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Primer

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Intervertebral disc degeneration

Bradley T. Hammoor [1,2,3] ✉, **Christopher S. Lai** [1,2,3], **Grace X. Xiong** [4], **Dawn M. Elliott**[5], **Brian Snyder**[3,6], **Edward Vresilovic** [5], **Christopher M. Bono**[2,3] & **Benjamin R. Freedman**[1,3] ✉

Abstract

Intervertebral disc (IVD) degeneration is a naturally occurring process that is a consequence of biological ageing and exposure to normal physiological loading over a lifetime and is characterized by loss of IVD tissue structural integrity. The nucleus pulposus changes with loss of pressurization, decreased collagen concentration and loss of distinction from annulus fibrosus. The annulus fibrosus and cartilaginous endplate suffer delamination, tears, fractures and clefts of their respective extracellular matrix at both microscopic and macroscopic scales. This loss of structural integrity generally follows a predictable pattern of degeneration, and it predisposes the IVD to pathological states. As the disc degenerates, the likelihood of functional failure to protect the neural elements and/or to provide stable spine motion and support increases. Functional failure takes the degenerated IVD to a state of disc pathology that has various phenotypes: the most common forms are disc herniation, mechanical instability, spinal stenosis, degenerative spondylolisthesis and degenerative scoliosis. IVD pathology is commonly self-limited and non-operative treatment remains the mainstay of treatment in most patients. For patients with refractory disease, surgical intervention focuses on neural decompression and, when indicated, motion segment stabilization. Future therapies for prevention of disc degeneration, targeted disc regeneration and biological modification of the degenerative cascade might prevent or reverse pathological changes across all spinal regions.

Sections

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[1]Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA. [2]Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston, MA, USA. [3]Department of Orthopaedic Surgery, Harvard Medical School, Boston, MA, USA. [4]Department of Orthopaedic Surgery, Stanford University, Palo Alto, CA, USA. [5]Department of Biomedical Engineering, University of Delaware, Newark, DE, USA. [6]Department of Orthopaedic Surgery, Boston Children's Hospital, Boston, MA, USA. ✉e-mail: bhammoor@bidmc.harvard.edu; bfreedm2@bidmc.harvard.edu

Introduction

Intervertebral discs (IVDs) are complex fibrocartilaginous structures that have a crucial role in the biomechanical function of the spine, transmitting loads from one vertebral body to the next and allowing controlled motion in multiple planes, including axial loading, flexion, extension, lateral bending and rotation[1] (Fig. 1). IVDs are composed of a central nucleus pulposus surrounded by the annulus fibrosus, which is bounded superiorly and inferiorly by cartilaginous endplates (CEPs)[2]. The morphology and function of IVDs is subtly different depending on their location. The spine is segmented into 7 cervical, 12 thoracic and 5 lumbar vertebrae[3]; in the cervical spine, IVDs function in concert with uncovertebral joints to allow flexion–extension and rotation while protecting the spinal cord[4]. The unique uncinate processes and smaller disc size relative to the dimensions of the vertebral body distinguish cervical anatomy from other regions. Thoracic discs, which are constrained by rib cage articulation, allow more limited motion than cervical discs, and prioritize stability for the protection of vital thoracic organs. The coronally oriented facet joints and rib attachments create a relatively rigid thoracic segment compared with the cervical and lumbar spine[5]. Lumbar discs bear the greatest axial loads and facilitate flexion–extension while limiting rotation through sagittally oriented facet joints. The larger disc size, greater anterior to posterior dimension and kidney-shaped morphology reflect adaptation to maximal load transmission requirements[2,6–9] (Fig. 2).

Age-related structural and biochemical deterioration of the IVD is near-universal and is characterized by proteoglycan loss, decreased hydration and progressive tissue damage. These biochemical changes manifest as structural deterioration, with loss of disc height, annular tears, and endplate damage, which fundamentally alter the biomechanical function of the spine (Fig. 1). The pathological progression of IVD degeneration typically follows an anterior-to-posterior trajectory, with posterior annular disruption and herniation representing later stages of disease[10]. However, nucleus pulposus degradation can also precede annulus fibrosis degeneration[11]. Altered biomechanics create pathological loading patterns that accelerate tissue failure in both the disc and adjacent structures (such as facet joints, ligaments and vertebral bodies), establishing a self-perpetuating degenerative cascade. Approximately one-third to two-thirds of individuals with degenerative changes will develop symptomatic pathology, which might manifest as back pain, neurological deficit or functional impairment[12]. In a symptomatically degenerated IVD, the annulus fibrosus has degenerated to a point that allows protrusion of the nucleus pulposus, an outpouching through an attenuated annulus fibrosus, or frank extrusion of the nucleus pulposus through a rent in the annulus fibrosus. Sequestration can occur when a portion of the extruded disc becomes completely detached[13]. As degeneration progresses, loss of disc height can lead to a reduction in the space available for neural elements such as the nerve roots, spinal cord or cauda equina, potentially resulting in spinal stenosis[14,15]. Cervical disc degeneration can result in radiculopathy or myelopathy owing to the close anatomical relationship between the degenerative discs and the spinal cord[16]. By contrast, thoracic disc pathology, although less prevalent, can produce severe myelopathy when clinical symptoms emerge[17]. The sequelae of pathological lumbar disc degeneration, which is the most common type of IVD degeneration, typically presents with discogenic back pain, radicular pain or neurogenic claudication[18,19].

Treatment for degenerative IVD disorders includes non-operative and operative modalities. Non-operative management typically involves a combination of lifestyle modifications, physical therapy, medications for pain control and inflammation, and targeted injections of steroids or a local anaesthetic. Surgical intervention might be indicated in individuals with functional or progressive neurological deficits or mechanical instability, or when non-operative measures have failed to provide adequate relief. Surgical options aim to decompress the affected neural structures and stabilize the affected motion segment. Both non-operative and operative interventions can lead to measurable improvements in quality of life (QOL), although the optimal treatment approach varies depending on specific characteristics of the patient and the severity of the pathology. Research into the development of novel therapies for IVD degeneration is ongoing, with a recent focus on biologic approaches; these therapies aim to address the underlying pathophysiology of disc degeneration, potentially promoting regeneration of the disc tissue and restoring its biomechanical functions. Although these therapies are in the early stages of development, they hold promise for improving the outcomes of patients with degenerative IVD disorders and reducing the need for invasive surgical interventions.

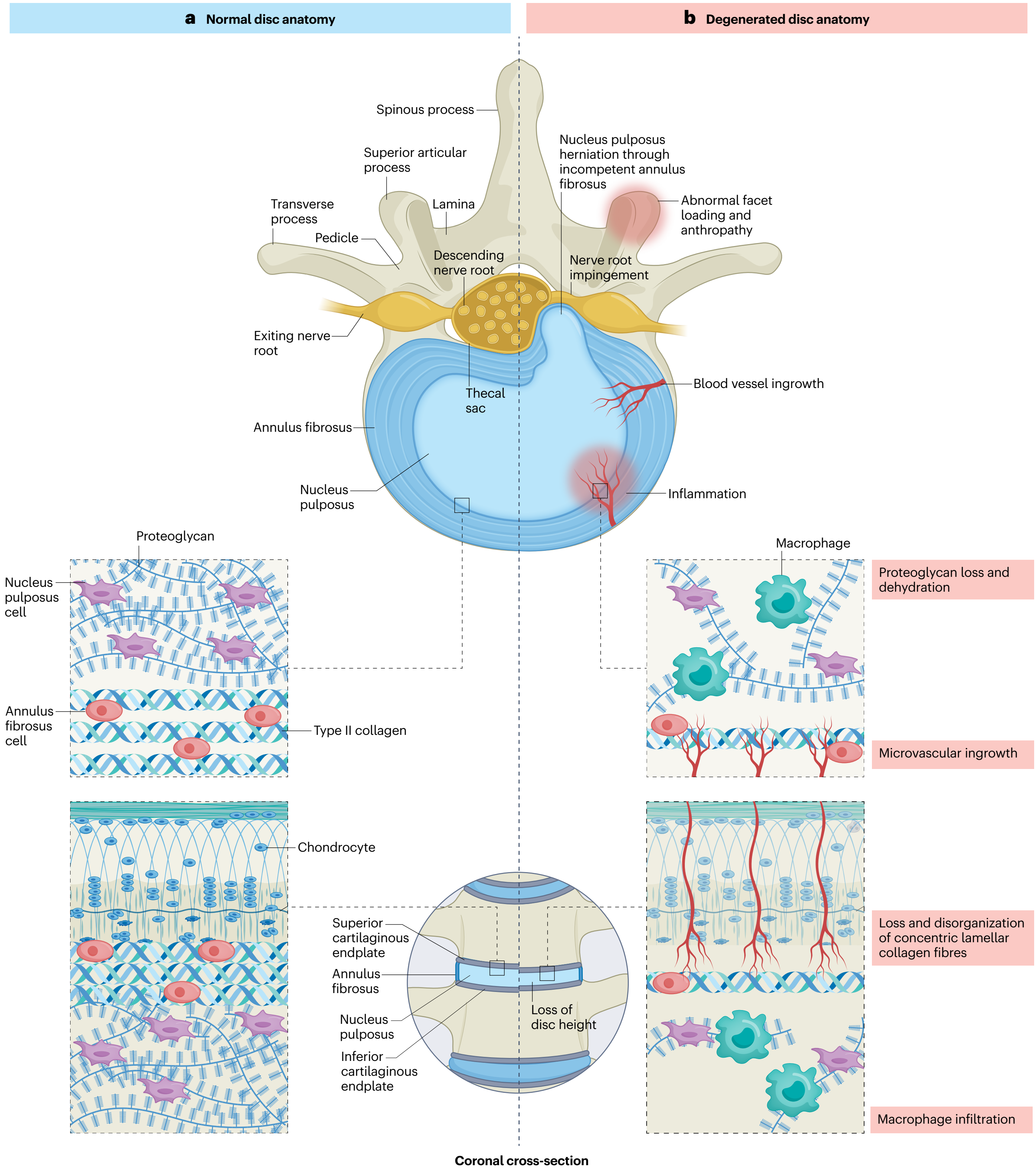
In this Primer, we discuss the epidemiology of IVD degeneration across the cervical, thoracic and lumbar regions, emphasizing the distinction between universal age-related structural changes and symptomatic pathological disease. We examine the pathophysiology of IVD degeneration, presenting both biological mechanisms (proteoglycan loss, cellular senescence and inflammatory responses) and biomechanical consequences (altered load distribution, tissue failure and motion segment instability) within an integrated framework. We describe clinical presentation and diagnostic approaches based on current professional society guidelines. We then review current management strategies, spanning conservative care, interventional procedures and surgical decompression or stabilization; assess the profound effect of symptomatic IVD pathology on QOL across multiple domains; and quantify the global burden of disability. Finally, we examine emerging diagnostic technologies, precision medicine approaches and regenerative therapies that might transform future care.

Epidemiology

Prevalence

The estimated prevalence of disc protrusion and extrusion, two major disc pathologies, range from 3% to 63% and from 0% to 24%, respectively[20].

Fig. 1 | IVD structure in health and disease. Cross-sectional anatomy demonstrating the progression from normal intervertebral disc (IVD) architecture to pathological degeneration. **a**, Normal disc anatomy, displaying the intact functional spinal unit with the nucleus pulposus contained within the organized lamellar structure of the annulus fibrosus, bounded superiorly and inferiorly by cartilaginous endplates. The nucleus pulposus maintains high proteoglycan content and hydration and the annual fibrosis exhibits organized concentric collagen fibre layers. Cells in the IVD are sparse but metabolically active, with chondrocyte-like cells in the nucleus pulposus and fibroblast-like cells in the annular fibrosus. **b**, Degenerated disc anatomy, illustrating the cascade of pathological changes that are characteristic of advanced disc degeneration. Loss of proteoglycan content and dehydration of the nucleus pulposus lead to decreased disc height and altered biomechanical loading patterns. Disruption of the organized lamellar structure of the annular fibrosus results in circumferential and radial tears, and predisposition to herniation of the nucleus pulposus. Abnormal facet joint loading secondary to disc collapse leads to facet arthropathy and hypertrophy, contributing to neural element compression. Inflammatory mediators and nociceptive nerve ingrowth accompany the degenerative process, and macrophage infiltration and neovascularization indicate tissue breakdown and attempted repair mechanisms. The original version of the figure was created using BioRender.



Large variations in reported prevalences exist owing to differences in reporting methodologies and patient age, sex and risk factor exposure across studies. Ageing is the greatest predictor of IVD degeneration, with radiographic prevalence increasing from 16% at 20 years of age to 98% by 70 years of age[21]. Most individuals with radiographic degeneration remain asymptomatic throughout life and these estimates

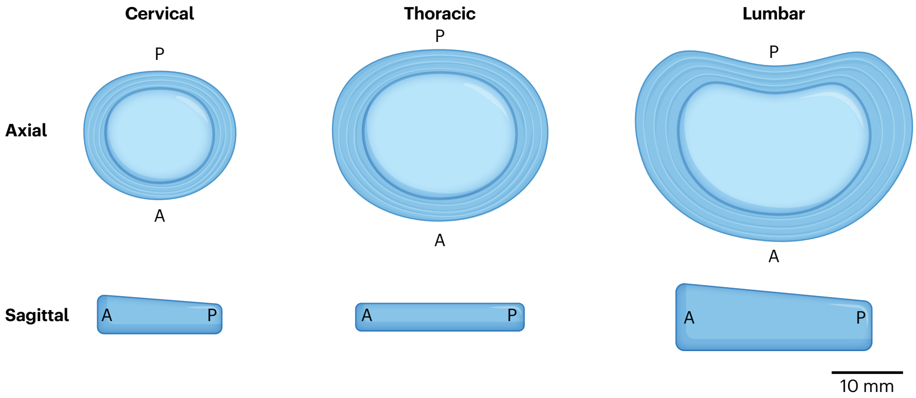


Fig. 2 | Regional variation in intervertebral disc morphology. Anatomical comparison of intervertebral disc morphology across spinal regions, demonstrating region-specific adaptations to local biomechanical demands. Axial cross-sections reveal progressive enlargement from cervical to lumbar regions. Cervical discs exhibit a more circular configuration, whereas lumbar discs demonstrate a characteristic kidney-shaped morphology with pronounced anterior convexity. The nucleus pulposus is denoted in light blue, and the annulus fibrosus is denoted in a darker blue. Sagittal views illustrate the wedge-shaped configuration characteristic of each region, with cervical and lumbar discs demonstrating greater anterior height to maintain physiological lordosis, whereas thoracic discs exhibit more uniform height distribution consistent with kyphotic alignment. These morphological adaptations reflect the evolutionary optimization of disc structure to regional functional demands: cervical discs prioritize mobility and neural protection, thoracic discs emphasize stability within the rib cage constraint, and lumbar discs maximize load transmission capacity. A, anterior; P, posterior. The original version of the figure was created using BioRender.

derive predominantly from imaging studies and histopathological analyses that capture structural changes regardless of symptoms, and do not represent the prevalence of symptomatic IVD disease. Of note, such post-mortem studies are limited to populations in which autopsy examination is culturally acceptable and performed systematically, creating geographical bias in understanding disease progression across different global regions[22]. Furthermore, regional epidemiological data have been captured mostly in Western and Asian countries, with racial demographics reflective of the populations of these areas. Prevalence data remain particularly sparse for sub-Saharan Africa, parts of Asia, and Latin America[23–25].

Lumbar disc degeneration is the most prevalent type of disc degeneration, with a radiographic prevalence of 37% at 20 years of age and a prevalence in post-mortem histopathological studies of 96% at 70 years of age. Lumbar spinal stenosis affects approximately 9.3% of adults, with foraminal stenosis in up to 75% and central stenosis in 76.5% of these patients[25]. Degenerative spondylolisthesis has a prevalence of 11.5% in the general population, with higher incidence among women and older individuals[26].

The annual incidence of radiographic cervical disc degeneration is 0.083%, with a peak incidence in the fifth decade of life[16,27]. Symptomatic cervical radiculopathy, or nerve root compression, secondary to IVD degeneration and its sequelae affects approximately 0.107% of men and 0.064% of women[27]. The C5–C6 disc is the most commonly affected (25–54% of patients with symptomatic cervical radiculopathy), followed by the C6–C7 disc (15–38% of patients with radiculopathy)[28–30]. Degenerative cervical myelopathy — a more severe manifestation arising from spinal cord compression — affects approximately 1.6–4.0 individuals per 100,000 population[31,32].

Thoracic disc herniation is relatively rare, with 0.25–0.75% of all disc herniations being symptomatic[33]. The rarity of symptomatic thoracic disc pathology is indicative of the biomechanical protection afforded by the rib cage and coronally oriented facet joints that limit motion. The highest incidence is for T8–T12, that accounts for approximately 75% of thoracic disc herniations. This area corresponds to the thoracolumbar transitional zone where spinal mobility increases[34]. Thoracic disc herniations are most commonly asymptomatic and are often discovered incidentally on MRI, with MRI studies revealing a prevalence of 11–37% in asymptomatic individuals[35]. Thoracic disc pathology correlates strongly with advancing age and demonstrates a slight female predominance (61.4%)[36].

Demographic and risk factors

Age and sex. Disc degeneration is strongly correlated with age, as attested by histological analyses and longitudinal studies elucidating predictors of IVD pathology (Table 1). A histological study of IVD degeneration in cadaveric spines (age 20–64 years) demonstrated that degeneration of the annulus is already present in 65% of individuals at 20 years of age, rising to 80% at 50 years of age; the presence of full annular tear increases from 10% at 20 years of age to 36% at 50 years of age[37]. Furthermore, the risk of general IVD degeneration increases with age, from 71–75% at 30–49 years of age to 83–86% at 50–59 years of age[37–39].

Sex-related differences in the prevalence and pattern of pathological IVD degeneration vary depending on spine region. Cervical radiculopathy shows a male predominance (0.107% of men versus 0.064% of women), potentially owing to differences in occupational exposure and biomechanical loading patterns[27]. Conversely, thoracic disc pathology demonstrates a female predominance (61.4% women), as does lumbar degenerative spondylolisthesis (prevalence 19.1% in men versus 25.0% in women); the latter is particularly common in post-menopausal women, possibly owing to hormonal influences on ligamentous laxity and bone quality[36,40]. These sex-specific patterns indicate that hormonal, anatomical and biomechanical factors interact to produce differential susceptibility to degeneration and phenotypic expression between sexes.

Lifestyle and environmental factors. Exposure-related and lifestyle-related risk factors associated with the degeneration of IVDs include BMI, smoking and occupation-related risks[41]. The association

Table 1 | Epidemiology and risk factors for disc degeneration

Risk factor	Association	Study design	Number of patients	Year	Risk estimate
Genetic associations					
Collagen synthesis gene *COL1A1* (TT genotype)[52]	Increased degeneration risk through altered collagen structure affecting disc integrity	Prospective cohort study with cross-sectional genetic analysis	966	2004	OR 3.6 (95% CI 1.3–10.0)
Inflammatory response genes *I1L1A*, *IL1B* (T alleles)[54]	Regulation of matrix metalloproteinases leading to accelerated disc matrix degradation through inflammatory pathways	Prospective occupational cohort study with genetic analysis	133	2004	*IL1A*: OR 2.4 (95% CI 1.2–4.8) *IL1B*: OR 1.9 (95% CI 1.0–3.7)
Vitamin D signalling gene *VDR* (1t allele)[55]	Vitamin D receptor polymorphism affecting calcium homeostasis and bone metabolism in vertebral endplates	Large-scale case–control study	804	2006	OR 2.6 (95% CI 1.15–5.90)
Vitamin D signalling gene *VDR* (Tt allele)[56]	Association with multilevel and severe disc degeneration patterns, suggesting systemic metabolic effects	Cross-sectional genetic association study	205	2002	Significantly increased incidence
Heritability (from twin studies)					
Familial component[47]	Familial aggregation explains majority of degeneration variance in upper lumbar segments, lower lumbar segments and severity of degeneration	Retrospective twin cohort study	115 male identical twin pairs	1995	Upper lumbar: 77% of total variance Lower lumbar: 43% of total variance
Severity of degeneration[50]	Overall heritability across spinal regions for advanced degenerative changes requiring clinical intervention	Prospective twin study with MRI assessment	326 twins (172 monozygotic, 154 dizygotic)	1999	Cervical: 79% of variance Lumbar: 64% of variance
Other factors					
Age[37]	Primary risk factor Progressive increase in degeneration risk with advancing age	Cadaveric study	157 male cadavers	2004	Risk 0.71–0.75 (age 30–49 years) to 0.83–0.86 (age 50–59 years)
Sex[36]	The relationship between biological sex and disc degeneration is complex and varies by age, spinal level and hormonal status.	Prospective observational population-based MRI study	2,007	2023	Cervical: men show higher prevalence in younger age groups (30–49 years), but this converges in older age groups Thoracic: men show notably higher prevalence in the age group 30–39 years (30.7% versus 17.8%), but women surpass men in the age group >60 years (88.0% versus 77.6%) Lumbar: women show slightly higher prevalence in the youngest (<30 years) and middle-age groups (50–59 years), but prevalence is similar in the oldest group
Tobacco exposure[40]	Increased risk of disc herniation across spinal regions through impaired nutrition and accelerated cellular senescence	Systematic review and meta-analysis	12 studies (six cohort studies and six case–control studies)	2016	RR 1.27 (95% CI 1.15–1.40)
Tobacco exposure (twin study comparison)[45,325]	Direct comparison demonstrates independent effect of smoking on disc health	Twin-discordant cohort study using MRI assessment	20 twin pairs with high smoking discordance	1991	18% greater degeneration versus non-smoking twin
Elevated BMI[42,43]	Weight correlation with presence, extent and severity of disc degeneration through increased mechanical loading and inflammatory mediators	Population-based cross-sectional study	Adults: 2,599 Juveniles: 83	2012; 2011	Obese adults: OR 1.79 (95% CI 1.17–2.74) Obese juveniles: OR 14.19 (95% CI 1.44–140.40)
Other site OA[325]	Joint degeneration associated with spinal disc degeneration, suggesting shared pathophysiological mechanisms	Population-based longitudinal inception cohort study	796 women with paired lumbar spine radiographs	2003	Hip OA: OR 1.8 (95% CI 1.1–2.9) Knee OA: OR 2.5 (95% CI 1.3–3.8)

OA, osteoarthritis; RR, relative risk.

of obesity with IVD degeneration has come into greater focus over time, and cross-sectional analyses have found that weight correlates significantly with the presence, extent and severity of IVD degeneration on MRI (OR 14.19, 95% CI 1.44–140.40)[42,43]. Smoking is also a strong predictor of IVD degeneration, and in a meta-analysis, smokers had a relative risk of 1.3–1.5 for lumbar and cervical disc herniations, respectively[40,44]. Studies examining differences in IVD degeneration between twins further established an 18%-greater mean IVD degeneration score in individuals who smoked compared with their non-smoking twin counterparts[45]. The association between IVD degeneration and occupation is less strong. Cervical disc degeneration might be associated with unique occupational risk factors, such as prolonged cervical flexion, repetitive shoulder movement and prolonged static loading; indeed, professional drivers show increased risk (HR 1.54) for cervical disc degeneration[46]. However, studies analysing occupational exposure in identical twins found that occupational exposure accounted for only 7% of the overall variance observed in disc degeneration, whereas leisure time physical loading accounted for only 2%[47]. Further twin studies of occupational exposure that examined differences in driving behaviour and exposure to whole-body vibrations found no significant difference in IVD degeneration between individuals who drove for their occupation and their twin counterparts who did not[48].

Genetic predisposition. IVD degeneration has been explored in a number of high-quality hereditary, twin and gene-sequencing studies, with some data suggesting a genetic link. IVD degeneration is significantly more likely to be observed in siblings than in the general population[49] and twin studies found that 77% of variability in upper lumbar and 43% of lower lumbar disc degeneration was explained by familial aggregation[47]. Furthermore, heritability has been implicated as responsible for 64% and 79% of cases of severe lumbar and cervical disc degeneration, respectively[50]. Several genes have been proposed as responsible for IVD degeneration (Table 1), with *COL1A1* polymorphisms most prominently associated with an increased risk of disc degeneration[51]. The *COL1A1* tyrosine–tyrosine (TT) genotype carries an elevated risk of IVD degeneration relative to alternative genotypes at the same locus (OR 3.6, 95% CI 1.3–10)[52]. IL-1 has also been implicated as a potential driver of IVD degeneration owing to its role in the regulation of matrix metalloproteinases[53] and the incidence of IVD degeneration in individuals with TT genotypes in *IL1A* is almost twofold higher than in individuals with the cytosine–cytosine (CC) genotype[54]. Polymorphisms in the gene encoding the vitamin D receptor (*VDR*) have also been linked to IVD degeneration; individuals with the *VDR* 1t allele have a 2.6-fold increased risk compared with individuals without this allele[55]. Similarly, patients with the *VDR* Tt genotype have significantly increased incidence of multilevel and severe IVD degeneration[56].

Genome-wide association studies have identified novel susceptibility loci for IVD degeneration, implicating genes involved in cartilage development (*CHST3*, encoding carbohydrate sulfotransferase 3), growth factor signalling (*IGFBP2*, encoding insulin-like growth factor-binding protein 2) and structural maintenance (*PARK2*, associated with mitochondrial quality control)[57]. These findings suggest that susceptibility to IVD degeneration involves diverse biological pathways including matrix synthesis, growth factor responses, cellular stress responses and metabolic regulation. Although none of these heritable factors have been singularly implicated in the biochemical mechanisms of disc degeneration, the pathways that they control are highly implicated in the process of degeneration (see the section 'IVD degeneration').

Mechanisms/pathophysiology

IVD degeneration is an inevitable consequence of living. The longer a person lives, the more likely it is that the IVDs have undergone changes that can be classified as degeneration[22,38,58]. Fortunately, IVD degeneration has little to no clinical consequences for most people. This observation underlies the fundamental clinical challenge: distinguishing age-appropriate degeneration from pathological disc disease.

Apart from chordomas, pathological diseases of the IVD are the consequence of degeneration leading to pathological mechanical conditions that compromise neural elements or spinal stability[59]. These pathological mechanical states alter spine mechanics in ways that most frequently manifest as altered neurological functions, primarily in the form of pain and also in the form of neurological disabilities such as radiculopathy and myelopathy. Although all IVDs degenerate with ageing in humans, genetic and environmental influences have a role in determining which of the degenerating IVDs lead to pathological mechanical states[60].

Normal IVD anatomy and physiology

Anatomy. The IVD is a small organ consisting of the nucleus pulposus – a well-hydrated, gel-like tissue – which is constrained circumferentially by the annulus fibrosus, a highly organized fibrous tissue, and superiorly and inferiorly by the CEPs, which are composed of a hyaline cartilage-like tissue[61]. The IVD is the largest avascular structure in the body and, as a result, has a uniquely low oxygen tension and metabolic physiology. The vascular blood supply and neurological innervation is limited to the outer annular fibrosus and to the vertebral bodies adjacent to the CEP[62,63]. As a result, cell nutrition and waste removal in the IVD occurs by diffusion and convective transport through the IVD's porous and permeable solid extracellular matrices (ECMs)[64–67]. The tissues of the IVD have extremely low cell densities. The CEP, similar to articular cartilage, has a cell density of 15,000 cells/mm^3, whereas the annular fibrosus has a cell density of 9,000 cells/mm^3. The cell density of the nucleus pulposus is 4,000 cells/mm^3, which is the lowest in the body, with nuclear pulposus cells only making up 0.25–0.5% of the nuclear pulposus tissue volume; the nucleus pulposus ECM makes up the remaining 99.5–99.75% of the volume[68–71]. Clearly, the mechanical behaviour of the IVD is entirely dependent on the properties of the ECMs associated with the IVD tissues.

ECMs of all parts of the IVD contain collagen, non-collagen proteins and proteoglycans. The CEP has an ECM structure very similar to that of hyaline cartilage[72–74]. The annulus fibrosus has a highly organized ECM with a dry weight of 50–70% type I and II collagen, 10–20% proteoglycans and ~25% non-collagen proteins[75–77], and when hydrated is 50–70% water. Of note, type I collagen is most abundant in the outer annulus fibrosus, with a decreasing gradient to the inner annulus fibrosus; conversely, type II collagen is most abundant in the inner annulus fibrosus with a decreasing gradient to the outer annulus fibrosus. The annulus fibrosus is organized into 15–25 layers of parallel collagen fibres with opposing angulation in adjacent layers[78–81]. In addition to this alternating angulation between layers, the collagen fibre angle to the transverse plane has a gradient from ~30° at the outer annulus fibrosus to ~45° at the inner annular fibrosus. These layers are not fully concentric; they are interwoven such that 50% intersect within a 20° section of the annular fibrosus. Individual lamellae are interconnected with interlamellar bridges, and elastin fibres between layers help to maintain structural integrity[61,82–86].

The nucleus pulposus accounts for 40–50% of the disc volume and 25–50% of its cross-sectional area, with the annulus fibrosus making up almost all of the remaining volume and cross-sectional area. The gelatinous nucleus pulposus ECM has few internal tissue mechanical constraints, with a loosely organized type II collagen network interspersed in a proteoglycan-dominant ECM[79,87,88]. The dry weight of this ECM is <25% type II collagen, >50% proteoglycan and ~25% non-collagen proteins, and it has a hydration level of 70–80%[89]. The nucleus pulposus ECM has a full complement of proteoglycans, with aggrecan as the major structural proteoglycan[90]. Aggrecan is a complex, very large proteoglycan (~2,500 kDa)[90–92] which can be visualized as a bottle brush molecule with a protein core and 100 side-chain glycosaminoglycan (GAG) bristles of keratan sulfate and chondroitin sulfate[92]. In the nucleus pulposus ECM, aggrecan molecules self-assemble into large aggregates of ~100 aggrecans linked to a hyaluronic acid[91–93].

Normal IVD mechanics

When considering IVD mechanical physiology, the IVD is frequently considered in the context of a solitary articulating unit termed the functional spinal unit (FSU)[94,95]. A single FSU consists of a superior vertebra and an inferior vertebra that are connected by passive and active tissues. The passive mechanical restraining tissues include a single IVD between the vertebral bodies, two diarthrodial facet joints between the posterior vertebral elements, and at least seven ligaments, whereas the dynamic restraints are the numerous interconnecting muscles. The IVD as part of the FSU contributes mechanically by providing load transmission, motion and energy absorption[1,96].

The mechanics in a young, healthy looking, non-degenerated IVD are primarily dependent on the interplay of the nuclear pulposus and annular fibrosus tissues. The GAG sulfated sugars of the aggrecan-rich nucleus pulposus provide an abundance of bound negative charge. The containing annulus fibrosus and CEP act as a semipermeable membrane that allows the passage of cations and water while preventing migration of the large aggrecan molecules. Considering the principles of Donnon equilibrium, cations enter the nucleus pulposus to balance the negatively charged aggrecan side chains and create a hyperosmotic environment[90]. In response to the increased cation concentration and osmotic pressure, water is pulled into the nucleus pulposus, swelling this tissue. As the swelling nucleus pulposus tissue is physically constrained by the lamellar ply structure of the annulus fibrosus and CEP, all these tissues are physically loaded with a resultant hydrostatic pressure within the nucleus pulposus. Consequently, the tissues of the healthy IVD are internally loaded in the absence of externally applied load. FSU mechanical responses to application of external loads, namely compression, bending and torsion, markedly affect the state of underlying internal IVD tissue loading or, more simply stated, are primarily dependent on the mechanical interaction of the nucleus pulposus and annulus fibrosus[97,98].

The osmotic pressure in the nucleus pulposus pulls water into this tissue, whereas hydrostatic pressure pushes water out. In a static IVD system, water would stop moving at equilibrium when the osmotic pressure equals the hydrostatic pressure. However, the varying external loading of the disc through activity creates a dynamic hydrostatic pressure, which results in water moving into and out of the IVD. The hydrostatic pressure in a healthy disc is 0.1–0.24 MPa when lying down and might exceed 2.0 MPa when lifting with forward flexion[99,100]. Water movements into and out of the nucleus pulposus have an amplitude determined by the hydration or water volume in the nucleus pulposus and a time dependence determined by the physical interaction of water with the tissue it is passing through, namely the annulus fibrosus and CEP, as well as the direction the water is moving — into or out of the nucleus pulposus. The longest time constants for nucleus pulposus water movement are in the order of hours and they are direction-dependent[66,101,102]. The dynamic balance between the osmotic and hydrostatic pressures driving water into and out of the disc is fundamental to the IVD biomechanical functions of load transmission, motion and energy absorption, and is essential for the metabolic functions of the IVD[64–66,103].

IVD degeneration

IVD degeneration starts in the second decade of life and continues steadily. Early IVD degenerative changes show as water loss from the nucleus pulposus, which is evident on MRI scans[101] (Fig. 3). These changes are associated with decreasing cell density and proteoglycan content and increasing collagen content, as well as early tissue damage to the annulus fibrosus and CEP, in the form of clefts, tears and delaminations[101,102]. The nucleus pulposus changes from a gelatinous structure to a solid fibrous material, with loss of distinction between the nucleus pulposus and annular fibrosus owing to loss of proteoglycans and increasing collagen content[88,104–106]. Continued water loss decreases the hydrostatic pressure of the nucleus pulposus, resulting in loss of IVD height. Water loss from the nucleus pulposus also changes the annulus fibrosus and CEP mechanical loading, which results in these tissues having altered mechanical stresses and strains, and a predisposition for mechanical structural damage under normal external loading conditions[101,107–115]. Moreover, accumulated structural damage can lead to further alterations in IVD tissue stresses and strains, and an acceleration of the degenerative cascade. This degenerative process is potentiated by both the extremely limited capacity of the IVD tissues to heal or repair, a property shared with some of the other mesenchymal tissues, and the avascularity of the IVD, which also contributes to the poor tissue healing response[101,107–115]. IVD degeneration is a complex process, but it can be argued that loss of aggrecan in the nucleus pulposus is fundamental to the IVD degenerative cascade[70]. Degenerative and pathological IVD phenotypes vary, as might be expected in a genetically and environmentally diverse population; however, loss of nucleus pulposus aggrecan is common to all phenotypes and is the major contributing factor to IVD degeneration. Aggrecan loss can occur due to a purely biological or a mechanical mechanism, but most likely occurs through a combination of these mechanisms.

Regarding the biological mechanism for loss of nucleus pulposus aggrecan, the loss of notochordal cells in the first decade of life is a major contributor. Notochordal cells are large vacuolated cells present in the developing and young nucleus pulposus and they produce proteoglycans and regulate tissue homeostasis. After the notochordal cells disappear, the nucleus pulposus is populated by smaller nucleus pulposus cells, which have a distinct phenotype and reduced matrix synthesis capacity. This transition coincides with the initiation of age-related degeneration[69,70,89,103]. The combination of the loss of notochordal cells and of the generally low concentration of nucleus pulposus cells that are adapted to low oxygen tensions, low nutrition, low metabolite transport and high osmolarities, creates an environment that supports only slow aggrecan synthesis[69,70,116], which is balanced by its gradual catabolism by aggrecanase and metalloproteinases from the nucleus pulposus tissue[117,118].

As previously noted, aggrecan is a very large bottle brush-like molecule with a protein core and (GAG) bristles which cannot migrate out of the confinement of the nucleus pulposus as a consequence of its size[92]. The slow metabolism of aggrecan is attested by the long half-life of aggrecan molecules (4–7 years) and total aggrecan-derived

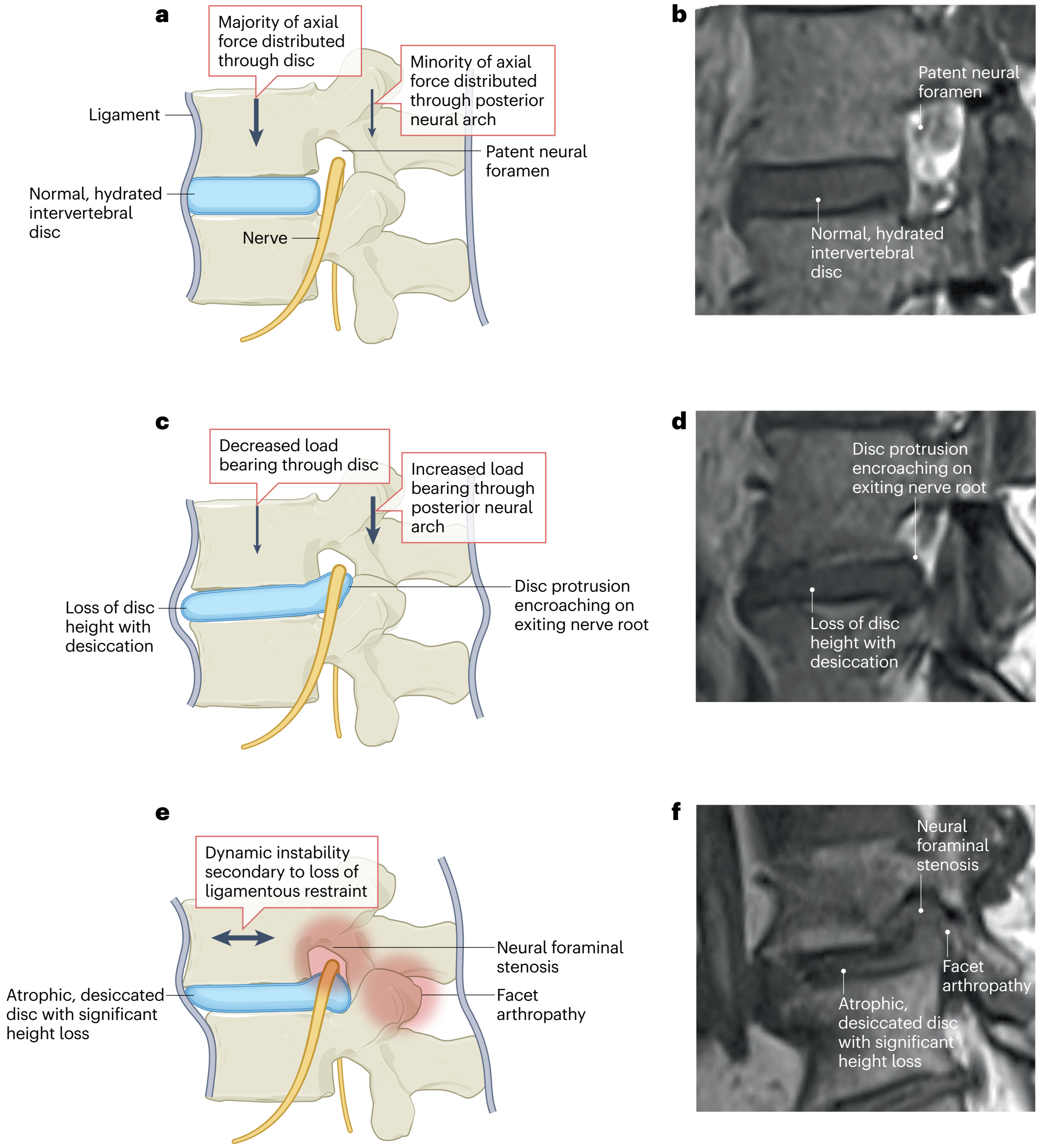


Fig. 3 | Biomechanical consequences of intervertebral disc degeneration. Progression of normal spinal biomechanics to pathological motion segment dysfunction with corresponding MRI findings. A normal functional spinal unit (parts **a** and **b**) exhibits optimal load distribution with axial forces transmitted primarily through the hydrated intervertebral disc. The posterior neural arch bears minimal compressive loads. The patent neural foramina provide adequate nerve root space, and the disc maintains normal height and T2-weighted MRI signal intensity. Early-to-moderate degeneration (parts **c** and **d**) demonstrates altered load-sharing mechanics, with decreased disc load-bearing capacity and a compensatory increase in posterior neural arch loading, predisposing the functional spinal unit to facet joint arthropathy. Disc protrusion encroaches upon neural foramina and disc height loss initiates motion segment dysfunction. MRI reveals decreased T2 signal intensity, reflecting proteoglycan loss and dehydration. Advanced degeneration (parts **e** and **f**) represents end-stage pathology with dynamic instability secondary to ligamentous restraint loss and disc structural failure. Severe neural foraminal stenosis compromises nerve root function and facet arthropathy contributes to posterior element pain and instability. The atrophic, desiccated disc demonstrates considerable height loss and complete T2 signal loss. Disc degeneration initiates a biomechanical cascade affecting the entire functional spinal unit, resulting in neural compression, pain generation and functional disability. Understanding this pathophysiological sequence is essential for determining appropriate therapeutic interventions targeting underlying mechanical dysfunction. The original versions of parts **a**, **c** and **e** were created using BioRender.

molecules (10–14 years). In non-degenerated IVDs, some smaller aggrecan fragments have a half-life exceeding 20 years, based on analysis of tissue samples from individuals of different ages[116,119]. The aggrecan concentration decreases with age when normalized to DNA content, suggesting that with ageing, the careful balance of aggrecan synthesis and catabolism is tipped towards catabolism[120]. This shift is potentially due to decreasing nucleus pulposus cell numbers and increasing nucleus pulposus cell senescence with age[2,121,122]. In a study evaluating progression of IVD degeneration in which patients without pain underwent MRI, T2 mapping to assess proteoglycan and water content suggested a reduction in aggrecan concentration with ageing through decreased water content[38].

The reduction in nucleus pulposus aggrecan, the major contributor to IVD degeneration, lowers nucleus pulposus hydrostatic pressure and consequently negatively alters the mechanical interaction of the IVD tissues. This change is particularly true in the IVD load displacement neutral zone – the range of physiological loading where the IVD exhibits low resistance to movement and the loading range which is associated with most activities of daily living[113,123,124]. The neutral zone length represents the amount of displacement that occurs in this low-stiffness region before tissue resistance increases substantially. When the nucleus pulposus hydrostatic pressure is decreased, the neutral zone modulus is decreased and the neutral zone length is increased, resulting in higher tissue strains in the annulus fibrosus, which predisposes this tissue to structural failure[113,125].

In conclusion, loss of aggrecan leads to decreased nuclear pulposus hydrostatic pressurization[114,126,127] associated with increased annular fibrosus loading and deformation[101,107–109,111–115,123]. Nucleus pulposus depressurization causes CEP loading to be less distributed at the endplate and results in portions of the CEP having higher stress and strains, whereas other portions of the CEP experience the opposite effect. The resultant altered IVD tissue mechanics can lead to both microscopic and macroscopic tissue failures in both the annular fibrosus and CEP, and lead to a cascade of biological and mechanical changes that enhance the degenerative cascade[110,112,124,128].

FSU mechanics in health and disease

Normal FSU. Within each FSU, loads in the superior and inferior vertebrae are transmitted during normal activity across the FSU articulation through static and dynamic restraints. As previously noted, the passive mechanical restraining tissues include a single IVD between the vertebral bodies, two diarthrodial facet joints between the posterior vertebral elements, and at least seven ligaments, whereas the dynamic restraints are the numerous interconnecting muscles. Considering simple axial (longitudinal) loading of the FSU, the IVD carries a large proportion of the axial load, sparing the facet joints[129–134] (Fig. 3). During axial compression, the superior and inferior CEPs are displaced axially towards each other. Since the nucleus pulposus is nearly incompressible because of the high water content, it expands radially and causes circumferential tensile loading of the annular fibrosus[123,124]. The annular fibrosus experiences tensile circumferential strain, compressive axial strain, and neutral-to-low radial tensile strain as a result of the nucleus pulposus tissue displacement[123,124]. Displacement of the CEPs is halted when the increased annular fibrosus compressive stress and nucleus pulposus hydrostatic pressure counter the applied axial loading across the vertebrae of the FSU.

A typical IVD axial load displacement curve is non-linear and well described by a low stiffness neutral zone at low loads that merges into high stiffness tension and compression zones as more load is applied[113,125]. It should be noted again that for most activities of daily living, the IVD operates in the neutral zone, with more strenuous activities occurring in the tension and compression zones[113,135,136].

Although only simple axial loading is considered above, normal FSU loading in vivo is a combination of three orthogonal forces in the orthogonal axis of the spine (that is, axial, anterior–posterior and lateral) and three orthogonal moments in the same three orthogonal axis of the spine (that is, axial torsion, flexion–extension and lateral bending). Hence loading has six degrees of freedom. True six-degree-of-freedom loading is a much more complex extension of the simple axial loading principles, with load sharing among all the static and dynamic restraints, as well as between the nucleus pulposus and contained annulus fibrosus[115,137]. IVD stiffness is largest in response to axial compression and axial torsion, and lowest in response to flexion and lateral bending loading[137,138].

FSU degeneration. As the degenerative cascade progresses, altered IVD loading can lead to increased tissue structural failure as FSU tissues are loaded in ways that they were not developmentally selected to sustain[124,128]. Beyond degenerative consequences within the IVD, degeneration of the IVD can alter other static and dynamic constraints, such as the facet joints and paraspinal muscles. Together, structural degeneration and damage to FSU tissue can lead to progressive and irreversible macroscopic changes, such as hyperintense zones (bright signal regions on T2-weighted MRI representing annular fissures and associated inflammatory tissue and vascularization), Modic changes (MRI signal changes at the vertebral endplate), IVD herniation, spinal stenosis, degenerated spondylolisthesis and degenerative scoliosis.

Loss of aggrecan can be caused by IVD mechanical loads exceeding tissue failure loads[139]. In the young, healthy, non-degenerated IVD, substantial loading or trauma can cause complete structural failure of the annular fibrosus or CEP, leading to a herniated nuclear pulposus with direct loss of aggrecan[140–142]. Lesser mechanical loads might partially injure these tissues and the accumulated tissue damage can reduce the load required for complete structural failure[143]. Mechanical disruption of the annular fibrosus and CEP ECMs at the microscopic scale can cause neurovascular invasion of the nucleus pulposus, resulting in exposure of the nucleus pulposus to macrophages and mast cells, and leading to increased levels of proteases and pro-inflammatory cytokines and more rapid catabolism of nucleus pulposus aggrecan[139,144–147]. This increased turnover overwhelms the limited proteoglycan synthetic activity, leading to accelerated aggrecan loss. Mechanical mechanisms alone can therefore result in a cascade of IVD degeneration at an aggressive pace, although, as previously mentioned, most IVD degeneration occurs through combined biological and mechanical mechanisms (Fig. 4).

Progressive changes can be graded macroscopically on the Thompson scale, an ordinal scale of 1 to 5, with 5 being the most degenerated[148]. Histopathology scoring systems were developed by the Orthopaedic Research Society Spine Section to standardize microscopic IVD degenerative changes for rats, rabbits and humans[149–151]. Eight significant degenerative features are scored, including nucleus pulposus shape; nucleus pulposus area; nucleus pulposus cell number; nucleus pulposus cell morphology; annulus fibrosus lamellar organization; annulus fibrosus tears, fissures or disruptions; nucleus pulposus–annulus fibrosus border appearance; and endplate disruptions or microfractures and osteophyte or ossification[149].

Pathological sequelae of IVD and FSU degeneration

IVD degeneration can lead to a host of defined pathological disorders, such as IVD herniation, facet cysts, spinal stenosis, segmental instability, degenerative spondylolisthesis and degenerative scoliosis. The origins of low back pain (LBP) caused by degenerative IVD remain speculative. However, the correlation between radicular and myelopathic neurological compromise and degenerative IVD is more clearly defined.

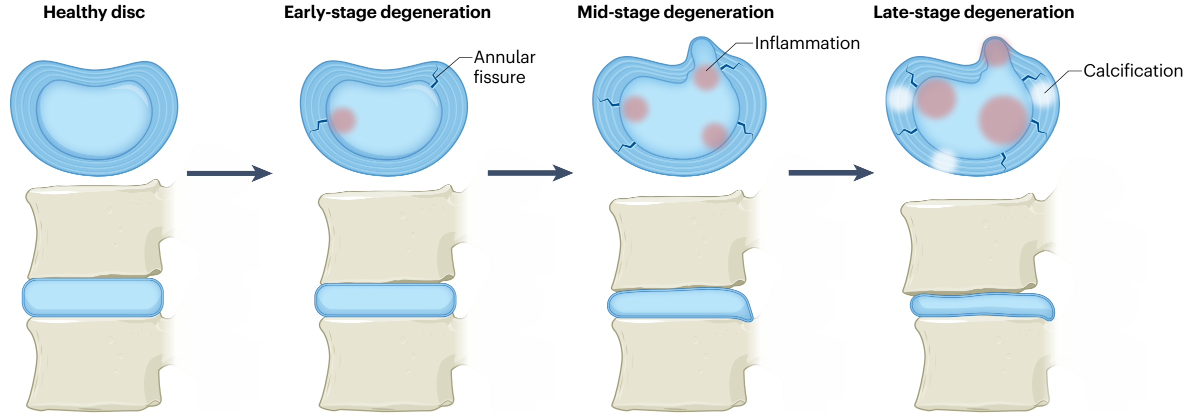


Fig. 4 | Timeline and compositional changes of intervertebral disc degeneration. The slow biochemical and structural changes that take place during decades of pathological transformation are revealed by the evolution of intervertebral disc degeneration over time. With high water content secondary to physiological aggrecan levels, the healthy disc sustains optimal biomechanical function, facilitating normal load transmission and spinal motion. Early-stage degeneration manifests with initial loss of proteoglycan, with the aggrecan concentration decreasing along with a reduction in water content and the appearance of pro-inflammatory mediators. As a result of changed cellular metabolism and decreased nutrient delivery. Mid-stage degeneration shows increased matrix disintegration, with collagen II levels falling and water content further decreased. A large proportion of disc cells show cellular senescence. Annular fissures appear all along the disc structure and inflammatory changes progress. Late-stage degeneration signifies end-stage pathology with a high degree of calcification, near-complete proteoglycan depletion and marked loss of disc height. The original version of the figure was created using BioRender.

Lumbar IVD herniation, spinal stenosis and degenerative spondylolisthesis are the three most common diagnoses for neurological symptoms attributable to IVD pathology[152,153] (Fig. 5). IVD herniation results from failure of the annular fibrosus or CEP to contain the nucleus pulposus. Once out of containment, the nucleus pulposus might cause neurological compromise by direct mechanical compression of the spinal cord or nerve roots, or invoke inflammatory processes with consequential radiculitis, radiculopathy or myelopathy[140–142,154]. Spinal stenosis and degenerative spondylolisthesis might cause neurological consequences through similar mechanisms. As IVD degeneration progresses, the IVD might collapse owing to tissue overloading[155,156]. Degenerative changes might compromise spinal or foraminal canals with resultant neural compression[27,157]. In the case of degenerative spondylolisthesis, spinal or foraminal canal compromise can also be the result of mechanical instability as a consequence of IVD degeneration[152,158,159].

Regional biomechanical considerations. Regional differences in biomechanical loading influence patterns of IVD degeneration and clinical manifestations. Cervical discs experience complex multiaxial loading, with substantial rotational and shear components[160,161]. The presence of uncovertebral joints alters load distribution, with these structures bearing approximately 10–15% of axial loads and providing lateral stability[162]. Cervical disc degeneration often manifests with posterior–lateral herniation patterns, reflecting the relative weakness of the posterior–lateral annulus and the constraint provided by posterior longitudinal ligament reinforcement centrally[163].

Thoracic discs experience primarily axial loading, with minimal rotational stress because of rib cage constraint. The reduced mobility in this region correlates with a lower prevalence of disc herniation; however, the narrow spinal canal diameter relative to cord size means that even modest disc protrusions can cause pronounced myelopathic symptoms[164,165]. Thoracic disc herniations are at high risk of calcification (approximately 40–70% of cases), potentially reflecting the lower mechanical demands and altered metabolic environment (reduced motion is associated with bone formation)[164].

Lumbar discs sustain the highest magnitude axial loads (up to 2.0–2.5 MPa during lifting activities) combined with substantial flexion–extension moments and modest rotation. The sagittal facet orientation permits flexion–extension but provides limited rotational constraint, making the lumbar spine vulnerable to torsional injury[166,167]. Lumbar disc degeneration and facet orientation predisposes the posterior or posterior–lateral IVD to herniations because of relative weakness in the posterior annulus and the concentration of nucleus pulposus pressure posteriorly during flexion activities[168]. In the lumbar spine, the L4–L5 and L5–S1 IVDs routinely have the greatest degenerative changes and highest Pfirrmann grade, and the prevalence of degeneration is highest for these IVDs. These findings of L4–L5 and L5–S1 degeneration are most likely the consequence of these IVDs being at the location of the highest spinal mechanical loads: greatest axial compression by body weight, greatest shear by maximal lordotic angulation, and greatest stress riser by bending modulus mismatch between the flexible lumbar spine and the rigid pelvis[166].

Diagnosis, screening and prevention

Clinical presentation

Pathological degeneration of the IVD can present with a wide range of patient-reported symptoms, which depend on the mechanism of the pathology and the region affected (Fig. 6). Patients might present with intrinsic discogenic pain, which often manifests as chronic LBP in individuals with lumbar IVD degeneration[19]. IVD degeneration that compresses adjacent neural structures can cause pain in other areas of the body. For example, cervical radiculopathy typically presents with neck pain radiating to the upper extremities in dermatomal patterns associated with specific nerve root distributions. Cervical myelopathy presents with a constellation of symptoms, including progressive imbalance and gait dysfunction, loss of manual dexterity, and upper motor neuron signs including hyperreflexia and the Hoffmann sign[16,169].

A majority of patients with thoracic disc herniation present with band-like thoracic pain, and some with myelopathic symptoms[170,171]. Patients with thoracic disc herniation might also develop lower extremity weakness, sensory changes and, in those with severe disease, bowel or bladder dysfunction[172]. Patients with lumbar pathology present with radicular symptoms that follow specific dermatomal distributions, and lumbar spinal stenosis can include neurogenic claudication – cramping pain in the lower extremities[173]. Age is a factor in evaluating pathology, and older patients are more likely to have symptomatic disease involving multiple spinal regions, display symptoms of radiculopathy and myelopathy, and have comorbid conditions that can either mimic symptomatic disc degeneration or obfuscate diagnosis[174,175].

Diagnosis is predicated on obtaining a thorough patient history and performing a detailed motor and sensory examination. Many patients present without objective physical examination findings; however, in those who do, altered deep tendon reflexes is the most common finding, followed by weakness[176]. Special examination manoeuvres, such as the straight leg raise or the Spurling manoeuvre, might be employed to provoke radicular symptoms[177]. These tests have varying reports of sensitivity and specificity owing to the heterogeneity of techniques for their use. Attribution of a history or examination finding to a spinal aetiology can be confounded by co-existing pathology from the shoulder, hip or knee, or peripheral nerve syndromes[178,179]. A focused history and physical examination are therefore critical for differentiating between these differential diagnoses. Electromyography is helpful in differentiating a spinal radiculopathy from a peripheral nerve disorder, although it is less useful for the diagnosis of myelopathy[180].

Imaging detection. The consensus among major American medical societies, including the North American Spine Society (NASS) and the American Academy of Family Physicians, underscores MRI as the primary non-invasive diagnostic tool for confirming compressive lesions in spinal pathology[180–182]. CT myelography can be used when MRI is contraindicated or its results inconclusive, but is generally reserved as a secondary option owing to its invasive nature. IVD degeneration can be graded using MRI for both clinical and research applications using the Pfirrmann grading system[183]. Nucleus pulposus T2 intensity, distinction between nucleus pulposus and annular fibrosus tissues, and disc height are the primary observations used to provide a five-level ordinal Pfirrmann measure of IVD degeneration, which is comparable to the Thompson scale[183,184]. T2 and T1ρ mapping, which evaluates the water and proteoglycan content of the nucleus pulposus, can be used

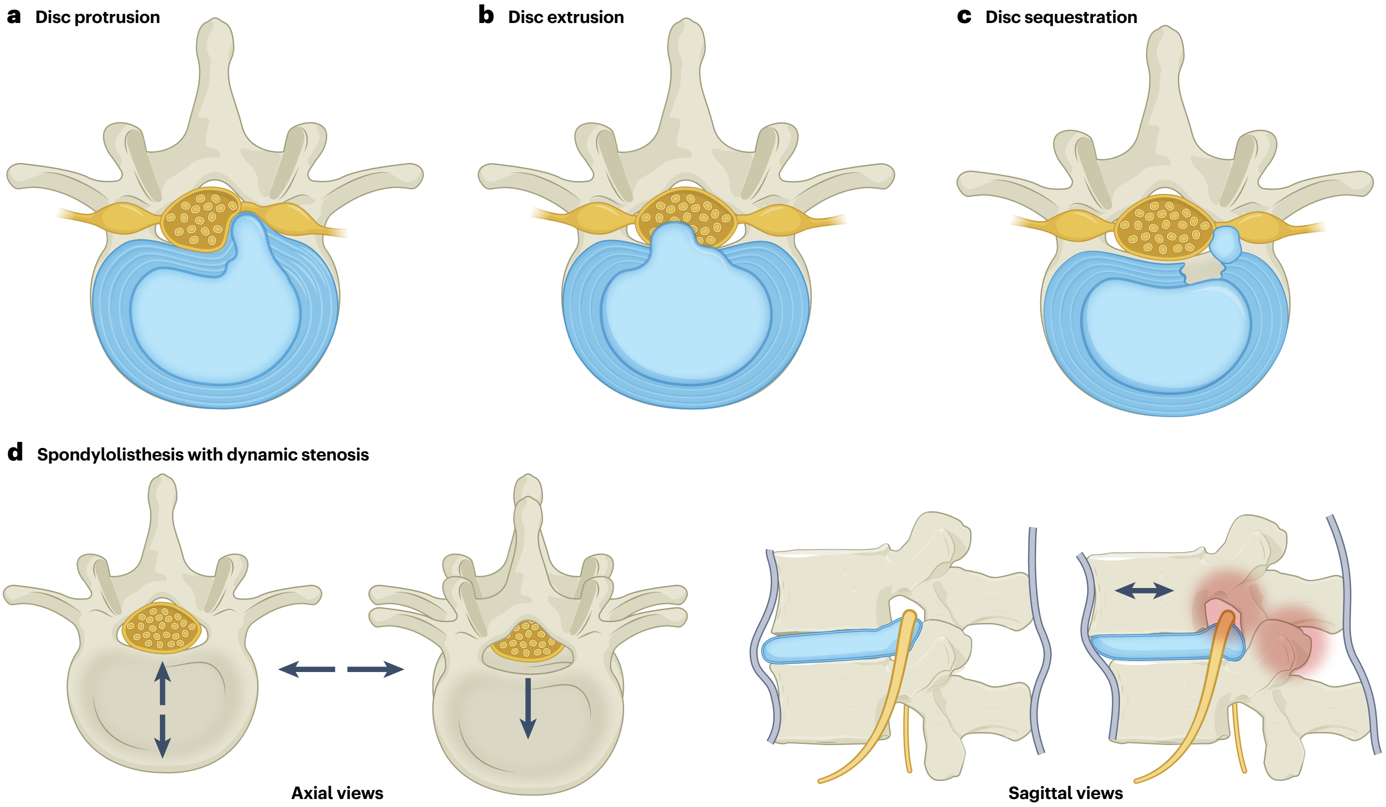


Fig. 5 | Pathological manifestations of intervertebral disc degeneration. Spectrum of pathological conditions resulting from intervertebral disc degeneration and their associated neural compression mechanisms. **a**, Disc protrusion. Focal bulging of the nucleus pulposus through a weakened but intact annulus fibrosus results in either nerve root compression or spinal stenosis. **b**, Disc extrusion. Complete rupture of the annulus fibrosus results in herniation of nucleus pulposus material beyond the confines of the disc space, creating a mass effect and inflammatory response affecting adjacent neural structures. **c**, Disc sequestration. The most severe form of disc herniation, wherein a fragment of extruded nucleus pulposus becomes completely detached from the parent disc and migrates within the spinal canal, potentially causing unpredictable neurological deficits remote from the original disc level. **d**, Degenerative spondylolisthesis with dynamic stenosis. The biomechanical consequences of advanced disc degeneration, where loss of disc height and ligamentous integrity results in abnormal vertebral translation (horizontal arrows) and dynamic compression of neural elements. The narrowed spinal canal (vertical arrows) exemplifies positional stenosis that varies with spinal positioning and loading conditions. The original version of the figure was created using BioRender.

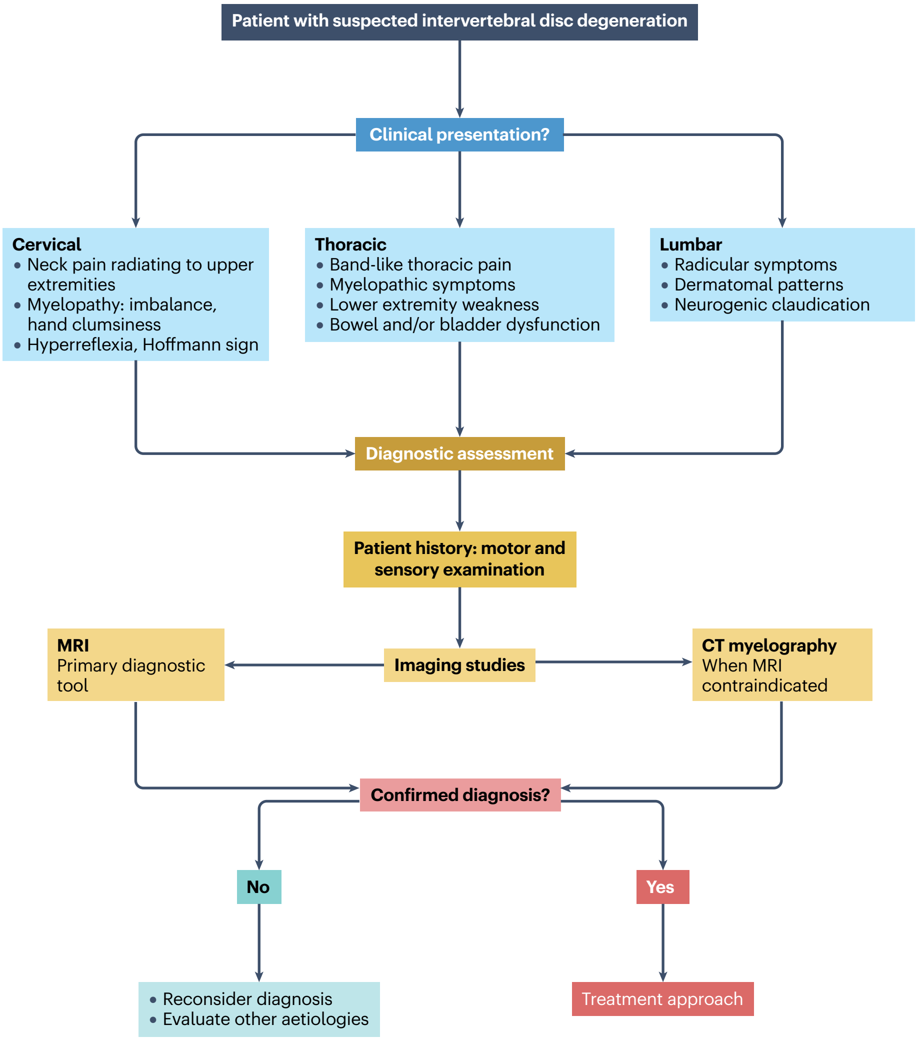


Fig. 6 | Diagnostic algorithm. Clinical decision-making flow chart for systematic evaluation of suspected intervertebral disc degeneration.

to identify IVD degeneration progression using MRI, with good correlation to histological and Pfirrmann grading[113,185–187]. These grading systems attempt to quantify the extent of IVD degeneration, although none provides a measure of pathology or is a biomarker for IVD disease.

Quantitative MRI approaches have been demonstrated to capture disc degeneration at early stages. These advanced imaging technologies have identified key features of degeneration, such as initial proteoglycan and GAG loss, changes in water content and distribution, and paraspinal fatty infiltration[188]. Multiple groups have leveraged deep convolutional neural networks to accurately detect and grade IVD degeneration on MRI images[172,189]. Although these advances in imaging, detection and artificial intelligence provide potential tools for early diagnosis and preventive care, they have not yet reached widespread application, in part because MRI-based changes in asymptomatic age-related degeneration appear similar to those in symptomatic, pathological IVD degeneration[22].

Other assessment tools. There are several validated instruments for measuring back-pain-related disability and QOL. The Oswestry disability index (ODI) and the Roland–Morris disability questionnaire (RMDQ) are commonly used for functional disability assessment[190–192]. The ODI consists of ten questions about daily activities, scored 0–5, and converted to a percentage to indicate level of disability. The RMDQ consists of 24 ‘yes or no’ questions, with scores ranging from 0 (no disability) to 24 (maximum disability). The Short Form 36 survey measures pain and disability but also provides a broader QOL assessment (for example, limitations in social activities, mental health and health perceptions)[193].

Screening and prevention

There are no current guidelines for screening or prevention of IVD degeneration, specifically, as the aetiology and pathophysiology remain poorly understood. Clinical guidelines from the NASS for degenerative spondylolisthesis, degenerative lumbar spinal stenosis, cervical radiculopathy from degenerative disorders and lumbar disc herniation with radiculopathy, focus on symptom management and not prevention or screening[180,194–196]. Counselling on risk factors for development of IVD degeneration might prove an important avenue for overall disease reduction, as tobacco smoking, obesity and occupational exposures demonstrate significant associations with radiographic and symptomatic disc degeneration[41,181,197]. Directing patients towards smoking cessation, weight loss and improved workplace ergonomics might therefore mitigate the burden of disease.

Precision medicine and machine learning. Recent research has begun to place increased emphasis on preventive measures and personalized care. In theory, the best treatment for IVD pathological degeneration is to mitigate, or even prevent, its initial development. One important step is therefore to understand who might be at risk. Although there is evidence to support genetic, demographic and modifiable risk factors for developing symptomatic IVD, large-scale predictive models are still lacking. In the surgical literature, there has been more published on predictive modelling for patient outcomes; however, the effect of such models on clinical outcomes and care remains to be determined. Specifically, multiple groups are developing machine learning models to identify predictors (such as preoperative demographics, comorbidities, preoperative functional status and radiographic findings) of postoperative patient outcomes and recovery, complications and cost[182].

Management

Management of symptomatic IVD degeneration is dependent on the patient's clinical manifestations and degree of disability (Fig. 7). Clinical presentation can span the spectrum from neck or back pain secondary to intrinsic disc pathology, to radiculopathy or myelopathy in the setting of mechanical nerve compression from disc degeneration. One of the main challenges in the treatment of pathologies associated with IVD degeneration is therefore quantifying the symptoms that can be reliably attributed to disc degeneration. Indeed, pain limited to the axial skeleton without radiating extremity pain is a multifactorial disease with possible contributions from multiple structural, biopsychosocial and nociceptive pathways[198].

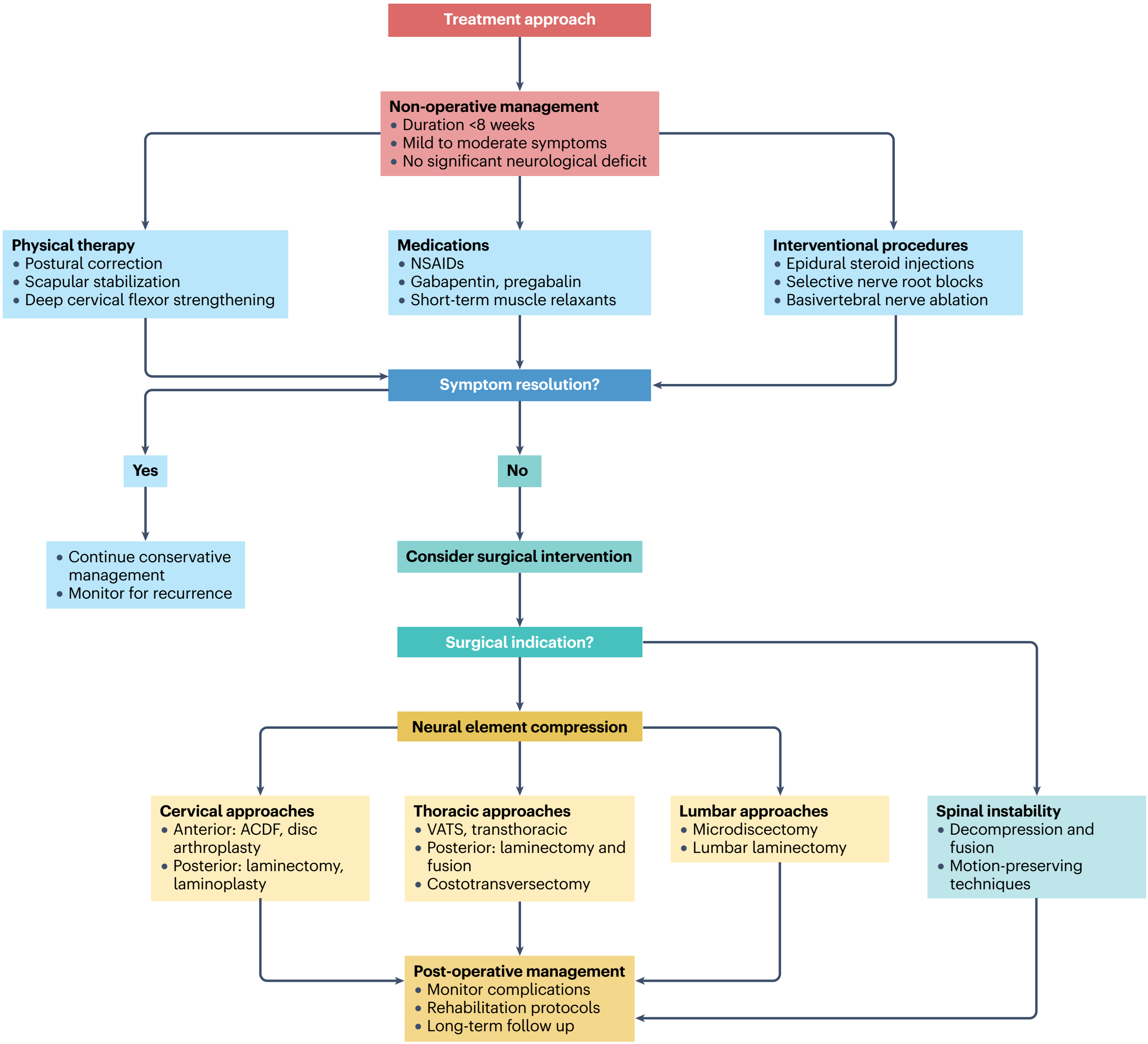


Fig. 7 | Management decision-making framework for disc-related disorders. Treatment algorithm for systematic management of intervertebral disc pathology. ACDF, anterior cervical discectomy and fusion; NSAID, nonsteroidal anti-inflammatory drug; VATS, video-assisted thoracoscopic surgery.

Treatment of symptomatic disc degeneration generally follows a predictable clinical pathway. Most patients improve with non-operative care, whereas those with persistent symptoms might benefit from surgery. This section reviews common non-operative therapies and options for discogenic pain, and provides a brief overview of surgical management, recognizing that surgery typically targets downstream sequelae of IVD degeneration, such as neural compression, rather than the disc itself. Emerging biologic therapies under investigation are discussed in the section 'Outlook'.

Non-operative management

The mainstay of treatment focuses on non-operative therapies. Key indications favouring non-operative management include acute symptoms for less than 6–8 weeks duration, mild to moderate radicular symptoms, and absence of considerable neurological deficit, such as progressive motor or sensory loss[199]. Given the multifactorial aetiology of pain syndromes caused by IVD degeneration, non-operative therapies often encompass a multimodal approach. This can include directed physical therapy, symptomatic management with medications, interventional pain procedures such as injections or nerve ablations, and other modalities such as chiropractic management or acupuncture[199]. Physical therapy emphasizes postural correction, scapular stabilization, and deep cervical flexor strengthening[199]. Postural training and ergonomic modification prove particularly important given the biomechanical relationship between thoracic alignment and adjacent spinal regions[171]. Medication typically begins with oral NSAIDs for acute pain, and for persistent symptoms, neuropathic agents such as gabapentin or pregabalin can provide relief of radicular pain[199,200]. Muscle relaxants demonstrate short-term benefit for acute pain, but should be limited owing to sedating effects[200–202]. Epidural steroid injections provide short-term relief in 60–70% of patients with cervical radiculopathy, although long-term outcomes remain comparable to those in non-injection cohorts[200–202]. Thoracic epidural steroid injections show modest results, with approximately 50% improvement in patient ODI scores at 6 months, although there are few high-quality comparative studies[203,204]. A meta-analysis of randomized controlled trials of moderate and high quality showed that lumbar epidural steroid injections achieve short-term symptomatic control in 70–90% of patients with acute radiculopathy[205]. Selective nerve root blocks can additionally provide diagnostic information and therapeutic benefit in patients with single-level radiculopathy[206].

Management of intrinsic discogenic pain

When non-operative management fails to provide adequate relief, treatment diverges based on the dominant pain mechanism: intrinsic disc pain, neural compression or mechanical instability. Attributing axial back pain to IVD degeneration and discogenic back pain remains a controversial topic and is an active area of research, as the management of discogenic pain shows considerable clinical equipoise and a lack of high-quality evidence. Surgical management of isolated IVD degeneration remains controversial owing to the multifactorial nature of axial LBP and the morbidity and invasiveness of surgery[207]. However, in patients with IVD degeneration that has progressed to vertebrogenic axial LBP with corresponding type 1 or type 2 Modic changes on MRI, ablation of the basivertebral nerve has shown promising results with level I evidence[208,209]. Two randomized controlled trials using this approach demonstrated an increase in ODI score of 20.3–20.5 points over sham interventions or standard care at 3–12 months[208,209]. Some authors have advocated fusion or even lumbar disc replacements as possible interventions in discogenic LBP, although adoption is limited owing to the substantially increased risk and rate of complications compared with conservative treatments[210]. Barriers to improved treatment options for discogenic or vertebrogenic axial LBP include substantial challenges in attributing a multifactorial clinical presentation to IVD degeneration alone. Biologics and regenerative therapies demonstrate some promise (see the section 'Outlook').

Operative management of neural element compression

Neural compression syndromes demonstrate a clearer correlation between symptoms and MRI imaging findings than discogenic pain. In the setting of symptomatic disc degeneration, neural compression or degenerative dynamic instability are common indications for operative intervention. Neural decompression becomes necessary when the FSU has degenerated disc herniations, facet arthropathy, or facet cysts that compress the nearby nerve roots and spinal cord, as identified from a concordance of MRI and physical examination or patient history findings[211]. Progressive neurological deficit at the spinal cord or nerve root level constitutes a clear indication for operative intervention, as natural history studies have demonstrated continued decline without surgical management[212,213]. Similarly, if persistent radiculopathy does not improve after 6–12 weeks of conservative treatment, surgical consideration is warranted[214–216]. The timing of neural decompression influences outcomes, with evidence indicating that patients experiencing moderate-to-severe myelopathy demonstrate superior recovery with early surgical intervention than with delayed surgery after prolonged conservative treatment[213]. Mild myelopathy can be monitored and managed non-operatively if clinical stability is maintained, although this remains an area of active investigation[217]. The surgical approach to decompression varies based on the location of the pathology, with anterior approaches (such as anterior cervical discectomy and fusion or cervical disc arthroplasty) providing direct access to ventral compressive elements and posterior approaches (such as laminectomy and laminoplasty) offering advantages for multilevel stenosis[218–223]. The thoracic region presents unique anatomical challenges that can be addressed by rib removal to facilitate access, video-assisted thoracoscopic surgery or transthoracic approaches[224–227]. In the lumbar spine, microdiscectomy and lumbar laminectomy provide effective decompression, with superior outcomes observed in patients with predominantly radicular symptoms than in patients with axial pain[176]. Although these surgical procedures often provide durable relief, patients must be counselled on the inherent risk of surgical complications, such as infection, blood loss, nerve or spinal cord injury or implant-related complications.

Operative management of spinal instability

Advanced degeneration might produce mechanical instability, requiring stabilization beyond simple decompression. Instability of the FSU can cause pain through abnormal vertebral motion, which becomes possible secondary to the loss of ligamentous constraint. Fusion of the vertebrae of the affected FSU, with or without concomitant decompression of any compressed neural structures, can halt abnormal motion, contributing to symptomatic relief[228–230]. In dynamic instability that causes repetitive compression of surrounding neural structures, stabilization and fusion of the FSU can also reduce dynamic neural compression to relieve positional or dynamic pain[228–230]. Motion-preserving techniques, such as cervical disc arthroplasty or laminoplasty, can effectively decompress neural elements and aid in restoring stable movement where neural compression alone contributes to symptoms, without painful instability. Motion-preserving techniques maintain

Box 1 | Quality of life assessment and the impact of back pain

Global burden

- 619 million people affected globally, representing 7.5% of the world population[23,24,238,326,327]
- Leading cause of years lived with disability worldwide[23,24,238,326,327]
- Sixth most costly health condition in the USA, exceeding US$100 billion annually[23,24,238,326,327]

Functional impact

- One-third of patients with chronic low back pain experience considerable disability[240,241]
- Commonly reported limitations include reduced sitting tolerance, restricted walking ability, and impairments in work capacity, social participation and self-care activities[240,241]

Psychological impact

- Patients with chronic low back pain demonstrate increased rates of depression, anger, sadness and hopelessness[249]
- Psychological distress exacerbates symptoms through mechanisms involving muscle tension and sleep disturbance[248]

Assessment tools

- Oswestry disability index (ODI): comprehensive ten-domain instrument assessing pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and travelling; scored 0–100% with minimal clinically important difference (MCID) of 10–12 points[190,191,328,329]
- Roland–Morris disability questionnaire (RMDQ): 24-item questionnaire evaluating disability attributable to low back pain; particularly sensitive for mild–moderate disability with MCID of 2 or 3 points; 5 points for chronic low back pain[191,329]
- Short Form 36 (SF-36): 36-item survey measuring eight health domains including physical functioning, role limitations, bodily pain, general health, vitality, social functioning, emotional role and mental health; provides both physical and mental component summaries with MCID of 3–5 points[330,331]
- Neck disability index (NDI): cervical spine-specific instrument comprising ten sections assessing daily activities; scored 0–50 points with MCID of 5–7 points[332]
- Visual analogue scale (VAS): simple pain intensity measurement ranging from 0 to 10 or 0 to 100 mm; typically demonstrates MCID of 1.5–2.0 points on 10-point scale[333]
- EuroQol-5D (EQ-5D): health utility measure for quality-adjusted life year (QALY) calculations; assesses mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression[192,193]

Disease-specific outcomes

- Cervical myelopathy: surgical treatment demonstrates high cost-effectiveness at US$20,548 per QALY gained, well below the WHO threshold of US$54,000 (ref. 269)
- Cervical radiculopathy: conservative management approach that is successful in 75–90% of patients managed non-operatively; remaining patients ultimately require surgical intervention[268]
- Lumbar intervertebral disc herniation: 90% of patients demonstrate improvement within 3 months; surgical benefits sustained at 8-year follow-up[216,334,335]
- Lumbar spinal stenosis: surgical decompression produces sustained improvement compared with conservative management[176,262]
- Lumbar degenerative spondylolisthesis: quality of life improvements following surgery approach those achieved with hip arthroplasty and are comparable to outcomes following knee arthroplasty[266]

physiological movement while addressing pathology, with long-term data demonstrating reduced transfer of physiological loads to adjacent FSU levels compared with fusion approaches[222,231,232]. However, patients with spinal instability and deformity might not be candidates for these procedures. Adjacent segment disease (accelerated degeneration above or below stabilized segments) occurs at an annual rate of approximately 2–3% following fusion procedures[233,234]. This phenomenon influences decisions regarding stabilization extent and technique selection. Instrumented stabilization has become standard practice when posterior decompression is indicated in the thoracic spine, as the natural kyphotic alignment of this area predisposes it to post-decompression kyphosis if not stabilized[235].

Quality of life

The pathological sequelae of IVD degeneration represent a major source of global disability and health-care expenditure. Individuals who develop symptomatic disc degeneration experience profound effects on QOL across multiple domains, including activities of daily living, employment and recreation[21,58,236,237] (Box 1). Because symptoms of LBP often overlap, isolating the share of disability caused specifically by IVD degeneration is challenging. Therefore, we report the overall burden of LBP, which includes disc-related pathology, and identify the portion attributable to disc degeneration when reliable data are available.

Global burden and economic impact

LBP stands as the leading cause of years lived with disability worldwide, affecting approximately 619 million people globally (7.5% of the population), with chronic LBP (lasting >3 months) affecting approximately 8% of adults in the USA[24,238]. Nearly one-third of individuals with chronic LBP experience a level of disability that limits work, social participation, self-care and overall well-being[239–241]. The economic burden of LBP is substantial, ranking as the sixth most costly health condition in the USA. Direct health-care costs combined with indirect costs (which are approximately fourfold greater) total over US$100 billion annually[242–244]. A small percentage of individuals with severe, chronic LBP account for a disproportionate share of this financial burden[245,246]. Compared with those with acute LBP, patients with chronic LBP report more severe psychological symptoms, including depression, anger, sadness and hopelessness[247,248]. Psychological stress can exacerbate symptoms through inflammatory hormonal effects, muscle tension and sleep disturbances, creating a positive feedback cycle[248,249].

Common IVD pathologies and their effect on QOL

The three most common pathologies that are related to IVD degeneration – IVD herniation, lumbar spinal stenosis and degenerative spondylolisthesis – markedly affect QOL. In the Spine Patient Outcomes Research Trial (SPORT), IVD herniation occurred in 52% of patients, approximately twice as frequently as lumbar spinal stenosis (26%) and degenerative spondylolisthesis (22%). Patients with IVD herniation were considerably younger (mean age 41 years) than those with lumbar spinal stenosis (mean age 64 years) or degenerative spondylolisthesis (mean age 66 years) and presented with worse baseline QOL measures[153].

IVD herniation. IVD herniation typically presents with LBP and radicular symptoms when herniated nucleus pulposus material compresses neural structures. Despite initially severe symptoms, 90% of patients experience substantial resolution within 3 months owing to the self-limited nature of the inflammatory response and resorption of herniated material[19,250,251]. Surgical discectomy is reserved for patients with cauda equina syndrome, dense radiculopathy, or persistent symptoms after 6–12 weeks of conservative treatment[252]. Young, active patients with predominant leg pain show better surgical outcomes than those with primarily back pain[253,254]. The SPORT study, a prospective randomized study comparing discectomy with non-operative treatment in individuals with unresolved symptoms after 3 months of non-operative care, demonstrated improved findings for pain and QOL in both groups, but the discectomy patients experienced faster and greater pain relief after surgery. The results for greater QOL in the discectomy group were sustained at evaluations at 2, 4, and 8 years after surgery compared with those following non-operative treatment[255,256].

Lumbar spinal stenosis. Lumbar spinal stenosis typically affects older people with advanced IVD degeneration. Structural changes include disc collapse with bulging, reduced neuroforaminal space, ligamentum flavum buckling, and osteophyte formation, leading to nerve root compression[257]. Clinical manifestations include LBP, radiculopathy and neurogenic claudication worsened by ambulation and lumbar extension. Radiographic lumbar spinal stenosis is present in over 20% of patients over 60 years of age, although symptomatic disease affects only about 4% of the population[26,258]. Non-operative treatments, including NSAIDs, physical therapy and epidural injections, show benefits in patients with mild or moderate lumbar spinal stenosis. Severe lumbar spinal stenosis, defined by limited sitting tolerance (<1 h) and walking ability (<50 feet), substantially affects QOL[259]. When individuals with severe spinal stenosis who failed to improve with non-operative care were randomly assigned to surgical decompression or continued non-operative care, individuals with surgical decompression demonstrated significantly greater improvements in pain and QOL scores than individuals receiving non-operative management. Whereas many patients receiving non-operative management improved, patients receiving surgical treatment had significantly larger gains in QOL at the final evaluation at 8 years[260–262].

Degenerative spondylolisthesis. Degenerative spondylolisthesis shares a similar profile with lumbar spinal stenosis, stemming from advanced IVD degeneration that allows vertebral translation (typically anterior slippage). As in the case of spinal stenosis, when individuals with severe symptoms who failed to improve with non-operative care were randomly assigned to surgical decompression or continued non-operative care, individuals with surgical decompression demonstrated significantly greater improvements in pain and QOL scores than individuals receiving non-operative management. Surgical intervention provides substantially better pain relief and improved QOL scores for up to 8 years than non-operative treatment[263,264]. Importantly, patients with worse preoperative QOL scores derive the greatest benefit from surgery[265]. When comparing degenerative spondylolisthesis surgical outcomes with other orthopaedic procedures, mean QOL improvements equal those following total hip arthroplasty and exceed those following total knee arthroplasty, suggesting results comparable with those of highly successful orthopaedic interventions[266].

Cervical spine considerations

Neck pain ranks fifth for global disability burden, with a 2.45% disabling prevalence affecting over 200 million people worldwide[23]. The highest incidence occurs in the age range 45–74 years, with a male to female ratio of approximately 40:60 (ref. 267). Identifiable causes of neck pain primarily include cervical disc herniation and cervical spinal stenosis, that both result from IVD degeneration with comparable structural and mechanical changes to lumbar pathology. Both can cause radiculopathy and myelopathy, with myelopathic changes having a greater effect on QOL. For cervical myelopathy, non-operative treatment achieves minimal improvement, with 23–54% of patients ultimately requiring surgical intervention[268]. Surgical treatment for myelopathy demonstrates high cost-effectiveness, with an estimated lifetime incremental cost–utility ratio of US$20,547.84 per quality-adjusted life year gained – well within the WHO 'very cost-effective' threshold of US$54,000 (refs. 218,269).

IVD degeneration affects QOL across multiple domains, including physical function, psychological well-being and socioeconomic status. The impact of the condition varies by spinal location, severity and specific pathology. Although non-operative management is effective in many patients, surgical intervention provides sustained QOL improvements in appropriately selected patients with severe or progressive symptoms. The substantial global burden underscores the importance of continued research into preventive strategies and more effective therapeutic interventions for this prevalent condition.

Outlook

Despite advances in our understanding of its pathophysiology and treatment options, IVD degeneration is a major burden on patients and health-care systems[270]. Current treatment modalities are reactive and either temporarily alleviate symptoms with a combination of physical therapy, analgesics and targeted steroid injections, or surgically address sites of compression and stabilize areas of pathological motion by fusing the affected levels. Although conservative management might alleviate symptoms, it does not necessarily target the underlying biology and pathophysiology. Although effective, surgical decompression and/or fusion might lead to loss of motion and presents inherent risks, including fusion failure, hardware complications, infections and spinal cord damage[271]. Recent research has moved focus towards advanced diagnostics, and biologic therapies, including protein-based, gene and mesenchymal stromal cell (MSC) therapies, have been proposed as advanced therapies for the treatment of IVD[272,273] (Fig. 8).

Protein-based therapies

Administration of recombinant bone morphogenetic protein (BMP) has received considerable attention in IVD degeneration models. In animal models of IVD degeneration, intradiscal delivery of BMP7 augmented disc height and activated matrix pathways responsible for maintaining normal disc pathology[274,275]. However, clinical studies have shown no improvement in ODI scores and worse fusion success

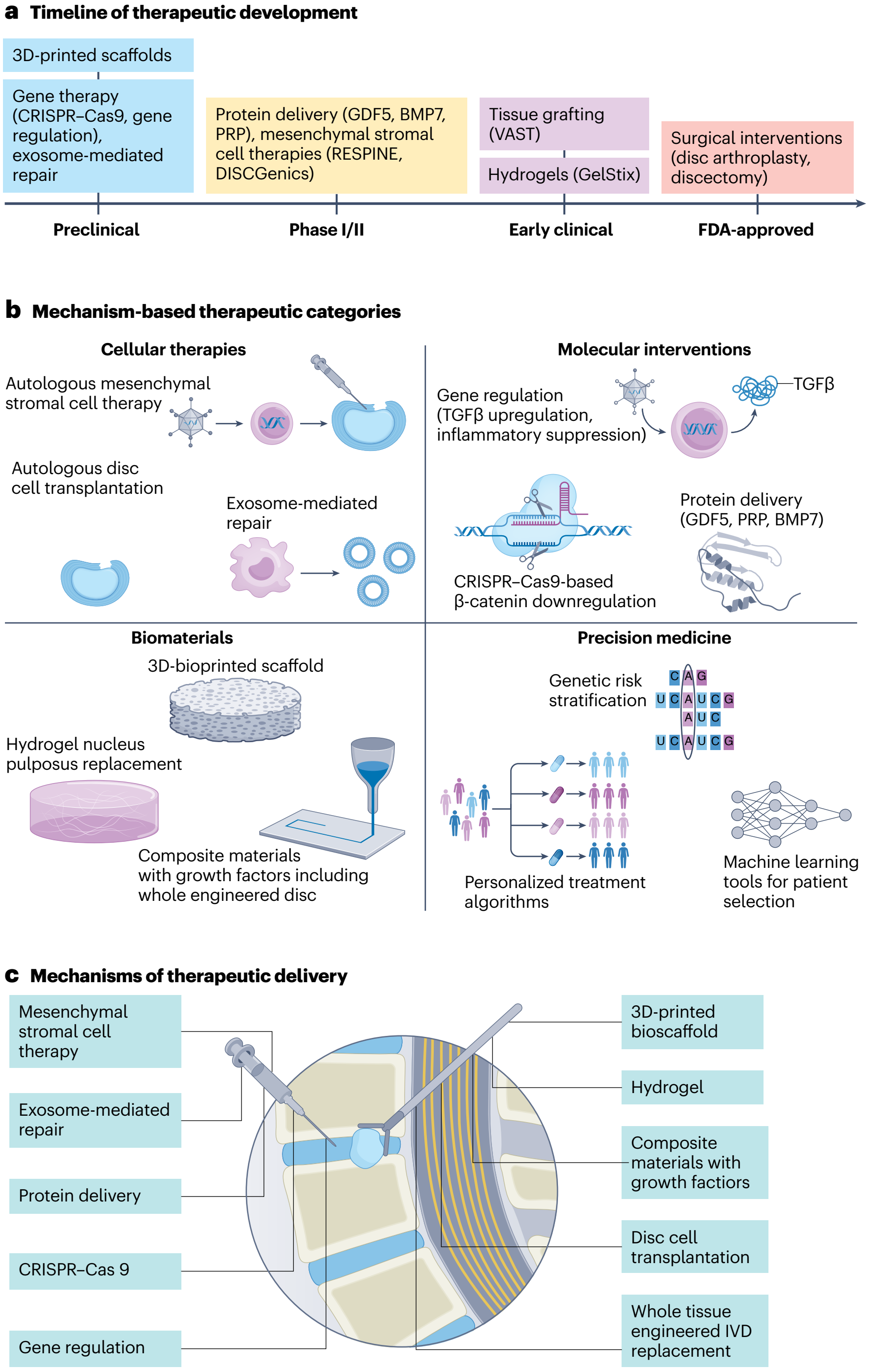


Fig. 8 | Emerging biological therapies for IVD degeneration. Comprehensive overview of regenerative treatment strategies under development for disc degeneration. **a**, A timeline of therapeutic developments, which illustrates the progression from preclinical research to clinical translation. Gene therapy approaches such as CRISPR–Cas9 and exosome-mediated repair are currently in preclinical stages, whereas protein delivery systems and mesenchymal stromal cell therapies have advanced to phase I/II clinical trials. Tissue grafting approaches (VAST trial) and hydrogel technologies (GelStix) represent early clinical applications, while established surgical interventions (such as disc arthroplasty and discectomy) have achieved FDA approval. **b**, Mechanism-based therapeutic categories demonstrate four complementary approaches targeting disc regeneration: cellular therapies encompass exosome-mediated repair, autologous disc cell transplantation, and mesenchymal stromal cell delivery to restore cellular populations and promote tissue repair. Molecular interventions include protein delivery (for example, growth/differentiation factor 5 (GDF5), bone morphogenetic protein 7 (BMP7) and platelet-rich plasma (PRP)), gene regulation techniques and CRISPR–Cas9-based β-catenin downregulation to modulate degenerative pathways. Biomaterials focus on hydrogel nucleus pulposus replacement (or tissue-engineered disc and annulus fibrosus repair), 3D-bioprinted scaffolds and composite materials that incorporate growth factors to provide structural support and biological signalling. Precision medicine approaches utilize genetic risk stratification, machine learning algorithms for patient selection and personalized treatment protocols to optimize therapeutic outcomes. **c**, Mechanisms of therapeutic delivery emphasize direct intradiscal injection or implantation as the primary route for therapeutic delivery, enabling targeted treatment while minimizing systemic exposure. This multifaceted approach represents the future of disc degeneration treatment, transitioning from reactive surgical management to proactive biological restoration of disc structure and function. IVD, intervertebral disc; TGFβ, transforming growth factor-β. The original versions of parts **b** and **c** were created using BioRender.

rates with intraoperative BMP7 administration compared with more commonly used autologous bone grafting in spinal fusion surgery for lumbar degenerative disease, and BMP7 is not widely used in current practice[276,277].

Intradiscal injection of growth/differentiation factor 5 (GDF5) has shown promise in mouse and rabbit models of IVD degeneration; it upregulates type II collagen content, downregulates catabolic metalloproteinase activity and increases disc height[278,279]. There are multiple phase I/II clinical trials that have evaluated intradiscal GDF5 in the treatment of lumbar degenerative disc disease (NCT01158924, NCT00813813, NCT01182337, NCT01124006), although no results have been published to date. Intradiscal injections of platelet-rich plasma (PRP) — a fraction of plasma produced by centrifugation of whole blood that contains various growth factors — has received interest given its success in other orthopaedic specialties, although preclinical models of IVD and clinical studies have shown mixed results[280–283].

Meta-analyses have suggested significant increases in disc height, MRI T2 signal hyperintensity and decreased histological degeneration grade in specimens from preclinical IVD degeneration models receiving intradiscal PRP, which suggests reconstitution of the nucleus pulposus to a normal makeup, although there are few details on the methods of PRP preparation in these studies, which remain highly variable across institutions and practitioners[284].

Cell-based therapies

Cell-based therapeutics delivered through intradiscal injection are emerging in preclinical models of IVD degeneration[285]. MSCs have been investigated owing to their potential to differentiate into healthy cells and potentially regenerate degraded IVDs, although the efficacy of this approach remains controversial[282,286] and studies examining MSC injection into the IVD in preclinical models of IVD degeneration have had mixed success[287–289]. There are several active clinical trials investigating intradiscal MSC administration. Results of the RESPINE trial (NCT03737461), a European multicentre phase IIb clinical trial studying the efficacy of intradiscal injection of allogeneic bone marrow-derived MSCs for chronic LBP, at up to 24 months follow-up were recently published and showed no significant improvement, although longer-term outcomes are still being collected[290]. DiscGenics recently published the results of its phase I/II trial (NCT03347708) of intradiscal MSC injection in patients with lumbar disc degeneration, showing clinically significant improvements in back pain and disc volume at 1 and 2 years follow-up, and recently received FDA approval for a phase III clinical trial[291]. The DREAM trial (NCT05066334) and the ACTIVE trial (NCT04759105) are ongoing phase IIb clinical trials investigating intradiscal MSC administration in patients with lumbar disc degeneration; the DREAM trial remains in recruitment while results from the ACTIVE trial have not yet been published. Other small studies suggest possible patient benefits from MSC therapies, although findings have proven heterogeneous and are subject to debate[286]. Exosomes derived from MSCs have shown utility in mitigating disc degeneration in preclinical IVD degeneration models via intradiscal injection[282].

Gene therapies

Gene-modulating therapies have been proposed as novel therapeutics for IVD pathology. In a rabbit model of IVD degeneration, intradiscal administration of an adenovirus-based gene therapy to upregulate transforming growth factor β1 (TGFβ1) induced a fivefold increase in TGFβ1 expression and a 100% increase in IVD proteoglycan content 1 week after administration[292]. Viral vector-mediated delivery and modulation of anabolic genes that promote ECM synthesis (such as *GDF5* and *SOX9*) and the suppression of catabolic genes encoding pro-inflammatory cytokines (such as IL-1 and TNF) is an active area of study in preclinical degenerative disc models[293,294]. CRISPR–Cas9 gene-editing technology has led to unique new possibilities in gene therapy in the degenerative disc and has been successfully used to downregulate the activity of inflammatory cytokines in human disc cells in vitro[295]. In a mouse model of IVD degeneration, the downregulation of the pivotal catabolic factor β-catenin by intradiscal injection of CRISPR–Cas9-expressing adeno-associated virus resulted in deceleration of disc catabolism and decreased pain[296]. Gene therapy is in its early stages and has not yet reached humans.

Biomaterials

Material science and biomaterials have been leveraged for potential treatment of IVD degeneration, focusing on mechanical support, disc regeneration and integration with native tissue[297]. IVD tissue-engineering approaches include using a hydrogel as a form of structural support and biological scaffolding[298,299], particularly for reconstitution of the nucleus pulposus in patients with an overall intact annulus fibrosus[300]. Although many hydrogel compositions are under investigation, they generally consist of a polymer with a three-dimensional mesh structure formed by crosslinking natural hydrophilic macromolecules (such as chitosan, hyaluronic acid and cellulose) or synthetic hydrophilic macromolecules (such as polyethylene glycol, polylactic acid and polyvinyl alcohol)[301]. Their material properties are considered to closely mimic those of the nucleus pulposus[302,303]. These materials have shown potential to restore biomechanical properties, promote extracellular membrane synthesis and promote MSC differentiation to nucleus-pulposus-like cells[304]. Numerous studies in animal models have demonstrated the delivery of hydrogel into the disc space and have provided evidence that it remains confined to the disc space[305]. However, in some cases, hydrogel is ejected from the disc due to defects in the annulus fibrosus, either naturally occurring or caused by the implantation procedure. Several small-scale studies have been performed in patients with lumbar disc degeneration, suggesting an improvement in patient subjective outcomes following intradiscal hydrogel injection, although their efficacy remains controversial[306,307]. In addition to their mechanical benefits, hydrogels can also be supplemented with biologic therapies to provide a synergistic benefit; composite hydrogel loaded with GDF5 demonstrated strong mechanical properties as well as promotion of nucleus pulposus regeneration in rat models of IVD degeneration[308–310].

Composite, fibre-reinforced scaffolds have emerged as a promising approach for entire IVD replacement. These scaffolds are designed to recapitulate the critical load-bearing capacity of the native annulus fibrosus while providing a matrix for cellular integration[45]. To do this, engineered constructs use multilayered fibre architectures that mimic the angle-ply organization of the natural annulus, incorporating synthetic polymers and biological materials to achieve requisite mechanical properties. Preclinical studies in large-animal models have demonstrated encouraging results, with tissue-engineered discs showing successful integration and maintained biomechanical function to at least 16 weeks[311,312]. Scaffolds have also been used for annulus fibrosus repair specifically, and novel non-woven scaffolds designed for interpenetration with native tissue have shown promise in preventing re-herniation while supporting tissue integration[313]. Challenges for the use of these scaffolds remain, including achieving robust integration with adjacent vertebral endplates, maintaining long-term cell viability within the avascular disc environment, and preventing scaffold degradation under repetitive physiological loading. Clinical translation faces substantial hurdles, as complete disc replacements are likely to require extensive open surgical procedures, similar to spinal fusion surgery. For repair applications (rather than full replacement), achieving secure attachment and hermetic sealing of annular defects under substantial nucleus pulposus hydrostatic pressures remains a critical engineering obstacle[314].

Tissue engineering

IVD tissue grafting has been attempted using both allograft disc matrix and ex vivo autograft in IVD degeneration[315]. The VAST clinical trial (NCT03709901) investigated the implantation of a structural allograft disc matrix into the affected disc space of patients with IVD degeneration and discogenic pain. Patients who received the allograft

Glossary

Annulus fibrosus	Fibrocartilaginous ring surrounding the nucleus pulposus of the intervertebral disc.
Cauda equina syndrome	Central compression of nerve roots in the spinal canal below the level of the spinal cord.
Chordomas	A rare type of slow-growing bone cancer that originate from remnants of the notochord, which is a tissue that helps to form the spine during fetal development.
Disc arthroplasty	Surgical removal and synthetic replacement of an intervertebral disc.
Discectomy	Surgical removal of all or part of an intervertebral disc.
Facet joints	Sites of articulation between adjacent vertebral segments.
Hoffmann sign	A physical examination finding comprising involuntary flexion of the thumb and/or index finger when the examiner flicks the middle fingernail down; suggestive of a cervical upper motor neuron lesion.
Kyphosis	A spinal curve in the sagittal plane with the curve apex posterior.
Laminectomy	Surgical removal of some or all of the lamina to allow neural decompression.
Laminoplasty	Surgical reshaping or repositioning of the lamina to allow neural decompression.
Ligamentum flavum	Ligament connecting the laminae of adjacent vertebrae.
Lordosis	A spinal curve in the sagittal plane with the curve apex anterior.
Lordotic angulation	The angle of posterior convexity in the sagittal plane.
Modic changes	Vertebral bone marrow signal intensity changes observed on MRI, commonly in association with intervertebral disc degeneration.
Myelopathy	Neurological impairment caused by compression of the spinal cord.
Neurogenic claudication	Intermittent, activity-dependent leg pain, cramping and weakness originating from nerve impingement in the spinal canal.
Nucleus pulposus	Soft, gel-like inner portion of the intervertebral disc.
Pfirrmann grade	Five-tiered grading system for intervertebral disc degeneration as measured by appearance of the intervertebral disc on T2-weighted MRI.
Radiculopathy	Radiating pain, weakness and/or sensory disturbance from compression of a spinal nerve root.
Spinal stenosis	Narrowing of the spinal canal.
Spondylolisthesis	Anterior displacement of a vertebra relative to the adjacent vertebra below.
Spurling manoeuvre	A physical examination manoeuvre comprising axial compression while the individual's neck is extended and rotated to the affected side; designed to reproduce radicular symptoms.
Thompson scale	Five-tiered scale for intervertebral disc degeneration based on the MRI appearance of the nucleus pulposus, annulus fibrosus, vertebral endplates and vertebral body.
Uncinate processes	Hook-shaped processes on the lateral margin of the superior vertebral endplate in the cervical spine.
Uncovertebral joints	Articulations between the uncinate process of a vertebra and the inferior aspect of the adjacent superior vertebra.
Visual analogue scale	(VAS). A grading system used to gauge patient pain, anchored at one end of the scale by 'no pain' and at the other by 'worst pain imaginable'.

demonstrated greater improvements in both visual analogue scale (VAS) for pain and ODI scores over a 1-year period than those receiving saline or non-operative care only, with a clinically meaningful reduction in ODI ≥15 points at 12 months that was statistically significant[316,317]. In the EuroDISC study, a prospective, multicentre, randomized controlled trial that examined the transplantation of autologous IVD cells to restore the nucleus pulposus after discectomy, patients who underwent discectomy followed by autologous disc chondrocyte transplantation had clinically significantly greater improvements in ODI and VAS scores, as well as increased disc heights, compared with patients who underwent discectomy alone[318]. The product tested became the NOVOCART Disk plus product, which remains under investigation by the FDA[319]. Autologous MSCs have shown promise in animal models, producing increases in disc proteoglycan content[320]. However, despite advances in the ability to synthesize biological therapies and materials with properties favourable for disc regeneration, further research is needed into the healing potential of the degenerated motion segment with an altered nutritional supply and hypoxic environment[321].

Conclusions

Pathology from IVD degeneration is a complex phenomenon that leads to a high degree of morbidity and degradation in quality of life. As understanding of the biochemical and macromechanical mechanisms of IVD degeneration has continued to grow, so has the ability to intervene to improve patients' lives. At present, clinical interventions are largely reactive and serve to stabilize degenerated motion segments to mitigate neurological harm and alleviate patient pain. Advances in diagnostics and imaging might offer improved patient selection, which could lead to improved outcomes or intervention earlier in the degenerative cascade through improved surveillance. Unfortunately, present surgical interventions involve surgical risk, motion limitation and predisposition to degeneration at adjacent FSUs. Developing biological and less-invasive, motion-sparing surgical therapies offers promise in mitigating these issues.

Considerable challenges remain in translating advances in biological and cell-based therapies to clinical practice. Regulatory pathways for biologic therapies are still evolving, and there are different approval requirements for the classification of a therapy as a drug, device or biologic[322]. The absence of validated disc-specific end points further complicates the definition of treatment success across trials[323,324]. The natural history of disc degeneration adds complexity: many degenerated discs are asymptomatic, and when symptoms do develop, they often take decades to manifest, necessitating follow-up far longer than typical clinical trial timelines. Manufacturing biologic therapies at scale is also difficult, and projected treatment costs (more than US$50,000) raise concerns about equitable access[323,324]. Despite these hurdles, rapid progress in materials science and understanding disc pathophysiology has brought truly disease-modifying therapies closer to transforming care for patients.

Several unanswered questions remain regarding the heterogeneity of disc degeneration outcomes. It is unclear why some individuals with radiographic degeneration develop symptomatic disease and others with similar structural changes remain asymptomatic. Understanding the genetic, metabolic and biomechanical factors that determine disease penetrance will enable more precise risk stratification and targeted interventions. In addition, comparative effectiveness research is needed to evaluate long-term outcomes across treatment modalities, including durability of symptom relief, complication rates, cost-effectiveness and patient-reported QOL. Such data are particularly critical for emerging biologic therapies, for which optimal patient selection criteria and treatment protocols remain undefined. Furthermore, personalized therapy strategies must be optimized for diverse health-care settings, particularly in resource-limited regions with restricted access to advanced diagnostics and interventions.

The progression from molecular understanding to clinical translation in IVD degeneration research requires bridging biological complexity with therapeutic development. Recent advances have substantially improved understanding of cellular senescence, matrix catabolism, inflammatory amplification and biomechanical feedback loops that drive degenerative cascades. These mechanistic insights now provide a rational foundation for therapeutic design targeting specific pathophysiological processes. However, translating laboratory discoveries into accessible patient treatments requires sustained multidisciplinary collaboration among basic scientists, clinicians, regulatory agencies and health technology assessment experts, to navigate the complex pathway from bench to bedside.

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Author contributions

Introduction (B.R.F., B.T.H., C.S.L., C.M.B., B.S., E.V., D.M.E. and G.X.X.); Epidemiology (B.R.F., B.T.H., C.S.L., C.M.B., B.S., E.V., D.M.E. and G.X.X.); Mechanisms/pathophysiology (B.R.F., B.T.H., C.S.L., C.M.B., B.S., E.V., D.M.E. and G.X.X.); Diagnosis, screening and prevention (B.R.F., B.T.H., C.S.L., C.M.B., E.V., D.M.E. and G.X.X.); Management (B.R.F., B.T.H., C.S.L., C.M.B., E.V., D.M.E. and G.X.X.); Quality of life (B.R.F., B.T.H., C.S.L., C.M.B., E.V., D.M.E. and G.X.X.); Outlook (B.R.F., B.T.H., C.S.L., C.M.B., E.V., D.M.E. and G.X.X.); overview of the Primer (B.R.F. and B.T.H.).

Competing interests

G.X.X. is an associate editor for *Spine* and *Spine Open*. E.V. has equity in Camber Spine Tech. C.M.B. is the Editor-in-Chief for *The Spine Journal*. B.R.F. has licensed intellectual property in Amend Surgical and equity in Limax Biosciences. The other authors declare no competing interests.

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