time-consuming manual removal of the nucleus pulposus with pituitary forceps. The theory was that the reduction of Intradiscal pressure would reduce irritation of the nerve root and the nociceptive nerve receptors in the annulus. The procedure remained limited in use until 1985, when Onik et al. developed a new and smaller type of aspiration probe, which reduced risk of injury to the peripheral nerves and the annulus, facilitated easier removal of the nucleus pulposus with an all-in-one suction cutting device, and decreased surgical time.[125]

Procedure. Both procedures use a posterolateral approach to the affected disc on an outpatient basis. The automated procedure is performed while the patient is in a lateral decubitus or prone position. An 18-gauge hubless sheath with a central trocar is guided toward the affected disc. The trocar is removed and a smaller 2.5 mm cannula with an inner blunt end sleeve is placed over the hubless sheath. Once correct placement is confirmed, the hubless sheath is removed, leaving the 2.5 mm cannula. A 2 mm saw is threaded through the cannula and a hole is cut into the annulus for the aspiration probe to be inserted. The aspiration probe is a sharpened cannula fitted through an outer needle. Using suction to pull in disc material, the inner, sharpened cannula uses a slide-like cutting motion to slice the tissue which is then aspirated, along with irrigation, through the inner cannula to a collection bottle. The probe, which is pedal activated, is gently moved back and forth within the disc until no more disc material is aspirated and then the probe is rotated. When aspirated disc material decreases significantly, the probe is removed from the disc space, usually within 20 to 40 minutes.[126–128]

3. Percutaneous Endoscopic Discectomy

Burman in 1931 was the first reported author who introduced the concept of the direct visualization of the spinal cord. A few years later, Mixter and Barr performed an open laminectomy with discectomy for the treatment of a disc herniation into the spinal canal.[129] Later, Pool introduced the concept of intrathecal endoscopy and reported the outcomes of more than 400 myeloscopic procedures.[130] Due to surgical complications of intraspinal surgery, endoscopy remained forgotten until the work carried out by Ooi et al. during the 1970s.[131]

Hijikata et al. in 1975 demonstrated a percutaneous nucleotomy by means of arthroscopy instruments for disc removal for the treatment of posterior or posterolateral lumbar disk herniation under local anesthesia.[132] Kambin described the safe triangular working zone (Kambin's triangle) and results of arthroscopic microdiscectomy, in which arthroscopic visualization of the herniation via the posterolateral approach was used for discectomy of contained herniations (Figure 22). In 1985, Onik et al.[133] reported the development of a 2 mm

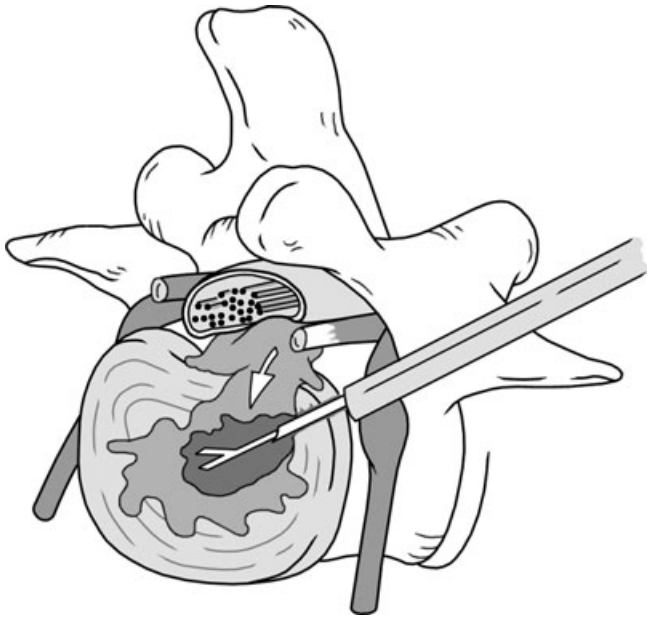


Figure 22. Lumbar Epidural Endoscopic procedure performed: technique of passing the cannula and other instruments in the disc space.

blunt-tipped suction cutting probe for automated percutaneous diskectomy at L4-L5 or higher levels.

Transforaminal Endoscopic Microdiscectomy. The technique of foraminal epidural endoscopic discectomy (FEES) was developed from epidural endoscopy. FEES differs from other percutaneous discectomy procedures in that direct visualization of the epidural space, the pathology, and neuroanatomic structures is possible.[134]

Recently, the use of spinal endoscopy has been enlarged to include closed decompression of spinal roots, use with lasers, epidural biopsies, percutaneous interbody fusion, and lysis of epidural adhesions.

As with other forms of minimally invasive surgical disc procedures, patient selection is critical. Patients should have leg pain more severe than back pain and 6 months of failed conservative therapy. The ideal pathology is a virgin (previously unoperated) paramedian, foraminal, or extraforaminal contained herniation, or one that is noncontained at less than 50% of the canal diameter.

Regional Endoscopic Techniques

Lumbar Discectomy. This is currently the ultimate form of minimally invasive spine surgery. In this technique, an endoscope is used. The whole procedure is performed under local anesthesia and the patient is fully awake during surgery. The patient is made to lie prone on the operating table. An exact entry point is mapped on the patient's body using an image intensifier X-ray system and a long spinal needle is introduced from the posterolateral aspect of the lumbar spine. Through this needle, a guide wire is inserted. Then, a 5 mm incision is made on the skin. Following that, a dilator and a working cannula are inserted under local anesthesia, through which the endoscope is passed. The camera and monitor attached to the endoscope allow the prolapsed part of disc to be removed under direct vision. The wound is closed with a single stitch. The patient usually gets immediate pain relief and can go home in 24 h.

Cervical Discectomy. The discs in the cervical region cannot be approached posteriorly (because of the spinal cord), anteriorly (because of the airway), or posterolaterally (because of the vertebral artery and the uncinate process). Many authors believe that a right-sided approach should always be used for right-handed practitioners and a left-sided approach when left-handed.

The C-arm is placed in the anterior-posterior position with cranial or caudal angulation of the C-arm to optimally visualize the disc space. The cannula puncture site should be made between the carotid sheath and the airway. The carotid pulse at the disc level is then palpated with the index and middle fingers, and the carotid sheath structures are displaced laterally by manual palpation.

OUTCOME

One large-scale prospective nonrandomized investigation followed 402 patients who were treated for disc herniation-associated sciatica.[135] Two groups were formed: The first consisted of 220 patients who had undergone surgery; the second consisted of 182 patients who had chosen to be conservatively (nonsurgically) treated. This study demonstrated that surgical treatment for disc herniation-associated sciatica is faster and slightly more effective than conservative nonsurgical conservative care. There have been reports of more than 7000 automated or manual PLD procedures performed. Published results indicate an overall success rate of 75% with a complication rate of 1%.

Evaluation of Intradiscal Therapies

IDET. Appleby et al.,[136] in a systematic review of the literature in 2006, concluded that there was compelling evidence for the relative efficacy and safety of IDET. Freeman[137] performed a critical appraisal of the evidence of IDET (also published in 2006) and concluded that the evidence for the efficacy of IDET remains weak and has not passed the standard of scientific proof. The present evidence includes one positive randomized trial, one negative randomized trial, seven positive prospective evaluations,[138–144] and two negative reports.[145,146] The evidence for IDET is moderate in managing chronic discogenic low back pain.

Disctrode Procedure. Finch et al.[147] studied 31 patients by heating annular tears with a flexible RF electrode placed across the posterior annulus and compared them to 15 patients receiving conservative management. The VAS decreased significantly. The evidence for RFA was limited for short-term improvement, and indeterminate for long-term improvement in managing chronic discogenic low back pain.

Percutaneous Disc Decompression. Waddell et al.[148] in a systematic review based on Cochrane Collaboration Review and meta-analysis of surgical interventions in the lumbar spine,[149] identified three trials comparing automated PLD (APLD) with other surgical techniques and

concluded there was limited and contradictory evidence. Randomized trials of APLD and microdiscectomy included Chatterjee et al.[150] and Haines et al.[151] Chatterjee et al. compared APLD with microdiscectomy in the treatment of contained lumbar disc herniation in a randomized study with blind assessment. The study included 71 patients with radicular pain as their dominant symptom after failure of conservative therapy for at least 6 weeks and with MRI demonstration of contained disc herniation at a single level with a disc bulge of less than 30% of the canal size. The study excluded patients with dominant symptoms of low back pain, disc extrusion, sequestration, subarticular or foraminal stenosis, or multiple levels of herniation. The results showed satisfactory outcomes in 29% of the patients in the APLD group and 80% of the microdiscectomy group. They concluded that APLD was ineffective as a method of treatment for small, contained lumbar disc herniations. Authors were criticized in that they failed to utilize CT discography.

Haines et al. conducted a randomized study comparing APLD to conventional discectomy as a first-line treatment for herniated lumbar discs.[151] The study measured outcomes with physical signs related to the severity of low back pain and sciatica, but used a modified Roland Scale for disability assessment, and the SF-36 for general health status. The primary endpoint was the patients' outcome ratings 12 months after surgery. The study included patients with unilateral leg pain or paresthesia with no history of lumbar spinal surgery, whereas exclusions included moderate or advanced lumbar spondylosis, spondylolisthesis, lateral restenosis, herniated disc fragment occupying more than 30% of the AP diameter of the spinal canal, herniated disc fragment migrating more than 1 mm above or below the disc space, calcified disc herniation, lateral disc herniation, or posterior disc space height less than 3 mm. Success rate for APLD was 41% compared with conventional discectomy at 40%. However, they concluded that the study did not have power to identify clinically important differences because of insufficient patient enrollment. Among the prospective evaluations and case series studies,[152,153] all of them reported positive results in greater than 50% of patients in a large population. The evidence is moderate for short-term and limited for long-term relief.[154]

Percutaneous Laser Discectomy. Based on the systematic review by Waddell,[148] there is no acceptable evidence for laser discectomy. Relevant studies evaluating the effectiveness of laser disc decompression included 14 studies meeting inclusion criteria. There were no randomized trials. The evidence is moderate for short-term and limited to long-term relief.[154–159]

Plasma Discectomy. There were no systematic reviews evaluating the effectiveness of Nucleoplasty thus far in the literature. The effectiveness of Nucleoplasty has been reported in six prospective studies.[160–165] Sharps and Isaac evaluated 49 patients.[161] The evidence of Nucleoplasty is limited for short- and long-term relief.

Mechanical Disc Decompression. There have been no systematic evaluations of percutaneous disc decompression utilizing DeKompressor. There also have not been any guidelines describing this technology. Amoretti et al.[162] published results of a clinical follow-up of 50 patients treated by PLD using the DeKompressor. Although the study was not a blinded, randomized study, the data collection was thought to be good. The evidence for percutaneous disc decompression utilizing DeKompressor is limited for short- and long-term relief.

NEW THERAPIES

Current treatments attempt to reduce pain rather than repair the degenerated disc. They are mainly conservative and palliative, and are aimed at returning patients to work. They range from bed rest (no longer recommended) to analgesia, the use of muscle relaxants or injection of corticosteroids, or local anesthetic and manipulation therapies. Various interventions (eg, Intradiscal electrotherapy) are also used, but despite anecdotal statements of success, trials thus far have found their use to be of little direct benefit.[144] Disc degeneration-related pain is also treated surgically, either by discectomy or by immobilization of the affected vertebrae, but surgery is offered in only one of every 2000 back pain episodes in the U.K.; the incidence of surgical treatment is five times higher in the U.S.A.[166] The success rates of all these procedures are generally similar. Although a recent study indicated that surgery improves the rate of recovery in well-selected patients,[167] 70% to 80% of patients with obvious surgical indications for back pain or disc herniation eventually recover, whether surgery is carried out or not.[168,169]

Because disc degeneration is thought to lead to degeneration of adjacent tissues and be a risk factor in the development of spinal stenosis in the long term, new treatments are in development that are aimed at restoring disc height and biomechanical function. Some of the proposed biological therapies are outlined below.

Oral Glucosamine and Chondroitin Sulfate Enhance Proteoglycan Synthesis

These agents have been used in multiple trials for peripheral joint osteoarthritis. These reports have generally been exaggerated by publication bias.[170] There is, however, evidence that Glucosamine and Chondroitin sulfate synergistically enhance the natural hypermetabolic repair response of chondrocytes and retard the enzymatic degradation of cartilage. Derby et al. performed a pilot study using Intradiscal injectable Glucosamine and Chondroitin sulfate with DMSO (dimethylsulfoxide) and hypertonic dextrose to promote a reparative response in the intervertebral disc.[171] They hypothesized that the reduction in the pain and disability seen in patients treated with Glucosamine and Chondroitin mixtures results from favorable alteration in the biochemical milieu of the intervertebral disc. Clinical efficacy is similar to that of IDET procedures, but with an improved cost–benefit ratio. There is a need for controlled randomized comparative studies to establish the efficacy of intradiscal glucosamine and chondroitin sulfate injections.

Cell-Based Therapies

The aim of these therapies is to achieve cellular repair of the degenerated disc matrix. One approach has been to stimulate the disc cells to produce more matrix. Growth factors can increase rates of matrix synthesis by up to fivefold.[172,173] In contrast, cytokines lead to matrix loss because they inhibit matrix synthesis while stimulating production of agents that are involved in tissue breakdown.[174] These proteins have thus provided targets for genetic engineering. Direct injection of growth factors or cytokine inhibitors has proved unsuccessful because their effectiveness in the disc is short-lived. Hence gene-therapy is now under investigation; it has the potential to maintain high levels of the relevant growth factor or inhibitor in the tissue. In gene therapy, the gene of interest (eg, one responsible for producing a growth factor such as transforming growth factor-β or inhibiting interleukin-1) is introduced into target cells, which then continue to produce the relevant protein.[175] This approach has been shown to be technically feasible in the disc, with gene transfer increasing transforming growth factor-β production by disc cells in a rabbit nearly sixfold. However, this therapy is still far from clinical use. Apart from the technical problems of delivery of the genes into human disc cells, the correct choice of therapeutic genes requires an improved understanding of the pathogenesis of degeneration. In addition, the cell density in normal human discs is low, and many of the cells in degenerate discs are dead;[20] stimulation of the remaining cells may be insufficient to repair the matrix.[176]

Cell implantation alone or in conjunction with gene therapy is an approach that may overcome the paucity of cells in a degenerate disc. Here, the cells of the degenerate disc are supplemented by adding new cells either on their own or together with an appropriate scaffold. This technique has been used successfully for articular cartilage[177,178] and has been attempted with some success in animal discs.[179] However, at present, no obvious source of clinically useful cells exists for the human disc, particularly for the nucleus, the region of most interest.[180] Moreover, conditions in degenerate discs, particularly if the nutritional pathway has been compromised,[50] may not be favorable for survival of implanted cells. Nevertheless, autologous disc cell transfer has been used clinically in small groups of patients,[180] with initial results reported to be promising.

S. Richardson, of the University of Manchester, in collaboration with Arthro Kinetics has successfully produced nucleus pulposus cells using mesenchymal stem cells (MSCs).[181] He has developed a clinical procedure to inject these cells into the intervertebral disks, thus building disk height and providing more cushion to degenerated disks. This procedure involves mixing the MSCs in a collagenous gel, and then implanting the gel in the intervertebral disc via an arthroscopic procedure. The idea of using one's own stem cells to "regenerate" a dysfunctional intervertebral disc shows promise.

At present, although experimental work demonstrates the potential of these cell-based therapies, several barriers prevent the use of these treatments clinically. Moreover, these treatments are unlikely to be appropriate for all patients; some method of selecting appropriate patients will be required if success with these therapies is to be realized.

Augmentation of Nucleus Pulposus

The objectives of augmentation of the nucleus pulposus following disc removal are to prevent disc height loss and the associated biomechanical and biochemical changes. Free-flowing materials may be injected via a small incision, allowing minimally invasive access to the disc space. Fluids can interdigitate with the irregular surgical defects and may even physically bond to the adjacent tissue. Injectable biomaterials allow for incorporation and uniform dispersion of cells and/or therapeutic agents. Injectable biomaterials have been

developed that may act as a substitute for the disc nucleus pulposus.[182]

Focused on the evaluation of a recombinant protein, copolymer consisting of amino acid sequence blocks has been derived as an injectable. This serves as a biomaterial for augmentation of the nucleus pulposus. This implant, NuCore™ Injectable Nucleus is being developed by Spine Wave (Shelton, CT, U.S.A.). The NuCore™ material is comprised of a solution of the protein polymer and a polyfunctional cross-linking agent. The material closely mimics the protein content, water content, pH, and complex modulus of the natural nucleus pulposus. Characterization studies indicate that the NuCore™ Injectable Nucleus is able to restore the biomechanics of the disc following a microdiscectomy. The material is nontoxic and biocompatible. The mechanical properties of the material mimic those of the natural nucleus pulposus. Thus, NuCore™ Injectable Nucleus is suitable to replace the natural nucleus pulposus following a discectomy procedure. Human clinical evaluation is under way in a multicenter clinical study using the material as an adjunct to microdiscectomy.

Regeneration of the Cartilage Endplate

New studies are under way to explore methods for repair and regeneration of the cartilage endplate.[183] The goal is to restore the endplates as closely as possible to their natural state prior to disease or degeneration. The nature of the treatment will depend upon the form of the endplate degeneration and on the type of scaffolding that is intended to be introduced into the nuclear cavity. Endplate therapy is a potential means of enhancing biomaterial integration and cell survival, but remains a long-term and currently untested methodology.

Disc Implantation

The newest technology in back surgery is the artificial disc replacement surgery or disc implantation surgery.[184] In this procedure, the biological injured or degenerated disc material is removed and an artificial disc is implanted in the spine. The technology has been used for many years in Europe, but is still mostly in trial stages in the U.S.A.

Spinal disc replacement is not only possible, but is an exciting area of clinical investigation that has the potential of revolutionizing the treatment of spinal degeneration. The development of a prosthetic disc poses tremendous challenges, but the results from initial efforts have been promising. The future for this field, and our patients, is bright.

REFERENCES

1. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000;84:95–103.
2. Luoma K, Riihimaki H, Luukkonen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. *Spine*. 2000;25:487–492.
3. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am*. 1990;72:403–408.
4. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs. Volvo Award in basic science. *Spine 2002*. 2002;27:2631–2644.
5. Miller J, Schmatz C, Schultz A. Lumbar disc degeneration. Correlation with Age, Sex, and Spine Level in 600 Autopsy Specimens. *Spine*. 1988;13:173–178.
6. Twomey LT, Taylor JR. Age changes in lumbar vertebrae and intervertebral discs. *Clin Orthop*. 1987;224:97–104.
7. Roberts S, Menage J, Urban JPG. Biochemical and structural properties of the cartilage end-plate and its relation to the intervertebral disc. *Spine*. 1989;14:166–174.
8. Inoue H. Three-dimensional architecture of lumbar intervertebral discs. *Spine*. 1981;6:139–146.
9. Yu J, Winlove CP, Roberts S, Urban JP. Elastic fibre organization in the intervertebral discs of the bovine tail. *J Anat*. 2002;201:465–475.
10. Maroudas A, Nachemson A, Stockwell R, Urban J. Some factors involved in the nutrition of the intervertebral disc. *J Anat*. 1975;120:113–130.
11. Marchand F, Ahmed AM. Investigation of the laminate structure of lumbar disc anulus fibrosus. *Spine*. 1990; 15:402–410.
12. Errington RJ, Puustjarvi K, White IR, Roberts S, Urban JP. Characterisation of cytoplasm-filled processes in cells of the intervertebral disc. *J Anat*. 1998;192:369–378.
13. Bruehlmann SB, Rattner JB, Matyas JR, Duncan NA. Regional variations in the cellular matrix of the annulus fibrosus of the intervertebral disc. *J Anat*. 2002;201:159–171.
14. Roberts S, Eisenstein SM, Menage J, Evans EH, Ashton IK. Mechanoreceptors in intervertebral discs. Morphology, distribution, and neuropeptides. *Spine*. 1995;20: 2645–2651.
15. Crock HV, Goldwasser M, Yoshizawa H. Vascular anatomy related to the intervertebral disc. In: Ghosh P, ed. *Biology of the Intervertebral Disc*. Boca Raton, FL: CRC Press; 1991:109–133.
16. Johnson WE, Evans H, Menage J, Eisenstein SM, El Haj A, Roberts S. Immunohistochemical detection of Schwann cells in innervated and vascularized human intervertebral discs. *Spine*. 2001;26:2550–2557.
17. Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine*. 1995;20:1307–1314.

18. Johnson WEB, Eisenstein SM, Roberts S. Cell cluster formation in degenerate lumbar intervertebral discs is associated with increased disc cell proliferation. *Connect Tissue Res.* 2001;42:197–207.

19. Hastreiter D, Ozuna RM, Spector M. Regional variations in certain cellular characteristics in human lumbar intervertebral discs, including the presence of alpha-smooth muscle actin. *J Orthop Res.* 2001;19:597–604.

20. Trout JJ, Buckwalter JA, Moore KC. Ultrastructure of the human intervertebral disc: II. Cells of the nucleus pulposus. *Anat Rec.* 1982;204:307–314.

21. Gruber HE, Hanley EN. Analysis of aging and degeneration of the human intervertebral disc—comparison of surgical specimens with normal controls. *Spine.* 1998;23:751–757.

22. Eyre DR, Muir H. Quantitative analysis of types I and II collagens in the human intervertebral disc at various ages. *Biochimica Biophysica Acta.* 1977;492:29–42.

23. Johnstone B, Bayliss MT. The large proteoglycans of the human intervertebral disc. Changes in their biosynthesis and structure with age, topography, and pathology. *Spine.* 1995;20:674–684.

24. Urban JP, Maroudas A, Bayliss MT, Dillon J. Swelling pressures of proteoglycans at the concentrations found in cartilaginous tissues. *Biorheology.* 1979;16:447–464.

25. Sztrolovics R, Alini M, Roughley PJ, Mort JS. Aggrecan degradation in human intervertebral disc and articular cartilage. *Biochem J.* 1997;326:235–241.

26. Roberts S, Caterson B, Menage J, Evans EH, Jaffray DC, Eisenstein SM. Matrix metalloproteinases and aggrecanase: their role in disorders of the human intervertebral disc. *Spine.* 2000;25:3005–3013.

27. Weiler C, Nerlich AG, Zipperer J, Bachmeier BE, Boos N. 2002 SSE Award Competition in Basic Science: expression of major matrix metalloproteinases is associated with intervertebral disc degradation and resorption. *Eur Spine J.* 2002;11:308–320.

28. Donohue PJ, Jahnke MR, Blaha JD, Caterson B. Characterization of link protein(s) from human intervertebral-disc tissues. *Biochem J.* 1988;251:739–747.

29. Lyons G, Eisenstein SM, Sweet MB. Biochemical changes in intervertebral disc degeneration. *Biochim Biophys Acta.* 1981;673:443–453.

30. Inkinen RI, Lammi MJ, Lehmonen S, Puustjarvi K, Kaapa E, Tammi MI. Relative increase of biglycan and decorin and altered chondroitin sulfate epitopes in the degenerating human intervertebral disc. *J Rheumatol.* 1998;25:506–514.

31. Antoniou J, Steffen T, Nelson F, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. *J Clin Invest.* 1996;98:996–1003.

32. Hollander AP, Heathfield TF, Liu JJ, et al. Enhanced denaturation of the alpha (II) chains of type-II collagen in normal adult human intervertebral discs compared with femoral articular cartilage. *J Orthop Res.* 1996;14:61–66.

33. Duance VC, Crean JK, Sims TJ, et al. Changes in collagen cross-linking in degenerative disc disease and scoliosis. *Spine.* 1998;23:2545–2551.

34. Johnson SL, Aguiar DJ, Ogilvie JW. Fibronectin and its fragments increase with degeneration in the human intervertebral disc. *Spine.* 2000;25:2742–2747.

35. Urban JPG, McMullin JF. Swelling pressure of the lumbar intervertebral discs: influence of age, spinal level, composition and degeneration. *Spine.* 1988;13:179–187.

36. Frobin W, Brinckmann P, Kramer M, Hartwig E. Height of lumbar discs measured from radiographs compared with degeneration and height classified from MR images. *Eur Radiol.* 2001;11:263–269.

37. Adams MA, McNally DS, Dolan P. "Stress" distributions inside intervertebral discs. The effects of age and degeneration. *J Bone Joint Surg Br.* 1996;78:965–972.

38. McNally DS, Shackleford IM, Goodship AE, Mulholland RC. In vivo stress measurement can predict pain on discography. *Spine.* 1996;21:2580–2587.

39. Adams MA, Dolan P, Hutton WC, Porter RW. Diurnal changes in spinal mechanics and their clinical significance. *J Bone Joint Surg Br.* 1990;72:266–270.

40. Postacchini F, Gumina S, Cinotti G, Perugia D, DeMartino C. Ligamenta flava in lumbar disc herniation and spinal stenosis. Light and electron microscopic morphology. *Spine.* 1994;19:917–922.

41. Maroudas A. Biophysical chemistry of cartilaginous tissues with special reference to solute and fluid transport. *Biorheology.* 1975;12:233–248.

42. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson M-IV. Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet.* 1997;350:178–181.

43. Johnson WE, Caterson B, Eisenstein SM, Hynds DL, Snow DM, Roberts S. Human intervertebral disc aggrecan inhibits nerve growth in vitro. *Arthritis Rheum.* 2002;46:2658–2664.

44. Melrose J, Roberts S, Smith S, Menage J, Ghosh P. Increased nerve and blood vessel ingrowth associated with proteoglycan depletion in an ovine anular lesion model of experimental disc degeneration. *Spine.* 2002;27:1278–1285.

45. Boos N, Rieder R, Schade V, Spratt KF, Semmer N, Aebi M. Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. *Spine 1995.* 1995;20:2613–2625.

46. Cavanaugh JM. Neural mechanisms of lumbar pain. *Spine.* 1995;20:1804–1809.

47. Kang JD, Georgescu HI, McIntyre-Larkin L, Stefanovic-Racic M, Donaldson WF, Evans CH. Herniated lumbar intervertebral discs spontaneously produced matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. *Spine.* 1996;21:271–277.

48. Kawakami M, Tamaki T, Weinstein JN, Hashizume H, Nishi H, Meller ST. Pathomechanism of pain-related behavior produced by allografts of intervertebral disc in the rat. *Spine*. 1996;21:2101–2107.

49. Olmarker K, Rydevik B. Disc Herniation and sciatica; the basic science platform. In: Gunzburg R, Szpalski M, eds. *Lumbar Disc Herniation*. Philadelphia: Lippincott. Williams & Wilkins; 2002:31–37.

50. Nachemson A, Lewin T, Maroudas A, Freeman MAF. In vitro diffusion of dye through the end-plates and annulus fibrosus of human lumbar intervertebral discs. *Acta Orthop Scand*. 1970;41:589–607.

51. Ishihara H, Urban JP. Effects of low oxygen concentrations and metabolic inhibitors on proteoglycan and protein synthesis rates in the intervertebral disc. *J Orthop Res*. 1999;17:829–835.

52. Ohshima H, Urban JPG. Effect of lactate concentrations and pH on matrix synthesis rates in the intervertebral disc. *Spine*. 1992;17:1079–1082.

53. Horner HA, Urban JP. Volvo Award Winner in Basic Science Studies: effect of nutrient supply on the viability of cells from the nucleus pulposus of the intervertebral disc. *Spine 2001*. 2001;26:2543–2549.

54. Holm S, Maroudas A, Urban JP, Selstam G, Nachemson A. Nutrition of the intervertebral disc: solute transport and metabolism. *Connect Tissue Res*. 1981;8:101–119.

55. Urban JP, Holm S, Maroudas A. Diffusion of small solutes into the intervertebral disc: as in vivo study. *Biorheology*. 1978;15:203–221.

56. Kauppila LI, McAlindon T, Evans S, Wilson PW, Kiel D, Felson DT. Disc degeneration/back pain and calcification of the abdominal aorta. A 25-year follow-up study in Framingham. *Spine*. 1997;22:1642–1647.

57. Kauppila LI. Prevalence of stenotic changes in arteries supplying the lumbar spine. A postmortem angiographic study on 140 subjects. *Ann Rheum Dis*. 1997;56:591–595.

58. Jones JP. Subchondral osteonecrosis can conceivably cause disk degeneration and 'primary' osteoarthritis. In: Urbaniak JR, Jones JP, eds. *Osteonecrosis*. Park Ridge, IL: American Academy of Orthopedic Surgeons; 1997:135–142.

59. Holm S, Nachemson A. Variation in the nutrition of the canine intervertebral disc induced by motion. *Spine*. 1983;8:866–874.

60. Holm S, Nachemson A. Nutritional changes in the canine intervertebral disc after spinal fusion. *Clin Orthop*. 1982;169:243–258.

61. Roberts S, Urban JPG, Evans H, Eisenstein SM. Transport properties of the human cartilage end-plate in relation to its composition and calcification. *Spine*. 1996;21:415–420.

62. Allan DB, Waddell G. An historical perspective on low back pain and disability. *Acta Orthop Scand Suppl*. 1989;234:1–23.

63. Puustjarvi K, Takala T, Wang W, Tammi M, Helminen H, Inkinen R. Proteoglycans in the interverterbal disc of young dogs following strenuous running exercise. *Conn Tiss Res*. 1993;30:1–16.

64. Iatridis JC, Mente PL, Stokes IA, Aronsson DD, Alini M. Compression-induced changes in intervertebral disc properties in a rat tail model. *Spine*. 1999;24:996–1002.

65. Lotz JC, Colliou OK, Chin JR, Duncan NA, Liebenberg E. 1998 Volvo Award winner in biomechanical studies—compression-induced degeneration of the intervertebral disc: an in vivo mouse model and finite-element study. *Spine*. 1998;23:2493–2506.

66. Osti OL, Vernon-Roberts B, Fraser RD. 1990 Volvo Award in experimental studies. Anulus tears and intervertebral disc degeneration. An experimental study using an animal model. *Spine*. 1990;15:762–767.

67. Lipson SJ, Muir H. Experimental intervertebral disc degeneration: morphologic and proteoglycan changes over time. *Arthritis Rheum*. 1981;24:12–21.

68. Heikkila JK, Koskenvuo M, Heliovaara M, et al. Genetic and environmental factors in sciatica. Evidence from a nationwide panel of 9365 adult twin pairs. *Ann Med*. 1989;21:393–398.

69. Matsui H, Kanamori M, Ishihara H, Yudoh K, Naruse Y, Tsuji H. Familial predisposition for lumbar degenerative disc disease. A case-control study. *Spine*. 1998;23:1029–1034.

70. Varlotta GP, Brown MD, Kelsey JL, Golden AL. Familial predisposition for herniation of a lumbar disc in patients who are less than twenty-one years old. *J Bone Joint Surg Am*. 1991;73:124–128.

71. Battie MC, Videman T, Gibbons LE, Fisher LD, Manninen H, Gill K. 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine*. 1995;20:2601–2612.

72. Sambrook PN, MacGregor AJ, Spector TD. Genetic influences on cervical and lumbar disc degeneration: a magnetic resonance imaging study in twins. *Arthritis Rheum*. 1999;42:366–372.

73. Battie MC, Haynor DR, Fisher LD, Gill K, Gibbons LE, Videman T. Similarities in degenerative findings on magnetic resonance images of the lumbar spines of identical twins. *J Bone Joint Surg Am*. 1995;77:1662–1670.

74. Watanabe H, Nakata K, Kimata K, Nakanishi I, Yamada Y. Dwarfism and age-associated spinal degeneration of heterozygote cmd mice defective in aggrecan. *Proc Natl Acad Sci USA*. 1997;94:6943–6947.

75. Li SW, Prockop DJ, Helminen H, et al. Transgenic mice with targeted inactivation of the Col2 alpha 1 gene for collagen II develop a skeleton with membranous and periosteal bone but no endochondral bone. *Genes Dev*. 1995;9:2821–2830.

76. Kimura T, Nakata K, Tsumaki N, et al. Progressive

degeneration of articular cartilage and intervertebral discs. An experimental study in transgenic mice bearing a type IX collagen mutation. *Int Orthop*. 1996;20:177–181.

77. 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: 2022–2028.

78. Videman T, Gibbons LE, Battie MC, et al. The relative roles of intragenic polymorphisms of the vitamin D receptor gene in lumbar spine degeneration and bone density. *Spine*. 2001;26:E7–E12.

79. Jones G, White C, Sambrook P, Eisman J. Allelic variation in the vitamin D receptor, lifestyle factors and lumbar spinal degenerative disease. *Ann Rheum Dis*. 1998;57:94–99.

80. Sachs BL, Vanharanta H, Spivey MA, et al. Dallas discogram description: a new classification of CT/discography in low back disorders. *Spine*. 1987;12:287–294.

81. Aprill C, Bogduk N. High intensity zone. *Br J Radiol*. 1992;65:361–369.

82. Schellhas KP, Pollei SR, Gundry CR, et al. Lumbar disc high-intensity zone. Correlation of magnetic resonance imaging and discography. *Spine*. 1996;21:79–86.

83. Brodsky AE, Binder WF. Lumbar discography. *Spine*. 1979;4:110–120.

84. Wiley JJ, Macnab I, Wortzman G. Lumbar discography and its clinical applications. *Can J Surg*. 1986;11:280–289.

85. Heggeness MH, Doherty BJ. Discography causes end plate deflection. *Spine*. 1993;18:1050–1053.

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

87. Oh WS, Shim JC. A randomized controlled trial of radiofrequency denervation of the ramus communicans nerve for chronic discogenic low back pain. *Clin J Pain*. 2004;20: 55–60.

88. Morinaga T, Takahashi K, Yamagata M, et al. Sensory innervation to the anterior portion of lumbar intervertebral disc. *Spine*. 1996;21:1848–1851.

89. Ohtori S, Takahashi Y, Takahashi K, et al. Sensory innervation of the dorsal portion of the lumbar intervertebral disc in rats. *Spine*. 1999;24:2295–2299.

90. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. Seattle: IASP Press; 1994:180–181.

91. Crock HV. Internal disc disruption. A challenge to disc prolapse fifty years on. *Spine*. 1986;11:650–653.

92. Schwarzer AC, Aprill CN, Derby R, et al. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine*. 1995;20:1878–1888.

93. Bernard TN. Lumbar discography followed by computed tomography. Refining the diagnosis of low-back pain. *Spine*. 1990;15:690–707.

94. Bogduk N. The lumbar disc and low back pain. *Neurosurg Clinics North Am*. 1991;2:791–806.

95. Vanharanta H, Sachs BL, Spivey M, et al. A comparison of CT/discography, pain response and radiographic disc height. *Spine*. 1988;13:321–324.

96. Osti OL, Vernon-Roberts B, Fraser RD. Volvo Award—anulus tears and intervertebral disc degeneration: an animal model. *Spine*. 1990;15:762–766.

97. Moore RJ, Osti OL, Vernon-Roberts B. Osteoarthrosis of the facet joints resulting from anular rim lesions. *Spine*. 1999;24:519–524.

98. Moore RJ, Vernon-Roberts B, Osti OL, Fraser RD. Remodeling of vertebral bone after outer anular injury in sheep. *Spine*. 1996;21:936–940.

99. Key JA, Ford LT. Experimental intervertebral disc lesions. *J Bone Joint Surg*. 1948;30A:621.

100. Moore RJ, Osti OL, Vernon-Roberts B, et al. Changes in endplate vascularity after an outer anulus tear in the Sheep. *Spine*. 1992;17:874–877.

101. Kim KS, Yoon ST, Li J, et al. Disc degeneration in the rabbit: a biochemical and radiological comparison between four disc injury models. *Spine*. 2005;30:33–37.

102. Jaikumar S, Kim DH, Kam AC. History of minimally invasive spine surgery. *Neurosurgery*. 2002;51(suppl 5): 1–14.

103. Maroon JC. Current concepts in minimally invasive discectomy. *Neurosurgery*. 2002;51(suppl 5):137–145.

104. Thomas L. Reversible collapse of rabbit ears after intravenous papain. *J Exp Med*. 1956;104:245–252.

105. Kamblin P, Savitz MH. Arthroscopic microdiscectomy: an alternative to open disc surgery. *Mount Sinai J Med*. 2000;67:283–287.

106. Kim YS, Chin DK, Yoon DH, et al. Predictors of successful outcome for lumbar chemonucleolysis: analysis of 3000 cases during the past 14 years. *Neurosurgery*. 2002; 51(suppl 5):123–128.

107. Buric j Molino Lova R. Ozone Chemonucleolysis in non-contained disc herniations: a pilot study with 12 months follow-up. *Acta Neurochir Suppl*. 2005;92:93–97.

108. Saal JA, Saal JS. Intradiscal electrothermal treatment for chronic discogenic low back pain: prospective outcome study with a minimum 2-year follow-up. *Spine*. 2002;27:966–973.

109. Deen HG, Fenton DS, Lamer TJ. Minimally invasive procedures for disorders of the lumbar spine. *Mayo Clin Proc*. 2003;78:1249–1256.

110. Saal JS, Saal JA. Management of chronic discogenic low back pain with a thermal intradiscal catheter: a preliminary report. *Spine*. 2000;25:382–388.

111. Yeurn AT. The evolution of percutaneous spinal endoscopy and discectomy: state of the art. *Mt Sinai J Med*. 2000;67:327–332.

112. Biyani A, Andersson GB, Chaudhary H, An HS.

Intradiscal electrothermal therapy: a treatment option in patients with internal disc disruption. *Spine*. 2003;28(155): S8–S14.

113. Appleby D, Andersson G, Totta M. Metaanalysis of the efficacy and safety of intradiscal electrothermal therapy (IDET). *Pain Med*. 2006;4:308–316.

114. Ackerman WE. Cauda equina syndrome after intradiscal electrothermal therapy. *Reg Anaesth Pain Med*. 2002;27:622.

115. Cohen SP, Larkin T, Polly DW Jr. A giant herniated disc following intradiscal electrothermal therapy. *J Spinal Disord Techn,*. 2002;15:537–541.

116. Kapural L, Mekhail N. Novel Intradiscal Biacuplasty (IDB) for the treatment of Lumbar Discogenic Pain. *Pain Practice J*. 2007;7:130–135.

117. Choy DS. Percutaneous laser disc decompression (PLDD): twelve years' experience with 752 procedures in 518 patients. *J Clin Laser Med Surg*. 1998;16:325–331.

118. Smith L, Garvin PJ, Jennings RB, et al. Enzyme dissolution of the nucleus pulposus. *Nature*. 1963;198:1211–1212.

119. Chawla J. Laser discectomy. *eMedicine J*. 2006;7. Available at: http://author.emedicine.com/neuro/topic683.htm (accessed June 4, 2007).

120. Tsou PM, Yeung AT. Transforaminal endoscopic decompression for radiculopathy secondary to intracanal noncontained lumbar disc herniations: outcome and technique. *Spine J*. 2002;2:41–48.

121. Nucleoplasty overview. Available at: http://www.nucleoplasty.com/video.aspx?video=1&rate=high (accessed June 4, 2007).

122. Dekompressor for Clinicians. *Interventional Pain Sitemap*. revisionhip.com/instruments/products/dekompressor/clinic.htm-22k: Stryker Corp.; 2004.

123. Ascher PW, Heppner F. CO-2 laser in neurosurgery. *Neurosurg Rev*. 1984;7:123–133.

124. Hijikata SA. A method of percutaneous nuclear extraction. *J Toden Hosp*. 1975;5:39.

125. Onik G, Helms CA, Ginsburg L, et al. Percutaneous lumbar diskectomy using a new aspiration probe. *Am J Roentgenol*. 1985;144:1137–1140.

126. Macroon JC, Onik G, Sternau L. Percutaneous automate discectomy: a new approach to lumbar surgery. *Clin Ortho Rel Res*. 1989;238:64–70.

127. Jacobaeus HC. Possibility of the use of cytoscope for investigation of serious cavities. *Munch Med Wochenschr*. 1910;57:2090–2092.

128. Macroon JC, Onik G, Vidovich DV. Percutaneous discectomy for lumbar herniation. *Neurosurg Clin North Am*. 1993;4:125–134.

129. Mixter WJ, Barr JS. Rupture of intervertebral disc with involvement of spinal canal. *N Engl J Med*. 1934;11: 210–215.

130. Pool JL. Myeloscopy: intraspinal endoscopy. *Surgery*. 1942;11:169–182.

131. Ooi Y, Sato Y, Morisaki N. Myeloscopy: the possibility of observing the lumbar intrathecal space by use of an endoscope. *Endoscopy*. 1973;5:901–906.

132. Hijikata S, Yamagishi M, Nakayama T, et al. Percutaneous diskectomy: a new treatment method for lumbar disc herniation. *J Toden Hosp*. 1975;39:5–13.

133. Onik G, Helms CA, Ginsburg L, et al. Percutaneous lumbar diskectomy using a new aspiration probe. *Am J Roentgenol*. 1985;144:1137–1140.

134. Mathews HH. Transforaminal endoscopic microdiscectomy. *Neurosurg Clin North Am*. 1996;7:59–63.

135. Atlas SJ, Keller RB, Wu YA, Deyo RA. Singer DE. Long-term outcomes of surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the Maine lumbar spine study. *Spine*. 2005;30:927–935.

136. Appleby D, Andersson G, Totta M. Metaanalysis of the efficacy and safety of intradiscal electrothermal therapy (IDET). *Pain Med*. 2006;4:308–316.

137. Freeman BJC. IDET. A critical appraisal of the evidence. *Eur Spine J*. 2006;15:S448–S457.

138. Kapural L, Hayek S, Malak O, et al. Intradiscal thermal annuloplasty versus intradiscal radiofrequency ablation for the treatment of discogenic pain: a prospective matched control trial. *Pain Med*. 2005;6:425–431.

139. Karasek M, Bogduk N. Twelve-month follow-up of a controlled trial of intradiscal thermal annuloplasty for back pain due to internal disc disruption. *Spine*. 2000;25:2601–2607.

140. Derby R, Eek B, Chen Y, et al. Intradiscal electrothermal annuloplasty (IDET): a novel approach for treating chronic discogenic back pain. *Neuromodulation*. 2000;3:82–88.

141. Gerszten PC, Welch WC, McGrath PM, et al. A prospective outcome study of patients undergoing intradiscal electrotherapy (IDET) for chronic low back pain. *Pain Physician*. 2002;5:360–364.

142. Saal JA, Saal JS. Intradiscal electrothermal treatment for chronic discogenic low back pain: prospective outcome study with a minimum 2-year follow-up. *Spine*. 2002;27:966–973.

143. Lutz C, Lutz GE, Cooke PM. Treatment of chronic lumbar diskogenic pain with intradiscal electrothermal therapy: a prospective outcome study. *Arch Phys Med Rehabil*. 2003;84:23–28.

144. Mekhail N, Kapural L. Intradiscal thermal annuloplasty for discogenic pain: an outcome study. *Pain Pract*. 2004;4:84–90.

145. Spruit M, Jacobs WC. Pain and function after intradiscal electrothermal treatment (IDET) for symptomatic lumbar disc degeneration. *Eur Spine J*. 2002;11:589–593.

146. Freedman BA, Cohen SP, Kuklo TR, et al. Intradiscal electrothermal therapy (IDET) for chronic low back pain in

active duty soldiers: 2-year follow-up. *Spine J*. 2003;3:502–509.

147. Finch PM, Price LM, Drummond PD. Radiofrequency heating of painful annular disruptions: one-year outcomes. *J Spinal Disord Techn*. 2005;18:6–13.

148. Waddell G, Gibson A, Grant I. Surgical treatment of lumbar disc prolapse and degenerative lumbar disc disease. In: Nachemson AL Jonsson E, eds. *Neck and Back Pain: The Scientific Evidence of Causes, Diagnosis and Treatment*. Philadelphia: Lippincott, Williams & Wilkins; 2000:305–326.

149. van Tulder MW, Assendelft WJ, Koes BW. The Editorial Board of the Cochrane Collaboration Back Review Group + Method Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine*. 1997;22:2323–2330.

150. Chatterjee S, Foy PM, Findlay GF. Report of a controlled clinical trial comparing automated percutaneous lumbar discectomy and microdiscectomy in the treatment of contained lumbar disc herniation. *Spine*. 1995;20:734–738.

151. Haines SJ, Jordan N, Boen JR, et al. Discectomy strategies for lumbar disc herniation: study design and implications for clinical research. *J Clin Neurosci*. 2002;9:440–446.

152. Bernd L, Schiltenwolf M, Mau H, et al. No indications for percutaneous lumbar discectomy? *Int Orthop*. 1997;21:164–168.

153. Fiume D, Parziale G, Rinaldi A, et al. Automated percutaneous discectomy in herniated lumbar discs treatment: experience after the first 200 cases. *J Neurosurg Sci*. 1994;38:235–237.

154. Delamarter RB, Howard MW, Goldstein T, et al. Percutaneous lumbar discectomy. Preoperative and postoperative magnetic resonance imaging. *J Bone Joint Surg Am*. 1995;77:578–584.

155. Bosacco SJ, Bosacco DN, Berman AT, et al. Functional results of percutaneous laser discectomy. *Am J Orthop*. 1996;25:825–828.

156. Choy DS. Percutaneous laser disc decompression (PLDD): twelve years' experience with 752 procedures in 518 patients. *J Clin Laser Med Surg*. 1998;16:325–331.

157. Siebert WE, Berendsen BT, Tollgaard J. Percutaneous laser disk decompression. Experience since. *Orthopade 1996*. 1989;25:42–48.

158. Ohnmeiss DD, Guyer RD, Hochschuler SH. Laser disc decompression. The importance of proper patient selection. *Spine*. 1994;19:2054–2058.

159. Liebler WA. Percutaneous laser disc nucleotomy. *Clin Orthop Relat Res*. 1995;310:58–66.

160. Singh V, Piryani C, Liao K, et al. Percutaneous disc decompression using coblation (nucleoplasty) in the treatment of chronic discogenic pain. *Pain Physician*. 2002;5:250–259.

161. Sharps LS, Isaac Z. Percutaneous disc decompression using nucleoplasty. *Pain Physician*. 2002;5:121–126.

162. Amoretti N, David P, Grimaud A, et al. Clinical follow-up of 50 patients treated by percutaneous lumbar discectomy. *Clin Imaging*. 2006;30:242–244.

163. Singh V, Piryani C, Liao K. Evaluation of percutaneous disc decompression using coblation in chronic back pain with or without leg pain. *Pain Physician*. 2003;6:273–280.

164. Marin FZ. CAM versus nucleoplasty. *Acta Neurochir Suppl*. 2005;92:111–114.

165. Gerszten PC, Welch WC, King JT. Quality of life assessment in patients undergoing nucleoplasty-based percutaneous discectomy. *J Neurosurg Spine*. 2006;4:36–42.

166. Waddell G. *The Back Pain Revolution*. Edinburgh: Churchill Livingstone; 1998.

167. Fritzell P, Hagg O, Wessberg P, Nordwall A. Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine 2001*. 2001;26:2521–2532.

168. Weber H. A controlled, prospective study with ten years of observation. *Spine*. 1983;8:131–140.

169. Gibson JN, Grant IC, Waddell G. Surgery for lumbar disc prolapse. *Cochrane Database Syst Rev*. 2000; *Spine*. 24 (17): CD001350.

170. McAlindon TE, LaValley MP, Gulin JP, et al. Glucosamine and Chondroitin for treatment of Osteoarthritis: a systematic quality assessment and met-analysis. *JAMA*. 2000;283:1469–1475.

171. Derby R, Eek B, Lee S-H, Seo KS, Kim B-J. Comparison of Intradiscal Restorative Injections and Intradiscal Electrothermal Treatment (IDET) in the treatment of Low Back Pain. *Pain Physician*. 2004;7:63–66.

172. Thompson JP, Oegema TR, Bradford DS. Stimulation of mature canine intervertebral disc by growth factors. *Spine*. 1991;16:253–260.

173. Osada R, Ohshima H, Ishihara H, et al. Autocrine/paracrine mechanism of insulin-like growth factor-1 secretion, and the effect of insulin-like growth factor-1 on proteoglycan synthesis in bovine intervertebral discs. *J Orthop Res*. 1996;14:690–699.

174. Takegami K, Thonar EJ, An HS, Kamada H, Masuda K. Osteogenic protein-1 enhances matrix replenishment by intervertebral disc cells previously exposed to interleukin-1. *Spine*. 2002;27:1318–1325.

175. Nishida K, Kang JD, Gilbertson LG, et al. Modulation of the biologic activity of the rabbit intervertebral disc by gene therapy: an in vivo study of adenovirus-mediated transfer of the human transforming growth factor beta 1 encoding gene. *Spine*. 1999;24:2419–2425.

176. Roberts S, Hollander AP, Caterson B, Menage J, Richardson JB. Matrix turnover in human cartilage repair tissue in autologous chondrocyte implantation. *Arthritis Rheum*. 2001;44:2586–2598.

177. Brittberg M. Autologous chondrocyte transplantation. *Clin Orthop Rel Res*. 1999;367(suppl):S147–S155.

178. Gruber HE, Johnson TL, Leslie K, et al. Autologous intervertebral disc cell implantation: a model using Psammomys obesus, the sand rat. *Spine*. 2002;27:1626–1633.

179. Alini M, Roughley PJ, Antoniou J, Stoll T, Aebi M. A biological approach to treating disc degeneration: not for today, but maybe for tomorrow. *Eur Spine J*. 2002;11(suppl 2):S215–S220.

180. Ganey TM, Meisel HJ. A potential role for cell-based therapeutics in the treatment of intervertebral disc herniation. *Eur Spine J*. 2002;11(suppl 2):S206–S214.

181. Richardson SM, Walker RV, Parker S, Rhodes NP. Intervertebral disc cell-mediated mesenchymal stem cell differentiation. *Stem Cells*. 2006;24 (3):707–716.

182. Boyd LM, Carter AJ. Injectable biomaterials and vertebral endplate treatment for repair and regeneration of the intervertebral disc. *European Spine J*. 2006;15(suppl 3):414–421.

183. Lotz JC, Kim AJ. Disc regeneration. *Why, When How Neurosurg Clin N Am*. 2005;16:657–663.

184. Huang RC, Sandhu HS. The current status of lumbar total disc replacement. *Orthop Clin North Am*. 2004;35:33–42.

View publication stats