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Future advances for treating lumbar disc herniation and degeneration: Nucleus replacement, annular repair, and biologics

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ABSTRACT

Intervertebral disc disease is a prevalent and costly clinical problem in the United States. Disease-modifying therapies applied at the early stages of disease are desirable compared to the traditional and variably effective surgical options for end-stage disease. A better understanding of the normal intervertebral disc and the molecular and cellular basis of disc degeneration has led researchers to investigate innovative therapies. Specifically the developments of biomaterial-based hydrogels and annular patches, cell implantation, growth factor modulation, and gene transduction techniques all hold clinical promise. The most powerful therapy may combine several of these modalities to achieve long-standing results.

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1. Background

Low-back pain is one of the most burdensome musculoskeletal disorders in the United States affecting nearly 29% of American adults and triggering 5% of health care provider visits annually.[1] The direct costs of back pain management are immense, and estimates of indirect costs (such as lost wages and productivity) are significantly greater.[2] Approximately 5% of the American work force misses at least one day of work annually due to low-back pain, and low-back pain is the single most common cause of disability among adults aged 45 years or younger. As the average age of the population increases and individuals are retiring later, these costs are anticipated to increase.[2] Given these concerns, a better understanding of the etiology of back pain and improved therapeutic interventions are needed.

The intervertebral disc (IVD) has long been considered a common source of low-back pain, and classically two etiologies have been proposed: (1) pain caused by herniation of IVD material and (2) pain emanating from the disc itself (i.e., discogenic back pain or degenerative disc disease).[3] The concept of a painful disc herniation dates back over 80 years[4] and possible pain generators include the inflammatory changes found in the herniated nucleus pulposus,[5] fissures in the annulus with neurovascular ingrowth,[6] and disc impingement on surrounding structures (e.g., nerve roots) (Fig. 1). Evidence suggests that most patients with symptomatic disc herniation will improve with non-operative therapy, but surgery may provide more effective relief in those patients with severe symptoms.[7] Lumbar discectomy is the most common surgical procedure performed in the United States for patients experiencing back and leg pain.[8] While

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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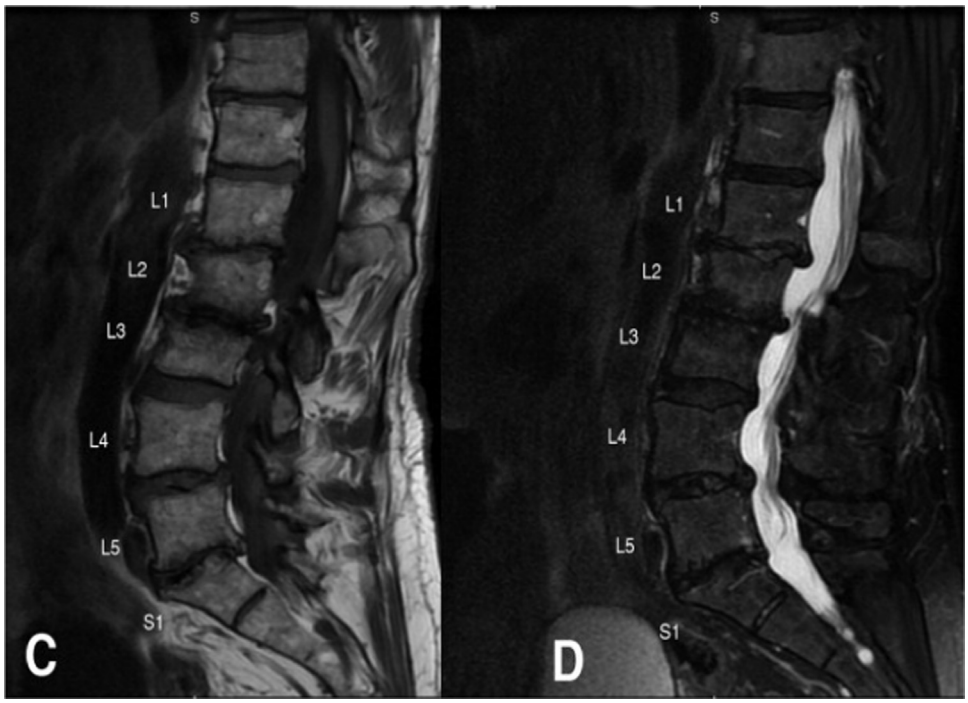

Fig. 1 – Sagittal T1- and T2-weighted MRI images demonstrating multilevel disc degeneration and herniation, worst at the L2–L3 level with associated type III Modic changes to the vertebral body end plates.
Source: Will BP, Mohr RA, Zdeblick. Current status of imaging of the intervertebral disc. Semin Spine Surg. 2007; 19(2): 58–64. Elsiever.

discectomy provides relief for the majority of patients,[9] approximately 20% of post-operative patients will have persistent symptoms attributed to recurrent disc herniation, loss of disc height, and disc degeneration.[10–12] Complicating the clinical evaluation of post-operative discectomy patients is that recurrent disc herniation is not uncommon and most of the cases are asymptomatic: a recent prospective study demonstrated that nearly 25% of patients undergoing lumbar discectomy demonstrated magnetic resonance imaging (MRI) evidence of recurrent disc herniation within two years of surgery and the majority were asymptomatic.[12] Poor structural integrity of the annulus fibrosus has been shown to be a risk factor of poor clinical outcome after discectomy and need for revision surgery.[13] A study reports a reoperation rate of 25% after lumbar discectomy,[14] and revision surgery does not always improve symptoms[15] and carries a higher risk of dural tear.[16]

Although often thought of as discrete clinical entities, disc herniation and degenerative disc disease likely coexist in most patients. Herniated disc tissue removed at surgery usually appears abnormal, suggesting that degenerative changes precede, or even cause, herniation.[17] It has also been demonstrated that disc herniation is a risk factor for subsequent degenerative changes.[18] There are characteristic findings of degenerative disc disease on radiographs and MRI, but poor correlation has been observed between imaging findings and the presence or severity of low-back pain.[19] As a result of the success of hip and knee arthroplasty, lumbar total disc arthroplasty has been the subject of clinical investigation with cautious optimism, but concerns remain regarding the long-term durability and revision rates.[20] Advances in the understanding of the cellular and molecular basis of disc degeneration have stimulated research into innovative ways to retard or even reverse the disease process. In this article, we aim to describe the pathophysiology of disc degeneration and the current state of therapeutic approaches including biomaterial implantation, cell-based therapies, growth factor or cytokine modulation, and gene therapy.

2. Structure of the intervertebral disc

The human intervertebral disc (IVD) is part of an anatomic unit that includes the nucleus pulposus (NP) centrally, the annulus fibrosus (AF) peripherally, and the cartilaginous end plates of the cranial and caudal vertebral bodies (Fig. 2). The healthy NP is the tissue most responsible for the IVD's characteristic viscoelasticity and compressive strength. At birth the cells of the NP are predominantly of notochordal origin, but with adolescence most of these embryonic cells are replaced by smaller chondrocyte-like cells characteristic of the adult tissue.[21] The chondrocyte-like cells produce primarily type II collagen arranged in a relatively amorphous pattern, giving the tissue its isotropic character. The NP is notable for its high proteoglycan content (approximately 50% of the dry weight and predominantly aggrecan), which accounts for its hydrophilic nature, high water content, and increased swelling pressure relative to the adjacent AF.[22] These structural characteristics make the NP well suited for resisting axial loads through the spinal column. The structure of the healthy AF is quite different from that of the NP, as is its biomechanical function. The AF envelopes and prevents the extrusion of the NP as it is compressed by axial loads. The AF is composed of elongated