Section II

Spinal Pathologies

II

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Section II-A

Bony Pathologies

II

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13 Degenerative Disk Disease

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Abstract
Intervertebral disks (IVDs) are essential components of spinal stability. Degeneration of IVDs is associated with structural failure and can lead to chronic back pain. IVDs have three main components: the nucleus pulposus (NP), annulus fibrosus (AF), and endplates (EPs), each with unique biochemical compositions that suit them for their respective roles. The NP helps to maintain IVD height and distribute loading forces, the AF contains the NP and maintains its pressurization, while the EP serves as a growth plate for vertebral bodies during childhood. Although disk degeneration has an assumed association with chronic low back pain, a clear causal relationship has not been established. The etiology of disk degeneration is a combination of genetic (various gene polymorphisms) and environmental factors (such as obesity and smoking). Disk degeneration begins with degradation of proteoglycans, resulting in disk dehydration and impaired ability to resist loading forces. Excessive stress in turn leads to the production of several inflammatory mediators and catabolic factors, further contributing to the degenerative cascade. MRI is the imaging modality of choice to evaluate suspected disk degeneration, although there is a high incidence of asymptomatic patients with radiographic disc degeneration. There are several potential treatments that are being developed with the potential to manage disk degeneration. These include biomolecular interventions and injection of protein solutions, cell implantation via gene-based therapy, and tissue engineering that can create implantable IVD material. These therapies have been studied to a relatively limited extent and have several potential drawbacks that should be considered.

Keywords: intervertebral disk, degeneration, chronic low back pain, interventions

13.1 Introduction

Intervertebral disks (IVDs) are fibrocartilaginous pads that resist compression while also allowing limited flexibility, spreading the load evenly across the vertebral bodies even when flexed.[1] Degeneration of IVD is associated with structural failure and commonly associated with chronic low back pain. Low back pain is the second leading cause of visits to a physician (second to upper respiratory problems), the most common cause of work-related disability in people under 45 years of age, and the most expensive cause of work-related disability. Up to 80% of the population is affected at some point in life, and 1 to 2% of the U.S. adult population are disabled because of low back pain.[2,3,4] The estimated annual direct medical cost was $315.4 billion from 2012 to 2014, while the indirect cost equated to about $264 million lost workdays in 2014–2015.[5]

Various factors have been implicated in the etiology of lumbar degenerative disk disease, and understanding these processes is crucial in the clinical management of this disease in terms of current and future therapies. This chapter will explore the basic disk anatomy, etiologic factors associated, pathophysiology of disk degeneration, and the current therapies being researched.

13.2 Disk Anatomy and Physiology

The IVD has three main components: a composite structure of gelatinous proteoglycan-rich nucleus pulposus (NP), a collagen-rich annulus fibrosus (AF) that surrounds the NP, and the cartilaginous endplates (EPs) that separate the NP and AF from the adjacent vertebral bones.[6] The NP consists of a proteoglycan and water gel held loosely together by an irregular network of collagen type II fibers and elastin fibers. Aggrecan is the predominant proteoglycan that has a high anionic glycosaminoglycan component that leads to the highly hydrated nature of the NP and helps maintain IVD height and distribute loading across EPs.[7,8] The AF consists of 15 to 25 lamellae composed primarily of collagen type I fibers. These collagen fibers are parallel within each lamellae and perpendicular between adjacent lamellae, thus creating the tensile strength of the AF.[9] The function of the AF is to contain the NP and maintain its pressurization under compressive loads. The EP is a thin, horizontal layer of hyaline cartilage that serves as a growth plate for vertebral bodies in childhood.[9]

Up until about 5 years of age, vascular channels that deliver nutrients throughout the IVD traverse the EPs; however, by adulthood, the EPs are avascular and the NP is 8 mm away from the nearest blood supply.[10,11] As blood vessels are restricted to the outermost aspects of the annulus, cell nutrition is delivered via diffusion for small molecules and bulk fluid flow for larger molecules.[10,12] The NP exhibits a low oxygen tension state that leads to anaerobic metabolism, resulting in a high lactic acid concentration and low pH. Based on in vitro studies, a chronic lack of oxygen can result in NP cells becoming dormant, whereas a chronic lack of glucose can kill them. Thus, this low oxygen microenvironment can negatively impact cellular function and the disk's ability to recover from any metabolic or mechanical injury.[9,12]

13.3 Etiology of Degenerative Disk Disease and Low Back Pain

It is understood that the socioeconomic impacts of lower back pain are enormous. However, while there is an assumed association between degenerative disk disease and lower back pain, there has yet to be a causal relationship formally established and a specific etiology is still to be determined.[13] There have been several studies examining asymptomatic patients with lumbar magnetic resonance imaging (MRI) demonstrating degenerative disk disease.[14,15,16,17] Based on conventional thinking, if degenerative disk disease were a predominant factor in the etiology of low back pain, then it would be uncommon in the asymptomatic patient.

There have been studies showing pain provocation associated with relatively innocuous mechanical stimulation of the outer

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posterior annulus and EP. The posterior annulus is supplied by the sinuvertebral nerve, a mixed autonomic and somatic nerve. Nociceptive fibers normally penetrate the outermost 1 to 3 mm of the annulus, but have been reported to progress toward the NP of severely disrupted disks.[18,19] Painful disks are always structurally disrupted and appear to become sensitized to mechanical loading. Based on animal studies, contact with the NP can lower nerve stimulation thresholds and therefore result in painful stimuli.[18,20,21,22] Disk features most closely associated with pain include prolapse, disk narrowing, and radial fissures, especially when they reach the disk exterior and "leak," and internal collapse of the AF. EP fractures and disk bulging have a variable relationship with the painful sensation of low back pain.[17,23,24,25]

Various factors, both genetic and environmental, play a role in disk degeneration. As one ages, there is a decrease in nutrient supply, which negatively impacts the ability of the IVD to adequately respond to increased load or injury. Structural damage accrued over time will further propagate the degenerative cycle.[26] However, genetics may play a larger role than both inadequate nutrition and mechanical injury, and twin studies have noted a 70% genetic contribution to an individual's risk.[27,28] Polymorphisms are in the various genes for catabolism that can contribute to IVD degradation. Any increases in the inflammatory cascade can cause the polymorphisms to affect the balance between anabolic and catabolic mediators. Polymorphisms within interleukin-1 (IL-1), IL-6, and cyclooxygenase-2 (COX-2) have been associated with degenerative disk disease, and COX-2 specifically has been thought to contribute to the pain cascade.[29,30,31]

Environmental factors also play a role in the degeneration of IVD. It was previously believed that repetitive physical loading was a major risk factor; however, twin studies have shown that this only plays a minor role in degeneration.[32] Obesity has been implicated as a risk factor, with recent studies indicating a body mass index (BMI) $> 25\,\text{kg/m}^2$ as an independent risk factor for radiographic findings and obesity at a young age as a strong risk factor for an increased number of degenerated disks.[33] Other studies indicate obesity increases IL-6 levels and thus the catabolic pathway leading to degeneration.[34] Cigarette smoking is the only chemical exposure that has been associated with disk degeneration as it is assumed to limit blood flow to vertebral EPs. An animal model showed increased production and release of proinflammatory cytokines with resultant chondrocyte decomposition.[35] Regardless of the etiology, the end result is degradation of the disk.

13.4 Pathophysiology

The functionality of the IVD depends largely on the extracellular matrix (ECM), a dynamic network of structural proteins that contributes to the IVD's ability to resist mechanical loading and tensile forces as well as the necessary environment for cell maintenance and survival.[36] The ECM is composed of macromolecules consisting of collagens, proteoglycans, and glycoproteins. Collagen is organized into fibrillar networks to provide the tensile strength, and elastin provides the needed elasticity to prevent delamination and help the lamellar recover after tensile loads.[37,38,39,40] Proteoglycans are negatively charged and enable for the IVD to remain hydrated. By attracting and retaining water, it allows a swelling pressure to develop and resist compression from axial loading. The glycoproteins provide structural support and help fine-tune tissue functionality as well as organize and assemble the ECM.[36] The IVD is also largely composed of water, and the concentration varies based on age, location in the disk, and body position.[41,42] The most hydrated area is the central region of the disk, the NP. In infancy, the water content of the NP is as high as 90% and subsequently falls to around 80% in the nondegenerate disk of an adult,[43] while the water content is around 65% in the outer AF.

The most important early change is the degradation of proteoglycans, including aggrecan, which leads to dehydration of the IVD and subsequent structural damage.[44] The AF must now resist compressive forces directly, which causes it to become stiff and weak, and propagates the degenerative pathway. Excessive stress causes production of inflammatory mediators and increases the number of catabolic factors. Degeneration also results in disorganization and destruction of the collagen matrix, which affects the mechanics of the disk and increases the risk of herniation and major annular tears.[45,46]

Various imaging modalities continue to be developed to better evaluate disk degeneration, and MRI is considered the modality of choice.[47] Based on MRI analyses, dehydration of the NP is indicative of IVD degeneration that progressively worsens and can be associated with tears within the AF or EP. These MRI changes are thought to be caused by failure of the tissue structures from ECM alterations. Tears in the AF may occur due to disruptions of organized collagen networks or mineralization of the EP, which, in turn, affects the nutrient supply and causes early cellular senescence or cell death.[36] Contrast enhancement for CT or MRI rapidly diffuses in a degenerated disk and will appear brighter due to the lower concentration of proteoglycans.[48] Magnetic resonance spectroscopy (MRS) is able to detect the metabolite concentration of a tissue. This modality can noninvasively detect the amount of lactic acid in the IVD, which increases in the degenerating disk.[48]

However, it is important to clinically correlate radiographic findings as many patients can be asymptomatic. In one MRI study of asymptomatic patients, 52% had a disk bulge on imaging, 27% with a protrusion, and 1% with extrusion.[17] Another study noted 24% of 300 myelograms performed on asymptomatic patients showed an abnormality of the lumbar disk.[49]

13.5 Advancements in Treatment

The increased burden associated with lower back pain has led to a greater need for understanding and improving existing treatment strategies. As such, animal models, both in vivo and in vitro, have been developed. In vitro models allow for a greater understanding of specific pathways and components of IVD degeneration, while in vivo models more accurately replicate the inherently complex process.[50] The mouse lumbar IVD most closely matches the human IVD.[51] Understanding the differences and similarities of animal models to the human IVD allows the implementation of interventions to better translate these findings to clinical therapies.

The amount of degeneration present in the IVD also provides an insight into the disk's biology at that time and determines

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what interventions are available. In earlier stages, biomolecular interventions could rebalance anabolic and catabolic pathways in the degenerative cascade.[18,50] Protein solutions can be injected directly into IVD in order to stimulate cell growth and/or anabolic responses with the goal of reversing the degenerative cascade and further degeneration.[52] Prior studies have shown the IVD responding to exogenous growth factors.[53,54] There have been various in vivo studies that have shown increased proteoglycan content of the NP, increased disk height, and improved MRI findings.[55,56,57,58] However, these interventions currently are limited by the short duration of its therapeutic benefits. The delivery method for therapeutic proteins involves puncturing the AF, which, in turn, can generate a catabolic cascade that has previously been shown to cause an acceleration of disk degeneration in a 10-year follow-up of patients undergoing discography.[59,60] Previous attempts have been made to repair the AF with suturing and anuloplasty on in vivo models; however, these techniques failed to improve tensile strength.[61,62] New modalities are being studied and developed, which, in time, could have great potential in conjunction with other modalities at clinically managing degenerative disk disease.

Intermediate stages of degeneration, characterized with less active and rapidly disappearing viable cells, allow for cell implantation via gene-based therapy in order to repopulate the disk and are based on inducing changes to the intradiscal gene expression.[50] Genes are delivered via vector and are either injected directly or transduced into the cell. Currently, viral vectors are being utilized as nonviral vectors are still in development.[63] The biggest drawback to using viral vectors is the potential for mutagenesis leading to malignancies, as with retrovirus vectors, or immune responses, as with adenovirus vectors. There is also a large expense associated with the preparation and the still unknown risks to patients.

Tissue engineering can be utilized in advanced stages to mimic the native disk[50] as there is little potential for reversal of damage via the other two therapies. Introducing a substitute for the damaged disk can function as a scaffold to maintain the disk integrity, and physical conditioning of the cells should also be performed.[64,65,66] With the current advancements in technology, tissue-engineered whole-implantable IVD has been created that allow both AF and NP composites to replace the degenerated disk. Its use has been successfully demonstrated in animal models with similar properties to the native disk in both biomechanical and biochemical testing.[67,68] These disk analogs can autonomously regenerate disk morphology and functionality after implantation; however, more studies are needed as there have only been two translational studies performed so far.[53]

13.6 Conclusion

Spinal disorders continue to be a challenge in both health care and for society. The increasing knowledge of the anatomy and pathophysiology of the IVD has already allowed for the development of therapies based on the level of disk degeneration. More advancements are being investigated, which will further shape the management and treatments for degenerative disk disease and lower back pain.

13.7 Tips and Pearls

- IVDs are important contributors to spinal stability, and degeneration can lead to structural failure and chronic low back pain.
- Disk degeneration is caused by underlying genetic factors, including gene polymorphisms that regulate metabolic and inflammatory pathways.
- Disk degeneration is also caused by environmental factors such as obesity and smoking.
- Treatment of disk disease is dependent upon the degree of degeneration present. Current and future options include injections of protein solutions, gene therapy to modify cell proliferation, and tissue implantation.

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