Pathophysiology of lumbar disc degeneration: a review of the literature

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Lumbar disc degeneration occurs because of a variety of factors and results in a multitude of conditions. Alterations in the vertebral endplate cause loss of disc nutrition and disc degeneration. Aging, apoptosis, abnormalities in collagen, vascular ingrowth, loads placed on the disc, and abnormal proteoglycan all contribute to disc degeneration. Some forms of disc degeneration lead to loss of height of the motion segment with concomitant changes in biomechanics of the segment. Disc herniation with radiculopathy and chronic discogenic pain are the result of this degenerative process.

KEY WORDS • lumbar • disc • degeneration • pathophysiology • review • anatomy

Lumbar disc degeneration occurs commonly in humans. There are a variety of factors that contribute to this condition. The disc itself is active tissue that contains significant mechanisms for self-repair.[26] Reviewing the available literature concerning the normal and abnormal physiology of the disc is useful in understanding why degeneration occurs, why certain conditions are painful, and which mechanisms can be used to prevent further degeneration.

ANATOMY OF THE INTERVERTEBRAL DISC

The intervertebral disc is composed of at least three elements. The central portion of the disc contains the nucleus pulposus, which is composed of cells from the primitive notochord. The outer portion of the disc is the anulus fibrosis, and it is composed of concentric layers of intertwined anular bands. These anular bands are arranged in a specific pattern to resist forces placed on the lumbar spine. The anular bands are subdivided into inner fibers, which are connected to the cartilaginous endplate, and outer Sharpy fibers, which are attached to the VB (Fig. 1). The ALL and PLL further strengthen the disc space. The ALL attaches more strongly to the VB edges than to the anulus. It provides a tension band to resist forces applied in extension and is a stronger ligament than the PLL. The PLL is not as strong as the ALL, but it provides a tension band to resist flexion forces. The PLL strongly attaches to the anulus fibrosis, and frequently is torn in cases of free fragment disc herniation.

A meningeal branch of the spinal nerve, better known as the recurrent sinuvertebral nerve, innervates the area around the disc space (Fig. 2). This nerve exits from the dorsal root ganglion and enters the foramen, where it then divides into a major ascending and lesser descending branch.[9] It has been shown in animal studies that further afferent innervation to the sinuvertebral nerve arises via the rami communicantes from multiple superior and inferior dorsal root ganglia.[43] In both human and animal studies, the outer anular regions are innervated, but the inner regions and nucleus pulposus are not innervated.[37,48] In addition studies have demonstrated that the ALL also receives afferent innervation from branches that originate in the dorsal root ganglion.[7] The PLL is richly innervated by nociceptive fibers from the major ascending branch of the sinuvertebral nerve. These nerves also innervate the adjacent outer layers of the anulus fibrosis.[7,37] Degenerated human lumbar discs have been shown to contain more nerve tissue and to be more vascular than normal discs.[9,12,48]

PROTEOGLYCAN AND WATER CONTENT

The strength of the lumbar disc is related to the fluid and proteoglycan content of the disc. Proteoglycan is a

Abbreviations used in this paper: ALL = anterior longitudinal ligament; IL = interleukin; MMP = matrix metalloproteinase; NO = nitric oxide; PG = prostaglandin; PGE = prostaglandin E; PLL = posterior longitudinal ligament; VB = vertebral body.

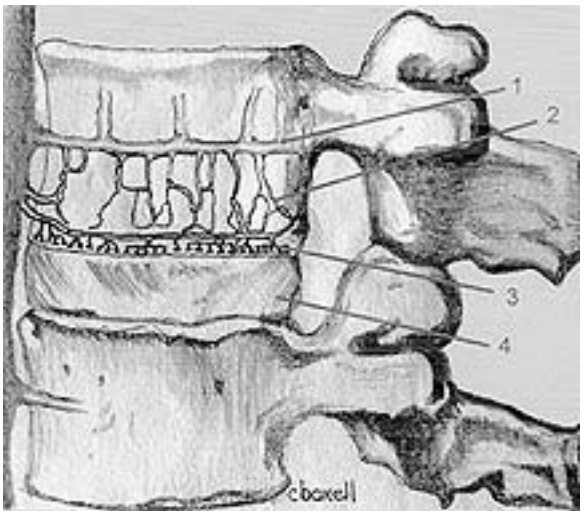

Fig. 1. Artist's illustration showing the vascular supply to the disc space from the cartilaginous endplate. 1 = segmental radicular artery; 2 = interosseous artery; 3 = capillary tuft; and 4 = disc anulus.

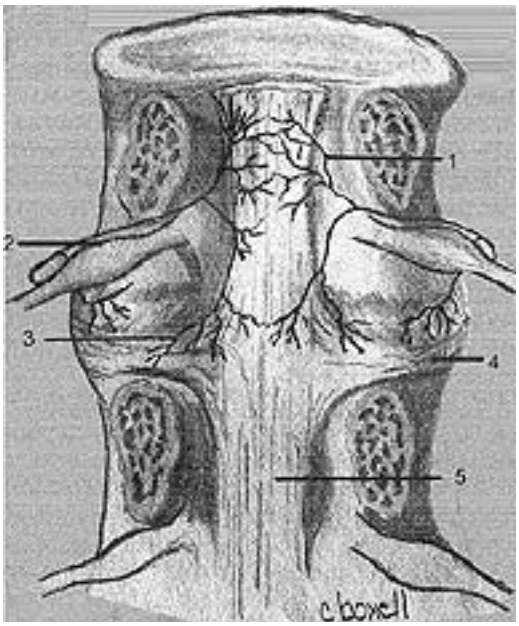

Fig. 2. Artist's illustration showing innervation of the PLL and the disc anulus; 1 = ascending branch of the sinuvertebral nerve; 2 = dorsal root ganglion; 3 = descending branch of the sinuvertebral nerve; 4 = disc anulus; 5 = PLL.

hydrophilic, negatively charged, branched chain molecule composed of a protein attached to an oligosaccharide. Proteoglycans are also known as glycosaminoglycans and include such structures as chondroitin and collagen. The negative charge on the branched chains and the hydrophilic nature of proteoglycan internally pressurize the disc by drawing water via osmosis into the nucleus pulposus. Unfortunately, proteoglycan and therefore water content in the disc tend to decrease with age.[1-3,51,65] Additionally the amount of hydration within the disc is inversely proportional to applied stress, suggesting that applied spinal loads lead to a loss of hydration and proteoglycan in the disc.[65] Interestingly, proteoglycan, and thus water content, has also been shown to be low throughout the entire spine in patients with degenerated discs.[51] Studies have shown that applied stress produces degenerative change in the disc; however, it remains unclear whether degeneration in vivo is the result of stress applied to an already biochemically altered disc or a response to stress by an otherwise normal disc. Disc degeneration may have a genetic basis; Sahlman, et al.,[59] have shown that mice that are heterozygotes for the knockout gene, *Col2a1*, related to Type II collagen, had 4% shorter spines and a decreased concentration of glycosaminoglycans in their endplates, vertebrae, and anuli fibrosis.

Degenerated discs have been demonstrated to vary specifically in the degree of sulfation of chondroitin.[27] Degenerated discs lacked adequate sulfation of chondroitin when compared with controls, and the degree of degeneration was greater in higher grade degeneration. The specific disaccharide involved was chondroitin sulfate,[6] which had been reduced to unsulfated chondroitin in degenerated sections. This study suggested a possible mechanism for the increased incidence of posterior failure of the disc, because the degree of undersulfation was accentuated in the nucleus pulposus as well as the posterior central segment of the anulus fibrosis. Another specific anular proteoglycan, fibromodulin, exhibits a structural change with increasing age that is characterized by a proportional increase in its glycoprotein form, which lacks keratin sulfate.[61]

VASCULARITY OF THE DISC

The disc itself has a low metabolic rate and receives most of its nutrition by diffusion.[26] Bulk transport contributes somewhat to nutrition of the disc and this is facilitated by spinal motion.[25] The majority of disc nutrition is supplied via the capillary beds of the cartilaginous VB endplate.[10] Blood flow to these capillary beds is under humoral control, which increases with application of acetylcholine.[58] Early research suggests muscarinic receptors exist on the cartilaginous endplate, implying a possible mechanism of the negative effects of nicotine on the endplate.[58] These capillary beds receive blood flow from the distal branches of the interosseous arteries supplying the VB. Disruption of the cartilaginous endplate leads to formation of Schmoral nodes.[34] Vascular and lymphatic tissue is present in the anulus of patients who are as old as age 20 years; however, lymphatics and blood vessels are not present in the nucleus pulposus at any age.[56] The concentration of oxygen has been found to be greatest at the disc edge, and the concentration of lactate is greatest in the center, which is the portion of the disc farthest from the blood supply.[4] Although the concentrations of oxygen and lactate vary widely from person to person, they do not seem to change in pathological states.[4]

Changes in the vascular supply appear in disc degeneration. Normal anastomotic arteries on the anterolateral surface are obliterated and replaced by small, tortuous arteries in degenerated anuli.[33] The arterial changes occur before the degenerative process and may be related to the

ingrowth of vessels from osteophyte formation.[33] This implies a relationship between nutrition to the disc and subsequent disease. Some authors believe that neovascularity occurs in response to injury as an attempt to supply the damaged portion of the disc with nutrients.[66] Others suggest that vascularization of the anulus occurs in response to trauma and that the new vessels are associated with endothelial cells, fibroblasts, and mononuclear cells.[53] Surgical specimens have been compared with those from normal cadaveric disc and it has been found that the vasculature of normal discs was not associated with additional cells, but instead with an inactive collagen matrix.[53] Both macrophages and blood vessels have been found to be prominent in herniated disc fragments, but the presence or absence of these entities could not be correlated with the timing of radicular pain.[67]

COLLAGEN DISTRIBUTION

Collagen is a widely distributed proteoglycan in the body. Type I collagen is usually found in skin, bone, tendon, and dentin. Types II and IX are normally found in hyaline cartilage and vitreous humor. Type III collagen can be found in skin and blood vessels. Type VI is found in most interstitial tissues. Type I collagen is found in the nucleus pulposus and anulus fibrosis in both normal and pathologically degenerated discs, whereas Type II and IX collagen are found to be increased in areas of minor degeneration but absent in areas of more advanced disease.[44] In contrast, Lotz, et al.,[40] found that Type II collagen is decreased at all levels of applied mechanical stress. In another study the total amount of collagen was found to be highest in patients 5 to 15 years of age, and in this study the amount of denatured Type II was decreased in degenerated discs.[2,3] Types III and VI were increased in areas of degeneration regardless of the degree.[44] A marker of oxidative stress related to modification of the protein structure of collagen, *N*-(carboxymethyl)lysine, has been shown to increase with advancing degenerative disease.[45]

Additional studies of the collagen composition of the disc have revealed the importance of collagen crosslinks to the mechanical stability of the intervertebral disc. A decrease in the presence of pyridinoline and an increase in pentosidine within the disc are associated with aging.[52] The concentration of pyridinoline found in patients older than 65 years was approximately 50% of that found in younger people. Decreases in pyridinoline crosslinks lead to alterations in the collagen matrix of the disc. Cells in the disc have the potential to produce a matrix that is inappropriate for the mechanical stresses placed on it.[20]

It has also been suggested that matrix degeneration within the nucleus may result from the increase in certain proteinases that do not appear in the normal disc. Leukocyte elastase, which is normally found in the VB, may be at least partially responsible for the degeneration of the extracellular matrix in the anulus, nucleus, and endplate.[13]

ROLE OF APOPTOSIS

Apoptosis is programmed cell death and occurs in both normal and pathological states. The role of apoptosis in lumbar disc degeneration is not fully understood. It is apparent that an inappropriate disc matrix is produced in degenerated lumbar discs.[20] This inappropriate matrix may isolate cells in the disc and lead to apoptosis. Further experimentation has indicated that apoptosis occurs at a higher rate in cases of free disc fragments compared with contained disc herniations.[50] This increased rate of apoptosis in free disc herniations may be a possible mechanism of resorption and remodeling of the extruded material. In vitro evidence suggests that certain cytokines, namely insulin-like growth factor-1 and platelet-derived growth factor, can inhibit apoptosis in cell cultures of disc material.[21] In vivo experiments indicate that disc tissue responds in an autocrine fashion; that is, the cells release substances to which the cells themselves respond.[31,36,49] This has been shown to be different in degenerated compared with normal disc tissue, and it has been hypothesized that these substances can lead to disc degeneration.[36,49] These studies all indicate that the disc is much more active biologically than previously thought, and further research may provide pharmacological means to change the natural history of disc degeneration.

MECHANICAL STRESS AND INFLAMMATORY COMPONENTS

Authors of multiple studies have evaluated mechanical stress as applied to the intervertebral disc. Disc degeneration is related to mechanical stresses. Degeneration may begin in early adulthood and may change the disc in such a way that herniation is imminent.[23] The levels most commonly affected are L4-5 and L5-S1. Although degeneration at one of these two levels is correlated with disease at the other, there is no correlation with disease in facet joints.[17] Disease in either the facet joints or the disc is not reliably correlated with patient age. Stress in the vertebral column is transmitted mostly to the endplates of the VB and less to the core of the body.[39] In healthy individuals the stress is transmitted from the center of the endplate, whereas in a degenerative state, stress is transmitted more to the peripheral rather than the central aspects of the VB. This is thought to be due to the loss of hydration of the nucleus pulposus that accompanies aging.[39]

Other biomechanical studies have focused on the effect of applied stress. A study in which cadaveric disc was used and with motion was applied in flexion-extension, axial rotation, and lateral bending showed that the laxity of a degenerated disc is increased and the range of motion is decreased.[41] Spine flexibility and, thus range of motion, was shown to be reduced in degeneration because of the increasing size of the endplate and the decreasing height of the intervertebral disc space. The increased laxity of the motion segment was found to be due to decreased disc height of the nucleus with resultant loss of tension of the surrounding ligaments.[41] When intradiscal pressure is increased, degenerated discs herniate at lower pressures than normal discs.[28] It may be possible that a certain critical pressure exists above which the stressed anulus is unable to counteract the force applied, resulting in rupture.[28] Umehara, et al.,[64] reported that the anulus in degenerated discs is abnormal and that its elastic modulus is lowest in the posterolateral section of the disc. The same group demonstrated that symmetry and regularity of the

elastic modulus decrease as the grade of degeneration increases. Others have shown that the degenerated disc had reduced ability to withstand applied stress and that the section of anulus most responsible for this is the middle portion.[14]

Applied stress may trigger certain biochemical events within the disc. Degenerated discs have higher than normal concentrations of fibronectin, which may be elevated as part of the response to injury.[47] This may translate to an increase in proteolytic activity.[47] Mechanical stress has also been shown to increase the activity of MMPs 2 and 9 in articular cartilage, indicating an increase in tissue turnover that has the potential to weaken the disc.[5] Increases in MMPs, NO, PGE-2, and IL-6 are also seen in herniated discs.[32] Cathespin G, a proteinase with a wide variety of biochemical actions, has been shown to be increased in the anulus of degenerated discs.[38] It has also been suggested that applied stress may decrease the expression of Type II collagen and result in disorganization of the anulus fibrosus.[40]

The herniated disc also induces an inflammatory response. In a dog model with autologous implantation of both nucleus and anulus, Hasegawa and colleagues[24] showed that nucleus fragments induce an inflammatory reaction. The number of lymphocytes, macrophages, and fibroblasts was markedly increased in samples from older dogs.[24] Others have examined human samples, finding that macrophages are the most commonly found cell type in both acute and chronic herniation.[19,22,29] Despite this finding, evidence of macrophage infiltration does not correlate with clinical symptoms in humans.[55] Interestingly, the presence of inflammation in patients does correlate with a better postoperative outcome when compared with those with herniated discs showing no inflammation.[69] A study in rats revealed an increase in the expression of IL-1β, IL-6, and NO synthetase 1 week after implantation of nucleus fragments.[35] Further progression of the inflammatory response may be caused by IL-1β; the addition of this cytokine to normal disc tissue in vitro causes an increase in MMPs, IL-6, PGE-2, and NO.[32] Degradation of the proteins in the extracellular matrix of the disc may also be caused by MMP's. Other inflammatory mediators, such as IL-1α and tumor necrosis factor-β, are also present in the herniated disc and may in crease the amount of PGE-2.[62] The painful disc may be the result of the effect of PGE-2, and, in fact, a positive straight-leg raise result has been correlated with the amount of PGE-2.[46] Some controversy exists as to whether levels of tumor necrosis factor-α and phospholipase A2 are increased in the herniated disc.[11,18,57,58]

In addition to the inflammatory mediators already mentioned, authors of one study found that two thirds of patients with lumbar disc disease and radicular symptoms had an increase in antiglycosphingolipid antibodies, suggesting an autoimmune component to lumbar disc disease.[8] Another group of authors showed that there are antigen-antibody complexes present in the herniated disc, although no conclusions were made regarding their clinical significance.[60] The theory that there is an autoimmune component to lumbar disc disease is controversial; others authors have demonstrated a lack of cells that were expected in an antigen-specific inflammatory response, although the number of macrophages is known to be increased.[22,34]

DISC HERNIATION

It has been widely held that symptoms of lumbar disc disease are the result of either herniation of the nucleus pulposus through a mechanically weak anulus fibrosis or from tearing of the anulus itself. This can lead to radiculopathy from nerve root compression or an inflammatory process affecting nerve roots or the spinal cord. Herniation is thought to be the result of a defect in the anulus fibrosis, most likely the result of excessive stress applied to the disc.[15] Histological evaluation has revealed that whatever the cause of the tear, the extruded portion always involves material from the nucleus pulposus.[42] Herniation most often occurs on the posterior or posterolateral aspect of the disc.[28] Morphological characteristics, namely the arrangement of the anular fiber bundles, seem to contribute to the propensity for disc herniation on the posterior aspect of the disc. This directs the herniation toward the exiting and traversing nerve roots.[63]

The degree of disease in the lumbar spine is characterized by the location of the abnormal portion of the disc.[30] A disc bulge is a symmetrical extension of the disc beyond the endplates, whereas a protrusion is a focal area of extension still attached to the disc.[16,30] An extruded fragment is one that is no longer connected to the disc, and a sequestered fragment is contained within the PLL.[16,30]

CONCLUSIONS

The lumbar discs most often affected by degeneration that leads to herniation are L4-5 and L5-S1, most probably because of a combination of longstanding degeneration and a subsequent change in the ability of the disc to resist applied stress. Discs that are degenerated show abnormal vascularity, and abnormal distribution of collagen and collagen crosslinks. They also show an abnormal and nonuniform elastic modulus that distributes stress to critical portions of the disc. Radicular pain is often associated with disc herniation, which may be due, in part, to an inflammatory response to the portion of nucleus that has been extruded. This inflammation is characterized by an increase in the number of macrophages and an increase in IL-1β, with a subsequent release of PGE-2. Although the relative importance of these diverse pathological changes is unclear, it is clear that lumbar disc degeneration and herniation are multifactoral processes and that both mechanical and biochemical derangements exist.

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