

# Pathomechanism and Biomechanics of Degenerative Disc Disease: Features of Healthy and Degenerated Discs

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## ABSTRACT

The human intervertebral disc (IVD) is a complex organ composed of fibrous and cartilaginous connective tissues, and it serves as a boundary between 2 adjacent vertebrae. It provides a limited range of motion in the torso as well as stability during axial compression, rotation, and bending. Adult IVDs have poor innate healing potential due to low vascularity and cellularity. Degenerative disc disease (DDD) generally arises from the disruption of the homeostasis maintained by the structures of the IVD, and genetic and environmental factors can accelerate the progression of the disease. Impaired cell metabolism due to pH alteration and poor nutrition may lead to autophagy and disruption of the homeostasis within the IVD and thus plays a key role in DDD etiology. To develop regenerative therapies for degenerated discs, future studies must aim to restore both anatomical and biomechanical properties of the IVDs. The objective of this review is to give a detailed overview about anatomical, radiological, and biomechanical features of the IVDs as well as discuss the structural and functional changes that occur during the degeneration process.

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Keywords: degenerative disc disease, pathophysiology, biomechanics, intervertebral disc, back pain, low back pain, lumbar disc herniation

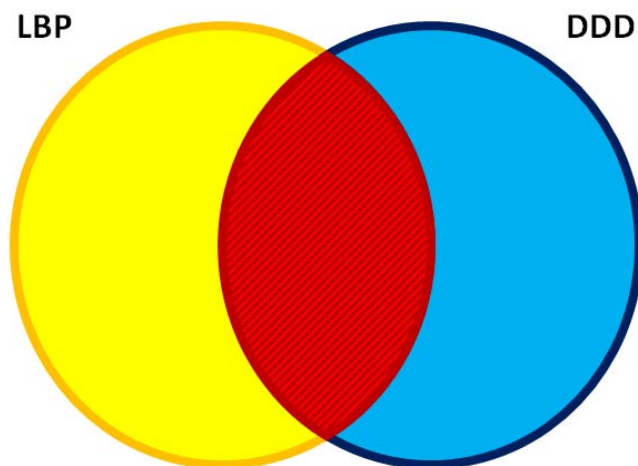
## INTRODUCTION

Chronic lower back pain (LBP) is one of the leading causes of disability and imposes a significant medical, economic, and social burden worldwide.<sup>1</sup> Moreover, its prevalence is continuously increasing, especially in high-income countries.<sup>2</sup> Although the etiology is not always clear, LBP often originates from the intervertebral disc (IVD), sacroiliac joint, facet joint, and soft tissues.<sup>3</sup> Among other pathologies, up to 40% of LBP cases are associated with degenerative disc disease (DDD), which is due to neoinnervation and inflammation within the degenerated discs<sup>4</sup> (Figure 1). Treatment methods such as physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs), and steroid injections are commonly used for alleviating discogenic pain.<sup>5,6</sup> However, neither operative nor nonoperative treatment methods actually address the underlying disease.

In recent years, biological treatment methods including gene therapy, growth factor and cell-based injections, as well as tissue-engineered approaches

including nucleus pulposus (NP) augmentation, annulus fibrosus (AF) repair, and total disc replacement have been extensively investigated to prevent further degeneration and promote IVD regeneration.<sup>7–13</sup> Although most of these novel therapies are still limited to in vitro and in vivo animal models, an increasing number of clinical trials have been conducted within the last decade.<sup>11,14</sup> To develop newer, safer, and more effective therapeutic approaches, it is crucial to understand the underlying pathomechanism of DDD.

Our group previously published a comprehensive textbook which gives a detailed overview of biological treatment approaches for IVD regeneration.<sup>15</sup> In this review, we aim to share the comprehensive data on the prevalence of LBP and lumbar disc herniation (LDH) to emphasize the importance of innovative biological treatment methods. We also cover relevant embryology, anatomy, and physiology of the IVDs. In addition, we discuss the structural and functional changes as



**Figure 1.** Low back pain (LBP) is a clinical entity, and degenerative disc disease (DDD) is a radiographic-anatomical finding. There are many reasons why patients can present with LBP. Conversely, DDD is frequently found in imaging studies of asymptomatic patients. However, there is an overlap, and patients with LBP can present with imaging findings consistent with DDD. The challenge for the clinician then is to establish whether there is a causative relationship.

well as the inflammatory responses that occur during IVD degeneration. Finally, we compare radiological and biomechanical features between healthy and diseased discs to highlight the effects of DDD.

#### Prevalence of LBP and LDH

In a systematic review on the global prevalence of LBP, Hoy et al<sup>16</sup> in 2008 reported a point prevalence of  $11.9 \pm 2.0\%$ , a 1-year prevalence of  $38.0 \pm 19.4\%$ , and a lifetime prevalence of  $39.9 \pm 24.3\%$ . The authors also demonstrated a strong positive correlation between the mean prevalence of LBP and a nation's human development index, although a significant difference for prevalence between rural and urban areas was not found. In a meta-analysis by Ravindra et al<sup>17</sup> in 2018, the global incidence of patients with degenerative lumbar disorder and LBP was found to occur 3 times more frequently in low- and middle-income countries than in high-income countries. A significant increase in the prevalence of chronic LBP over a 14-year interval has been reported by Freburger et al,<sup>18</sup> while severity of symptoms and general health conditions were unchanged during this period. The rise in prevalence of LBP is possibly accounted for by the recent increased propensity to crucial risk factors such as obesity, sleep deprivation, and chronic stress.<sup>19</sup> Other significant risk factors associated with LBP include smoking and occupational hazards such as heavy lifting and poor

posture.<sup>20,21</sup> However, prevalence estimates of LBP in older adults vastly differ due to the lack of a standard definition of LBP and variations in sampling and experimental methods as reported by clinical and administrative studies.<sup>22</sup> Authors of these studies also provide limited information regarding location and severity of pain, as well as LBP-induced limitations on normal functioning. Nevertheless, LBP persists as a worldwide problem according to the 2010 Global Burden of Disease Study<sup>1</sup>: LBP is deemed as the leading cause of years lived with disability and sixth highest burden in terms of disability-adjusted life years. The economic impact of degenerative spinal disorders in the United States alone is estimated between \$20 billion to \$50 billion per year.<sup>23</sup> According to the Healthcare Cost and Utilization Project, at least 900,000 spinal surgeries are performed annually in the US including 413,000 spinal fusions, 370,000 discectomies, and 103,000 laminectomies.<sup>24–26</sup>

Several studies have suggested that at least 40% of LBP is associated with DDD, and patients showing increased modic changes in magnetic resonance imaging (MRI) scans are more likely to have LBP.<sup>4,5,27</sup> However, the relationship between DDD and LBP remains controversial in the literature since MRI findings do not necessarily correspond to clinical outcomes, and the etiology of pain is often unclear.<sup>28</sup> Pain can arise from degenerated discs via 2 different yet usually co-occurring mechanisms: (1) radicular pain due to disc bulging and subsequent compression of nerve roots and (2) discogenic pain without disc herniation.<sup>29</sup>

LDH is often caused by a tear in the AF due to preexisting degenerative changes in the IVD. However, LDH can also be observed in early stages of DDD and can exacerbate the degenerative process.<sup>30</sup> The treatment method chosen is crucial since more invasive procedures may accelerate disc degeneration, whereas regenerative therapies can prevent long-term complications such as delayed onset discogenic pain.<sup>31,32</sup> Furthermore, authors of a recent meta-analysis reported that clinical outcomes and disc bulge will improve through nonsurgical treatment alone in more than half of LDH patients.<sup>33</sup> On the other hand, the authors of the Maine Lumbar Spine Study reported that 31.2% of patients who underwent surgery and 40.1% who received nonsurgical treatment had persisting LBP after a 10-year follow up.<sup>31</sup> Similarly, Parker et al<sup>32</sup> showed that 32% of patients who underwent single-

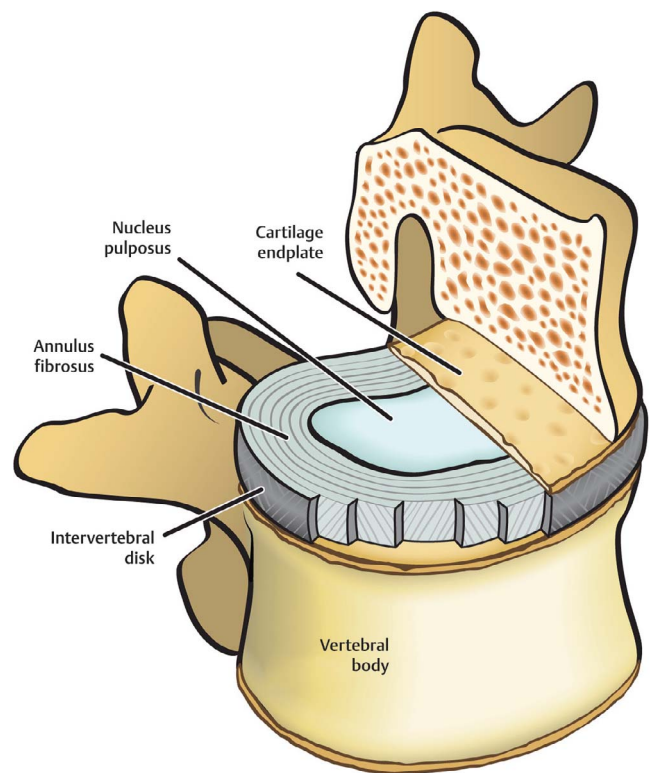
level discectomy for LDH and radiculopathy exhibited moderate to severe back pain after a 3-year follow up. Due to the high prevalence rate of long-term discogenic pain, regenerative therapies such as stem-cell injections have recently been gaining popularity.<sup>34</sup>

One of the main complications after lumbar disc surgery is reherniation. Authors of a systematic review in 2015 based on 28 studies involving 6255 patients showed that reherniation rates may be as high as 23% after surgical treatment.<sup>35</sup> Moreover, authors of several multicenter studies worldwide have shown that the cumulative risk of reoperation is around 20% in a 10-year follow-up period.<sup>36,37</sup> The patient-reported satisfaction rate is significantly lower after recurrent LDH surgery than outcomes after primary operation (58% versus 79%).<sup>38</sup> Miller et al<sup>39</sup> demonstrated that patients with large (>6 mm) annular tears after lumbar discectomy are more likely to have symptom recurrence (odds ratio [OR] = 2.5) and reoperation (OR = 2.3) than those who have small annular tears (<6 mm). Therefore, the innovative tissue-engineered annular repair approaches offer a promising solution to the prevention of reherniation and further degeneration in LDH patients.<sup>7,9,10</sup>

### Anatomy of the IVD

The human IVD is a complex organ composed of fibrous and cartilaginous connective tissues that serves as a boundary between 2 adjacent vertebrae. It provides a limited range of motion in the torso as well as stability during axial compression, rotation, and bending.<sup>15</sup> The IVD comprises anatomically distinct yet synergistic structures: the gelatinous NP, the concentric layers of fibrocartilaginous AF surrounding the NP core, and 2 vertebral endplates (VEPs) covering the entire superior and inferior surfaces of the disc<sup>40</sup> (Figure 2). During the early stages of development, the notochord and mesodermal somites give rise to the structures of the IVD.<sup>15</sup> However, the notochordal cells are replaced almost entirely by round chondrocyte-like cells in the NP beyond the first 10 years of life.<sup>41</sup> This, in addition to the avascular nature of a mature IVD, possibly limits a disc's ability to self-regenerate<sup>42</sup> (Figure 3).

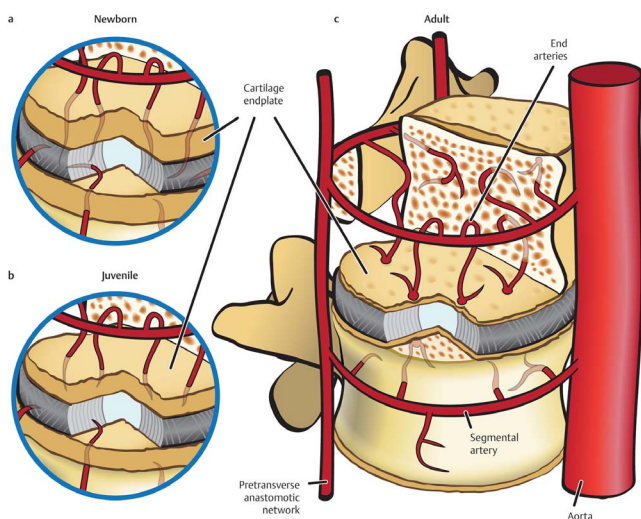
The highly hydrated gel-like NP core is mainly composed of Type II collagen that acts as a mesh in which matrix elements such as aggrecan, hyaluronic acid, and other molecules are entrapped.<sup>43</sup> Aggrecan is the most abundant proteoglycan (PG) in NP, and



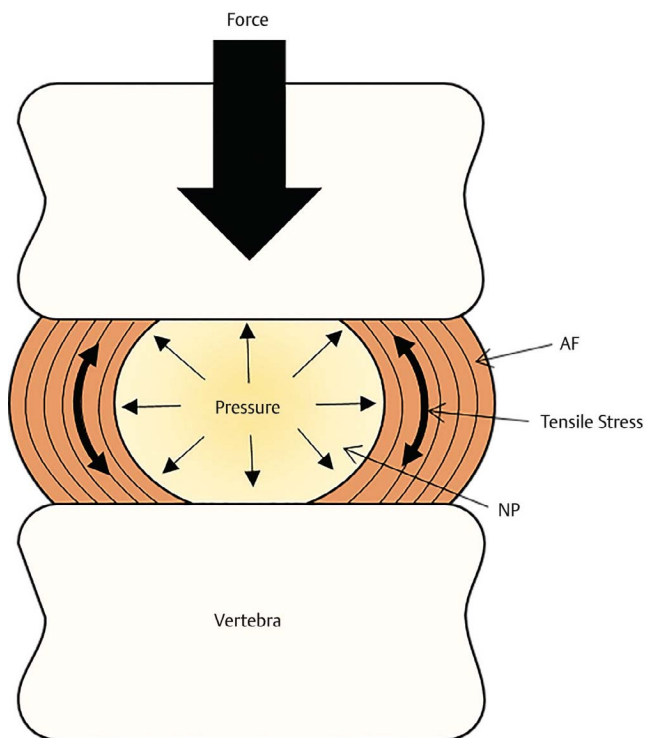
**Figure 2.** Anatomical composition of the human intervertebral disc. Centrally located nucleus pulposus and concentric organization of annulus fibrosus lamellae surrounding the periphery. Superiorly and inferiorly cover by cartilaginous endplate. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>15</sup>

it contains numerous glycosaminoglycan (GAG) chains that attract water within its network<sup>44,45</sup> (Figure 4). Water retention in turn generates a swelling pressure that endows the NP its ability to resist compressive loads and maintain disc height<sup>45</sup> (Figure 5). Aggrecan is highly concentrated within the center of the NP and diminishes radially outward.<sup>44</sup> Furthermore, several studies<sup>46,47</sup> revealed that the predominantly aneural nature of a mature and healthy IVD is attributed to a high concentration of aggrecan, the negatively charged moieties of which play a key role in preventing nerve ingrowth into the IVD.

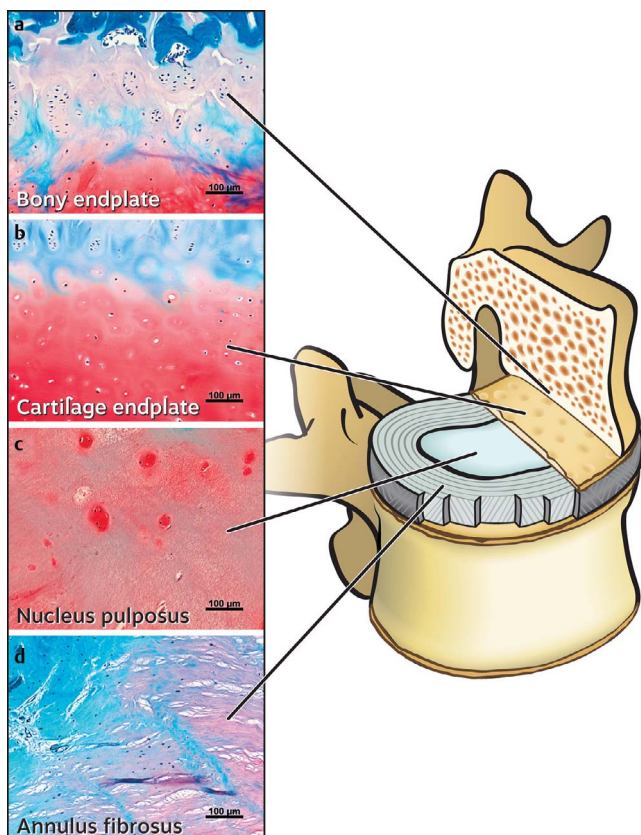
Surrounding the NP core is the fibrocartilaginous AF, and its matrix composition varies by region.<sup>48</sup> The inner AF region has a composition like the NP, since it consists mainly of Type II collagen and aggrecans<sup>49</sup> (Figure 4). In fetal and juvenile discs, the delineation between the AF and NP regions is clear.<sup>50</sup> In adult discs, however, the outer NP transitions smoothly into the inner AF, making the boundary between the 2 regions indiscernible due to their similar matrix compositions. In contrast to the round chondrocyte-like cells of the mature



**Figure 3.** (a) Neonate's vertebral body and disc vascular network; blood supply can extend into the innermost regions of the annulus fibrosus (AF). (b) Vessels retract further from the disc to the outer region of the AF during adolescence. (c) Vessels are regressed further away from the AF and fix themselves within and surrounding the end plate and connective tissues in adult spines. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>15</sup>



**Figure 5.** The intervertebral disc (IVD) undergoes load bearing, bending, flexing, and torsion while under mechanical stressors. The annulus fibrosus (AF) and the nucleus pulposus (NP) form the IVD within the intervertebral space to fill the joint and maintain disc height. When the IVD is undergoes the previously mentioned physical stress, then the NP reacts by resisting the downward force against it by pressing vertically back into the compression and radially into the AF. The pressure from the NP generates tensile stress on the AF in the direction of the organization of the fibers within the AF. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>15</sup>



**Figure 4.** Histology images of human intervertebral disc. (a) and (b) Bony and cartilaginous endplates of a young healthy patient. The bony endplate is distinct and contains hypertrophic cartilage. (c) and (d) The nucleus pulposus (NP) and annulus fibrosus (AF). Histology stains were Safranin-O, fast green FCF, and Weigert's hematoxylin. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>15</sup>

outer NP and inner AF, the cells found in the outer AF layers are elliptic and fibroblast-like.<sup>43</sup> The composition of the outer AF layer is mostly of parallel collagen Type I fibers arranged in concentric lamellae and are oriented obliquely by about 30° with respect to the longitudinal axis of the spine.<sup>51,52</sup> Moreover, these fibers form an angle-ply structure by alternating the direction of fibers between successive lamellae.<sup>42,52</sup> The tensile strength contributed by this structure provides the AF its resilience to omnidirectional forces, thereby preventing NP content leakage during axial compression.<sup>53</sup>

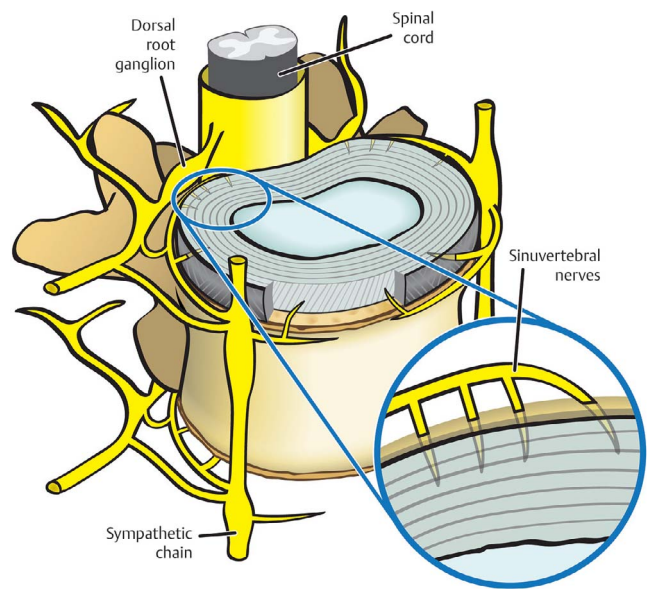
Lining the superior and inferior surfaces of both the NP and AF are the VEPs, which consist of 2 distinct layers: the cartilage endplate (CEP) composed of Type II collagen and aggrecan, as well as the bony endplate composed of cortical bone (Figure 4). The CEP portions of healthy VEPs have a thickness that is uniform and does not infiltrate the adjacent vertebra.<sup>54,55</sup> Compared to the 27:1 PG-to-collagen ratio of the NP, the ratio is 2:1 such

as in the hyaline cartilage of the CEP.<sup>56</sup> VEPs serve 2 functions: one is to provide an attachment between the disc and vertebra, and the other is to provide a route for material transport to the disc. Vascularity is limited to the periphery of the CEP; therefore, nutrients and oxygen ultimately reach the AF and NP regions through passive diffusion.<sup>57</sup>

A healthy IVD is largely aneural, except for the outer AF layers innervated by sensory and sympathetic perivascular nerve fibers<sup>42</sup> (Figure 6). Neoinnervation extending into the inner IVD thus provides a clear distinction between healthy and degenerated discs. Due to the absence of immune cells residing within the IVD,<sup>58</sup> this implicates a good candidacy of degenerated IVDs for cell-based biological treatments. Furthermore, animal models for DDD research are required to exhibit loss of notochordal cells like in human IVDs.<sup>59</sup> NP notochordal cells are generally retained throughout life in most animals, except for a limited number of species such as cattle and sheep.<sup>30</sup>

### Pathophysiology of DDD

DDD generally arises from the disruption of the homeostasis maintained by the structures of the IVD, and genetic and environmental factors can accelerate the progression of the disease.<sup>42,60</sup> Authors of multiple studies have identified several risk factors linked to DDD such as genetics,<sup>61</sup> obesity,<sup>62</sup> smoking,<sup>63</sup> and aging<sup>64</sup>; although the impact of each risk factor on the DDD progression is still unclear. Authors of a review in 2008 have demonstrated 34% to 61% heritability rates of DDD and suggested that the complex inheritance pattern is associated with multiple genes.<sup>61</sup> Furthermore, polymorphisms in the growth differentiation factor 5,<sup>65</sup> vitamin D receptor,<sup>66</sup> and matrix degradative protease<sup>67</sup> genes among others have been linked to IVD, although the extent of each gene's influence on the disease is still unknown. Mutations in the genes encoding for Type II collagen—a major component of the NP and inner AF extracellular matrix (ECM)—as well as Type XI collagen are found to be more related to spinal deformations involving the VEPs but not to DDD.<sup>68,69</sup> On the other hand, polymorphisms on the COL1A1 (Type I collagen) genes have been linked to DDD by authors of multiple studies.<sup>70–72</sup> Moreover, Solovieva et al<sup>73</sup> implied that sequence variations in the collagen type IX (COL9A3) in conjunction with obesity increases DDD severity, as shown by reduced disc heights and lowered intensity



**Figure 6.** The sinuvertebral nerve innervates the disc. In a healthy adult disc, the nerve endings cannot reach into the innermost layers of the annulus fibrosus (AF). Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>15</sup>

of MRI signals of the NP (black disc). Furthermore, polymorphisms in aggrecan genes are also linked to DDD: these sequence variations affect the lengths of the aggrecan core proteins as well as the number of chondroitin sulfate (CS) chains bound to aggrecan.<sup>74–76</sup> A lower number of CS chains compromises the ability of the NP to retain water, leading to reduced disc height and improved conditions for neoinnervation.<sup>46,77</sup>

Other significant risk factors associated with DDD are obesity, smoking, and aging. In a population-based study, Samartzis et al<sup>78</sup> on juveniles of ages 13 to 20 have shown that overweight and obese individuals showed a significantly higher severity of DDD than underweight and normal body mass index (BMI) individuals. Excessive compressive forces are exerted on the discs of overweight and obese individuals, making the discs more susceptible to early wear and tear and exacerbation of preexisting DDD.<sup>79</sup> Moreover, being overweight or obese is a disorder in which inflammation is associated with increased serum levels of IL-6, C-reactive protein, TNF- $\alpha$ , and leptin.<sup>79</sup> Inflammation in the IVD tissues often leads to a cascade of catabolic processes in the disc associated with DDD onset.<sup>42,80</sup> Authors of several studies<sup>63,81</sup> have implicated the risk of smoking for DDD, and the most accepted rationale for this association so far is that poor nutrition of spinal disc cells occurs via carboxy-hemoglobin-induced

anoxia.<sup>82</sup> Moreover, Akmal et al<sup>63</sup> showed that bovine NP disc cells cultured in vitro with nicotine concentrations of 100, 200, and 300 nmol/L after 21 days exhibited significant dose-dependent lowering of IVD cell proliferation and synthesis of ECM. They also found that there was a shift in NP ECM composition from Type II collagen to Type I.<sup>63</sup> Authors of another study suggest the role of smoking as a significant risk factor for the onset of DDD since lowering the cell density of the NP in murine models and alteration of its matrix composition may lead to premature degeneration of an IVD.<sup>81</sup>

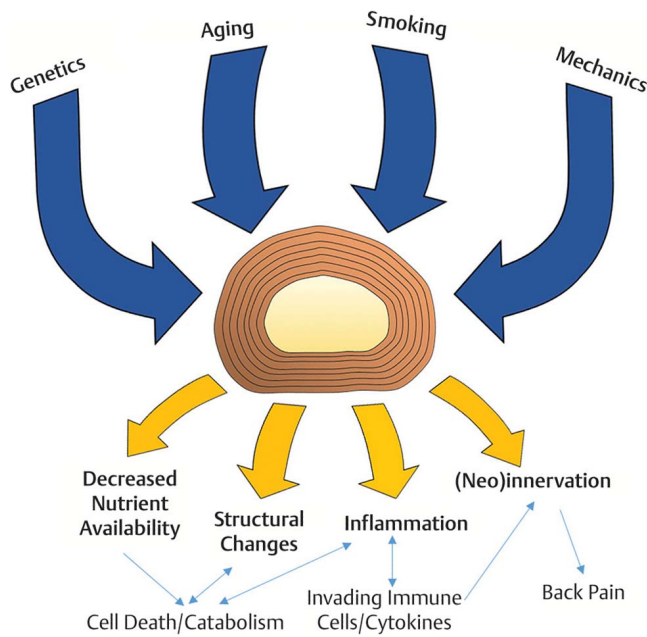
Aging is a natural process during which an organism accumulates molecular and cellular damage over time. Compared with other types of tissues, IVDs can exhibit age-related degeneration as early as the second decade of life. This is mainly attributed to the loss of notochordal cells in the NP that are associated with anabolic activities in the cell such as enhancing cell proliferation and ECM synthesis, upregulating growth factors, and down-regulating matrix metalloproteinase (MMP) expression.<sup>83</sup> During the early onset of DDD, increased Type II collagen production is observed in the NP possibly as an attempt to self-repair.<sup>42</sup> As disease progression continues, production of Type I collagen increases significantly as Type II collagen synthesis declines.<sup>84</sup> This shift in collagen types in the NP and inner AF is accompanied by a decrease in aggrecan content, which results in loss of hydration and turgor pressure in the disc.<sup>42,43,84</sup> These changes in the ECM of the NP thereby decrease disc height and induce fibrosis, negatively impacting its resilience to axial loading.<sup>85</sup> Furthermore, changes in the ECM of the outer AF involve a slight increase in Type II collagen, which compromises its ability to contain the NP during axial compression.<sup>86</sup> Excessive forces on the weakened outer AF lamellae eventually lead to formation of cracks and fissures, which increase the likelihood of NP material leaking into the outer AF. Furthermore, these defects in the outer AF of the degenerated disc consequently allow for neoinnervation and angiogenesis within the IVD.

Vascularization is only present as deep as the outer AF in a mature and healthy IVD, leaving the rest of the disc largely avascular.<sup>87</sup> The inside of the disc therefore receives oxygen and nutrients via passive diffusion.<sup>88</sup> Authors of recent studies<sup>89,90</sup> have shown that, in degenerated IVDs, increased

porosity of the endplate and trabeculae is associated with decreased nutrient transport to the disc in conjunction with endplate calcification.<sup>91</sup> Inefficient nutrient transport to the disc induces a deleterious milieu characterized by an inadequate amount of oxygen and a buildup of lactic acid since the disc primarily derives its energy via glycolysis.<sup>92</sup> Moreover, a drastic increase in acidity is linked to increased senescence and apoptosis of disc cells,<sup>93</sup> while moderate pH changes affect metabolism of the IVD cells.<sup>94</sup> Impaired cell metabolism due to pH alteration and poor nutrition (low supply and high demand) may also lead to autophagy and disruption of the homeostasis maintained by the IVD and thus plays a key role in DDD etiology.<sup>95</sup> Derby et al<sup>96</sup> also concluded that loss of PG induces neovascularization to compensate for the low supply and high metabolic demand in the disc. Authors of multiple studies have also established that the secretion of nerve growth factors and brain-derived neurotrophic factor by invading immune cells in the disc enhance fibroblast activity, neoinnervation, and angiogenesis in the IVD.<sup>97–99</sup>

Innervation inside a healthy IVD is absent due to the negatively charged CS chains of aggrecan which have been shown to inhibit neoinnervation within the disc.<sup>46</sup> Consequently, loss of aggrecan in the NP and inner AF in conjunction with the loss of structural integrity of the outer AF layer both induce favorable conditions for growth of nociceptive and a few proprioceptive nerve fibers accompanied by angiogenesis in the disc.<sup>100</sup> Furthermore, evidence from a study by Brown et al<sup>101</sup> has shown that Substance P—a neuropeptide involved in regulating the perception of pain—is found to be overexpressed in degenerated IVDs. These transformations in the disc morphology, genetics, as well as the inflammatory milieu induced by the release of cytokines by native disc and invading immune cells are believed to cause discogenic pain<sup>102,103</sup> (Figures 7 and 8).

Authors of multiple studies have established that cytokines and chemokines are present in large quantities in discs showing varying degrees of degeneration as well as in herniated discs.<sup>104–106</sup> Nutrient-deprived resident IVD cells secrete chemokines that attract immune cells such as T- and B-cells, macrophages, and neutrophils to the once immune-privileged IVD.<sup>106</sup> These immune cells further enhance the expression of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ ; these 2

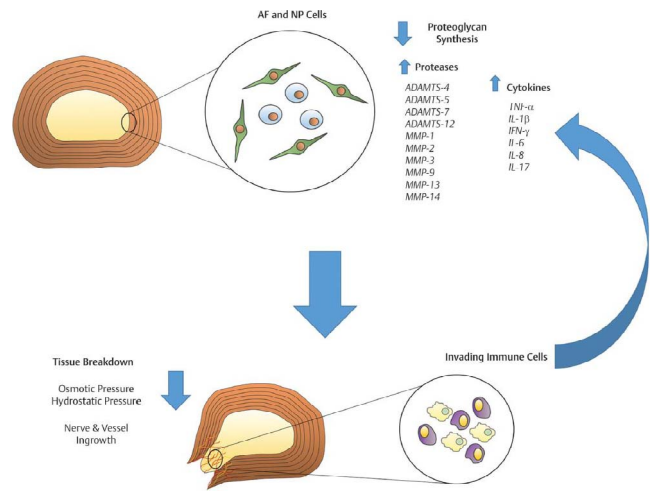


**Figure 7.** Degenerative disc disease (DDD) in a cascading multifactorial process involving the interaction of risk factors and pathophysiology. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>186</sup>

cytokines among others associated with DDD have been studied extensively and found to induce inflammation and cell apoptosis.<sup>107,108</sup> TNFR1 and IL1R1 signaling is believed to induce the activation of the transcription factor NF-κB.<sup>109</sup> Activation of NF-κB in turn induces the expression of genes associated with tissue and ECM degradation such as aggrecanases and MMPs in the IVD.<sup>110</sup> Authors of a study conducted on degenerated rodent IVDs in vitro showed that inhibiting NF-κB activity lowered the expression of several MMP genes and thus slowed the progression of the degenerative process in the discs.<sup>111,112</sup> In addition to upregulation of matrix degradative enzymes, NF-κB activity also enhances the expression of some pro-inflammatory genes in the disc, thereby upregulating the expression of several MMPs and aggrecanases that degrade collagen Type II and aggrecan in the NP and inner AF.<sup>113,114</sup> This positive feedback loop perpetuates the deleterious environment within the disc, subjecting the IVD to further degeneration over time.

### Radiological Analyses of Healthy and Diseased Discs

DDD is characterized by biochemical and structural alterations of the IVD under physiological and pathological stresses.<sup>115</sup> MRI is a crucial noninva-



**Figure 8.** The physiological alterations to the disc are controlled directly by cells within the disc, which are caught in a closed degenerative cycle. These cells increase production of cytokines and proteases while decreasing production of proteoglycans, both of which are essential to the retaining the disc's height as well as maintaining the basic physical function of the intervertebral disc. The increase of proteases expedites the tissue degeneration process. The proteases also alter the extracellular environment, which incurs catabolic reaction and inflammation. This process results in the activation of nearby immune cells that exacerbates the inflammatory processes by continuing to increase cytokine production. The increase in cytokines enhances neovascularization and neoinnervation in the disc. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>186</sup>

sive method of IVD assessment, allowing for detection of collagen degradation, proteoglycan depletion, and other potential pain generating defects of the IVD.<sup>115</sup> Effectively interpreting these images requires an understanding of the endogenous disc and endplate morphology, as visualized and quantified in MRI.<sup>116</sup> Methods of consistent and reliable disc assessment are necessary for accurate inter- and intra-institutional communication, providing methods for diagnosis and future elucidation of disease pathogenesis.<sup>115</sup>

Discography, radiography, and computed tomography myelography have all previously been used to image discogenic pain. MRI, however, provides a method of direct multiplanar imaging with high-contrast resolution and lacks ionizing radiation.<sup>117</sup> Thus, MRI has become increasingly prominent as a method of evaluation for disc degeneration. Biochemical and structural alterations of the IVD are pathognomonic of DDD, including alterations in water, collagen, and aggrecan-proteoglycan-GAG content, 3 of the major biochemical constituents in disc degeneration.<sup>118</sup> MRI analysis is especially applicable in this regard. T1-ρ is the time parameter of MRI relaxation, sensitive to low-frequency interactions between macromolecules, providing visualization of proteoglycan matrix

within the NP of the IVD.<sup>119</sup> T1- $\rho$  relaxation times have been observed to have a positive correlation with GAG content, providing insight into the mechanical properties of the IVD, such as swelling pressure.<sup>119</sup> T2 mapping correlates strongly with water content and, subsequently, with proteoglycan content.<sup>120</sup> Degradation of these biochemical components may lead to fibrocartilage formation and annular disruption, perpetuating disc degeneration.<sup>118</sup> Thus, visualizing these constituents through T2 mapping may provide a greater understanding of disc degeneration.<sup>121</sup> Pfirrmann et al<sup>122</sup> provided a widely accepted scale for assigning quantitative values to qualitative features present in T2 MRI of the human IVD (Figure 9). This scale has been used clinically in association with T2 values for both diagnostic and investigative purposes.<sup>122</sup> Analyzing T1 in relation to T2 intensity may elucidate the health of the endplate, the subchondral bone underlying the IVD.<sup>118</sup> Ultra-short TE MRI techniques have also been shown to be useful in investigating the health of the cartilaginous endplate.<sup>116</sup> The classification of endplate damage may be indicative of underlying disorders of the adjacent IVD. In the future, ultrashort echo time (UTE) and diffusion weighted imaging (DWI) methods may be further advanced to provide information on the microstructure of the IVD and cartilaginous endplate, potentially showing collagen fiber alignment as it relates to DDD.<sup>118</sup>

MRI is also beneficial in analyzing the effectiveness of preclinical treatment methods of animal models. Typically, animal models are established due to similarities in morphology, physiology, or biomechanical features to that of the human IVD. MRI provides a noninvasive method for evaluating structural and biochemical commonalities between animal models and precedes methods for assessing the effectiveness of treatment methods applied to these models. MRI analysis has proven valuable in visualizing disc degeneration in preclinical models; however, interspecies variation in IVD structure and imaging characteristics calls to question the validity of the use of human-specific grading scales, such as the Pfirrmann grading scale.<sup>122</sup> For this reason, future work must be performed to create valid measures of assessing MRIs of model IVDs.

MRI provides a method for detailed visualization of the endogenous IVD. Though MRI has yet to be reliably correlated to symptomology, key characteristics of degenerated discs have been assessed



**Figure 9.** T2-weighted sagittal magnetic resonance images of three different patients. Roman numerals present the Pfirrmann grades. (Left) A female adolescent patient with healthy discs, (center) a young adult female patient with mild disc degeneration, and (right) a senior male patient with advanced disc degeneration. Printed with permission from *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*.<sup>115</sup>

through various MRI modalities, allowing for qualitative and quantitative evaluation of biochemical and structural degeneration within the IVD.<sup>115,116,118</sup> Advancing this noninvasive method of analysis and enhancing physician interpretation of the resulting images may provide a robust foundation for understanding and diagnosing DDD.

#### Biomechanics of Healthy and Diseased Discs

One of the primary functions of the IVD is to resist compression while limiting or enhancing flexibility based on the magnitude of the loads to which the spine is subjected, thereby ensuring even distribution of the loads across the vertebral bodies while maintaining their mobility.<sup>43,123,124</sup> The disc's complex structure—ie, the presence of the water- and proteoglycan-rich NP and the highly oriented AF—contributes directly to its ability to act as a “cushion” for the spine, sustaining loads while functioning as a shock absorber.<sup>43,125</sup>

In a healthy disc, the high water content of the NP results in a buildup of hydrostatic pressure, which increases as a result of compressive loading.<sup>126,127</sup> This pressurization in turn generates tension in the surrounding AF and results in outward bulging.<sup>43,128</sup> Proteoglycans in the NP trap water and cause the tissue to swell as a result, balanced by the tensile forces distributed to the AF, until the tissue achieves equilibrium.<sup>43</sup> The complex translamellar arrangement of fibers throughout the AF enables the development of tensile and circumferential stresses in response to the pressure buildup in the NP, while simultaneously providing resistance to shear between adjacent lamellae.<sup>129–132</sup> As a result, the AF is loaded primarily in tension in



response to typical loading conditions. Meanwhile, the outer region of the AF, composed of lamellae approximately 2 to 3 times stiffer than those at its interior, acts as a boundary in conjunction with the endplates to contain the NP as it swells.<sup>52,133,134</sup> As the applied loads are removed, the pressure in the NP stabilizes, restoring normal disc height and allowing the disc to return to its equilibrium state.

As the disc matures and the process of degeneration unfolds, the disc undergoes a combination of structural and compositional changes (disc height loss, depletion of endogenous cell population, sclerosis, loss of AF-NP boundary, etc).<sup>135-138</sup> The highest degree of degenerative change occurs in the NP, which becomes less gel-like and instead becomes stiffer and less compliant.<sup>139-141</sup> As the disc degenerates, the biochemical content of the degenerated NP matrix shifts from proteoglycan-rich Type II collagen toward a more fibrous Type I collagen.<sup>142</sup> This depletion of proteoglycan content leads to an inability to bind water, rendering the NP increasingly unable to hydrate and potentially altering the viscoelastic behavior of the disc as a whole.<sup>143</sup> The AF meanwhile thickens with degeneration, the fiber network becoming highly disorganized with progression, though these changes are not as well understood.<sup>135,139</sup>

With these alterations come direct consequences to the disc's mechanical response to loading. Rather than behaving as a fluid, as is the case in a healthy disc, the degenerated NP exhibits more solid-like behavior,<sup>144</sup> while the AF begins to function as the sole compressive resistance.<sup>43</sup> The NP's inability to hydrate results in a loss of pressurization<sup>124</sup> and swelling capability, therefore rendering the disc unable to sustain and redistribute loads. Rate of recovery after loading is also significantly impaired in degenerated discs, as are disc height, motion segment flexibility, and overall axial compliance.<sup>139,145,146</sup> Reduced pressure leads to decreased tension in the AF portion after compression, as well as increased shear stresses in the disc as a whole.<sup>147</sup> In the NP, these shear forces can directly contribute to remodeling of the ECM as well as elicit inflammatory responses from the cellular population.<sup>148-150</sup> In the AF, reduced annular tension results in increased bulging of the AF, which further increases shear forces between adjacent lamellae and subsequently leads to tears (radial, circumferential, or rim lesions) and delamination or structural failure of the disc.<sup>143,151,152</sup> In fact, the combination

of elevated shear stress and separation of the annular lamellae is thought to be one of the major causes of failure propagation in the AF<sup>151,153,154</sup> as well as an initiator in a proposed degenerative cascade affecting the entire IVD.

Reduced motion segment flexibility and axial compliance generated by the IVD degeneration might provoke collateral damages and lead to further spinal degeneration. Authors of previous studies have shown that patients with DDD often simultaneously have facet joint degeneration.<sup>155-158</sup> While facet arthrosis and IVD degeneration are the most prevalent factors in chronic LBP, the sequential relationship between the 2 processes is not well defined.<sup>159-162</sup> Both types of degeneration have been shown to restrict spinal motion which could increase the loading in both IVD and facet joint.<sup>163,164</sup> However, further research is needed to clearly identify the relationship between the 2 degenerative processes. Overall, DDD is not an isolated phenomenon as such a disease can cause the degenerative cascade in the spine and ultimately impact quality of life through factors such as severity of pain.<sup>165</sup>

#### Assessment and Quantification of IVD Mechanics

The IVD has interesting yet intricate mechanical properties due to its unique composition and architecture. The NP has a relatively homogenous composition and is often thought to have isotropic mechanical properties.<sup>166-168</sup> On the other hand, the AF has anisotropic mechanical properties due to the collagen fiber alignment, as previously stated.<sup>169</sup> During axial compression, pressure increases in the NP due to the compression transfer to the AF as a hoop or circumferential stress. The collagen fiber alignment in the AF allows the IVD to stretch radially and effectively mitigate the stress generated by the compression. The oblique orientation of the collagen fibers also helps to support various other loading modes such as tension, bending, and torsion.<sup>170</sup> In addition to anisotropy, the existence of water within the IVD adds another layer of complexity to its mechanical behavior. The interaction between the water and collagen fibers within the IVD creates poroelasticity where temporal mechanical behavior is observed due to water leaving or entering the structure. During DDD, these structures and the overall composition within the IVD which dictate its mechanical properties are disrupted, ultimately changing the mechanics.<sup>171</sup> Multiple

analysis methods have been applied to fully characterize and understand the effect of DDD on the IVD's mechanical properties.

### IVD Degeneration and Mechanics

Both in vivo and in vitro mechanical analysis methods have been applied to fully characterize the differences in mechanical properties between healthy and degenerated IVDs. MRI has been used widely to analyze the mechanical properties of the IVD in vivo and is promising due to its noninvasive nature. Multiple techniques exist for the application of MRI, such as obtaining T1  $\rho$  relaxation time or T2\* relaxation time.<sup>147,172,173</sup> However, the basic principle of these analyses is the same and involves looking at the biochemical composition, particularly proteoglycan content, of the IVD. The resulting compositional data are then correlated with in vitro mechanical testing of motion segments. Authors of various studies have identified the relationship between relaxation time and multiple parameters such as bending stiffness and swelling pressure. In vivo analysis has indicated that as IVD degeneration continues, swelling pressure can decrease to about to 35% that of a healthy IVD, while bending stiffness can increase to more than twice a healthy value.<sup>174,175</sup> These changes result in lower range of motion (ROM) for patients and decrease stability of the spinal segment.<sup>176,177</sup> Despite its promise, MRI can only estimate the mechanical stability of each patient due to its empirical nature.

In vitro mechanical testing generally involves spinal motion segments and a testing frame where compression and multi-axial torsion can be applied. Using such a testing frame, multiple mechanical properties such as compressive modulus and bending and torsional stiffness can be studied. The healthy IVD has compressive modulus which ranges from 10 to 20 MPa, while the degenerated IVD possesses a decreased compressive modulus of 5 to 12 MPa.<sup>178,179</sup> Torsional stiffness increases with degeneration: the healthy IVD has a torsional stiffness ranging from 700 to 1100 Nmm/°, while that of the degenerated IVD ranges from 600 to 1800 Nmm/°.<sup>180</sup> Interestingly, surgical intervention to treat degeneration has been shown to further worsen mechanical performance.<sup>181,182</sup> These bulk mechanical analyses may give a false impression that stress is distributed evenly across the structure; however, authors of multiple studies have shown stress is spatially dependent. Under axial compression,

healthy IVDs have a relatively uniform stress distribution from anterior to posterior region.<sup>183</sup> As degeneration continues, intradiscal pressure is reduced by 30% and the AF starts to carry more load than the NP.<sup>184</sup> Furthermore, in the lumbar disc, the posterior AF appears to carry more load than the NP or anterior AF; however stress and load distribution within the IVD is poorly understood.<sup>183</sup>

The abundance of water within the IVD plays a critical role in the mechanical response of the structure.<sup>185</sup> The fluid flow in and out of the system due to external load causes the IVD to display poroelastic or temporal mechanical behavior. Once external load is applied to the structure, fluid moves outward and back in when the load is removed. As degradation continues, the time for this process to occur triples, and recovered disc height is decreased.<sup>179</sup>

## CONCLUSIONS

LBP remains a prevalent and challenging problem to treat, often linking directly or indirectly to degenerative changes within IVDs. Disc degeneration usually arises from the disruption of homeostasis maintained by the anatomical components of the IVD. The degenerative cascade usually starts with degradation of the ECM, resulting in the loss of proteoglycans, water content, and ultimately, disc height. In addition, the release of cytokines from ECM breakdown upregulates the production of aggrecanases and proteases while promoting the inflammatory signal pathways. This vicious cycle leads to continuous degeneration and induces neovascularization and neoinnervation of the IVD. To develop regenerative therapies for degenerated discs, authors of future studies must aim to restore both anatomical and biomechanical properties of the IVDs.

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