Structure and Biology of the Intervertebral Disk in Health and Disease

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KEYWORDS

• Intervertebral disk • Degeneration • Extracellular matrix
• Development • Biology

Low back pain is a leading debilitating condition that affects every population worldwide,[1] and can lead to diminished physical function, loss of wages, decreased quality of life, and psychological distress.[1–4] In fact, chronic low back pain may also lead to brain tissue destruction.[5–8] As a consequence, low back pain is one of the most common conditions for which to seek medical consultation and one of those preeminent for analgesic use in the United States.[3,4] Furthermore, the management of patients with low back pain can be a challenge, often requiring a multidisciplinary approach to treatment (see the article by Karppinen and colleagues elsewhere in this issue).[9–13]

Although low back pain is a multifactorial condition (eg, biopsychological, muscular, socioeconomic), intervertebral disk (IVD) degeneration has been indicated to be a strong etiologic factor (**Fig. 1**).[14–24] Intervertebral disk degeneration occurs in every population worldwide, mainly involving the lower lumbar segments (L4 to S1) where disk height narrowing also commonly occurs and generally affects almost all individuals by the sixth and seventh decade of life.[24,25] However, the development or, rather, severity of IVD degeneration is not linearly based on age; degenerative changes can be noted in young children and not yet be manifested in other adults.[19,24] Overall, the true prevalence of IVD degeneration in populations has yet to be determined, due to improper surveillance methods (ie, patient-based versus population-based), sampling issues, heterogeneity in the operational definition and imaging modalities in assessing the phenotype of disk changes, and an incomplete understanding of the risk-factor profile and its interaction effects that may affect degenerative changes and their manifestation in different age, gender, and ethnic groups.[14,15,26] Along these lines, the incidence rates of annular tears, disk bulging, and endplate defects/abnormalities are also not conclusive, and vary between studies.

The development of IVD degeneration is a complex, multifaceted condition. Various studies have suggested that, age, male gender, abnormal physical loading, trauma, infection, hormonal, overweight and obesity, altered metabolism, Schmorl's

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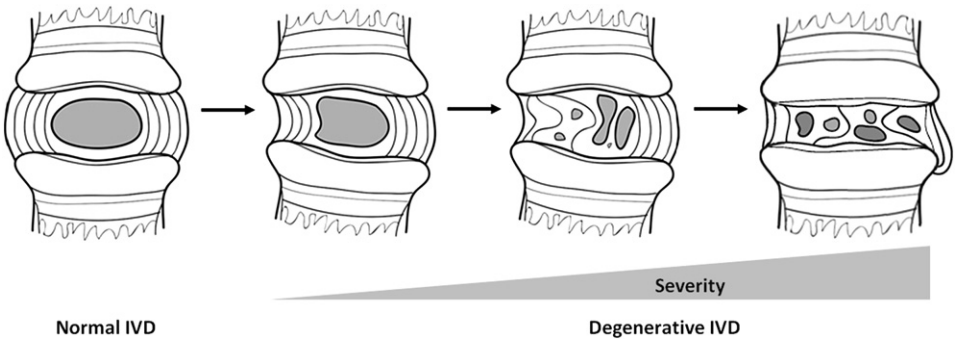

Fig. 1. Illustration of the different stages of intervertebral disk degeneration. Note the normal disk on the left and the progression of degenerative changes from left to right, which are characterized as chemical and structural changes of the disk (eg, dehydration of the nucleus pulposus, disruption of the annulus fibrosus, decreased disk height, and endplate changes). IVD, intervertebral disk.

nodes, cigarette smoking, and occupation are risk factors related to the development of IVD degeneration.[20,27–41] Several investigators have also noted that systemic conditions, such as atherosclerosis, may contribute to IVD degeneration, due to the "vascular insufficiency" provided to the vertebral body that may affect diffusion of metabolites and nutrients into the disk necessary to maintain a healthy environment.[42–46] Furthermore, it has been strongly suggested that IVD degeneration may be attributed to genetic factors. Familial aggregation studies have indicated that individuals with severe forms of IVD degeneration that are often symptomatic have family members with a history of disk-related problems, often seeking medical attention themselves.[47–51] Twin studies have also noted that more than 70% of variability of IVD degeneration may be attributed to genetics.[52–55] Moreover, observational cohort studies have identified specific genes that may play a role in the development of IVD degeneration, some of which may have a synergistic effect with environmental exposures and perhaps be age dependent (see the article by Kao and colleagues elsewhere in this issue).[56–59] As such, understanding the genetic epidemiology of IVD degeneration is imperative in comprehending the scope of the degenerative condition, why degenerative changes occur in certain individuals rather than others, and in developing a better understanding of the use of biological therapies for the prevention or regeneration of the disease process (see the articles by Sakai, Woods and colleagues, Leung and colleagues, and Bae and Masuda elsewhere in this issue). However, at a more basic level, understanding the structure and biology of the IVD in health and disease, in particular the developmental process, cellular origin, changes in the extracellular matrix (ECM) components, and maintenance in adult life, is essential.

INTERVERTEBRAL DISK

The IVD is a functional unit connecting the vertebral bodies of the spine. In humans there are 25 IVDs interposed from the axis to the sacrum. Each IVD consists of 3 structural components: a soft gelatinous nucleus pulposus (NP) in the center surrounded by a tough peripheral lamellar annulus fibrosus (AF), sandwiched between 2 cartilaginous endplates (EP) (**Fig. 2**). The components of the disk act synergistically, facilitating motions of the spine and acting as shock absorbers between vertebral bodies.[60–62]

Traditional concepts on the function of the disk relate to specific ECM proteins that assemble and interact to form the 3 distinct structures. While one can describe the NP, AF, and EP separately with distinct functions, the homeostasis of the IVD as a unit must have optimal function from all 3 structures. The impairment of one or more of these structures can lead to dire consequences with IVD degeneration. The ECM is produced and maintained by resident cells, and there are feedback mechanisms for cells to sense the ECM, while the ECM regulates extrinsic signals to cells for disk homeostasis.

DEVELOPMENT OF THE INTERVERTEBRAL DISK

The notochord is central to the development of IVD. The notochord is a rod-shaped midline structure of mesodermal origin found in chordate embryos during gastrulation, and represents a primitive axial skeleton.[63,64] As a structure that is recognized in all vertebrate embryos, its development has been well studied and described since the nineteenth century.[65] It is composed of cells derived from the organizer tissue at different stages of development.