Journal of Pain Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

EXPERT OPINION

A Primer on Anatomy, Biophysics, Pathology, Imaging and Treatment of the Intervertebral Disc and the Anterior Spinal Column: The Discogenic, Intervertebral, Spinal Column (DISC) ASPN Workgroup

Jay S Grider[1], Timothy R Deer[2], Douglas P Beall[3], Melissa Z Murphy[4], Jacob W Fleming[5], Steven M Falowski[6], Christopher J Mallard[7], Hamzah A Ramawad[8], Rosa Amelia Garcia[9], Usman Latif[10], Chau M Vu[11], Anne Christopher[12], Michael E Harned[7], Raj G Patel[13], Anuj J Shah[2], Iden M Cowan[13], Kristin Jarzombek[14], Jordan L Tate[15], Nasir Khatri[16], Mateusz J Graca[17], Marcin K Karcz[2], Timothy T Davis[18], Kaku Barkoh[19], Olivier Clerk-Lamalice[20], Brian Durkin[21], Mark N Malinowski[22], Dagmar K Gross[23], Thomas Hedman[24], Matthew Green[25], Michael J Dorsi[26], Kasra Amirdelfan[27], Dawood Sayed[28]

[1]University of Kentucky, College of Medicine, Division of Interventional Pain, Lexington, KY, USA; [2]The Spine and Nerve Centers of the Virginias, Charleston, WV, USA; [3]Clinical Radiology of Oklahoma, Edmond, OK, USA; [4]North Texas Orthopedic and Spine Center, Grapevine, TX, USA; [5]Radiology Associates of North Texas, Fort Worth, TX, USA; [6]Neurosurgical Associates of Lancaster, Lancaster, PA, USA; [7]University of Kentucky College of Medicine, Division of Interventional Pain Medicine, Lexington, KY, USA; [8]Ochsner Health, New Orleans, LA, USA; [9]University of Florida, Gainesville, FL, USA; [10]University of Kansas Medical Center, Department of Anesthesiology, Division of Pain Medicine, Kansas City, KS, USA; [11]Evolve Restorative Center, Santa Rosa, CA, USA; [12]St. Louis Pain Consultants, Creve Coeur, MO, USA; [13]Capital Pain Institute, Austin, TX, USA; [14]Greater Austin Pain Center, Kyle, TX, USA; [15]Southern Pain and Spine, Jasper, GA, USA; [16]Insight Institute of Neurosurgery & Neuroscience, Flint, MI, USA; [17]Florida Spine Care, Fort Lauderdale, FL, USA; [18]Source Healthcare, Santa Monica, CA, USA; [19]Orthopaedic Associates LLP, Houston, TX, USA; [20]University of Calgary, Calgary, Alberta, Canada, USA; [21]New York Spine and Pain Specialists, Port Jefferson Station, NY, USA; [22]OhioHealth Neurologic Physicians, OhioHealth, Inc, Columbus, OH, USA; [23]MedSci Communications & Consulting Co., Brampton, ON, L6T 4N4, Canada; [24]Spinal Simplicity, Overland Park, KS, USA; [25]MUSCMED, Pain, PainMedSA, Wayville, South Africa; [26]Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA; [27]Boomerang Healthcare, Walnut Creek, CA, USA; [28]University of Kansas Medical Center, Kansas City, KS, USA

Correspondence: Jay S Grider, Email jay.grider@uky.edu

Objective: As therapeutic options are rapidly expanding to treat pain of discogenic and vertebrogenic origin, it is important for the clinician to have an evidence-based understanding of the latest information regarding the normal and pathological anatomy of the intervertebral disc as well as imaging characteristics and treatment strategies. The American Society of Pain and Neuroscience (ASPN) commissioned the DISC project to inform and update the interventional spine community about anterior column pain syndromes.

Methods: Using established literature review methods a clinical oversight group was convened to create an outline covering topics that will be key to meeting the objectives delineated by the ASPN scientific and guidelines leadership. This oversight group, using the created outline, selected key opinion leaders and experts to assemble the latest information on anterior column and intervertebral disc anatomy and treatment to serve as a living document that can be continuously updated to drive best practices and innovation.

Results: A review of normal and pathological anatomy, a comprehensive understanding of biophysics applied to the anterior spinal column, and understanding of the current state of practice with regard to imaging, diagnostic classification systems and treatment.

Keywords: ASPN, disc, anatomy, pathology, imaging, intradiscal, anterior column pain, functional spinal unit, regenerative medicine

Introduction

The motion of the lumbar spine can be described in the most basic terms as a load bearing unit consisting of three points: the facet articular complex in the posterior column and vertebral body/intervertebral disc creating an anterior column

Received: 22 July 2025
Accepted: 11 November 2025
Published: 11 December 2025

while the neural elements comprise what would be described as a central or middle column. It is a complex interaction of this functional spinal unit (FSU) that creates the dynamic range of motion between the relatively fixed positioning of the thoracic spine and absolutely fixed sacral spine (Figure 1a). As early as 1984, Koeller et al[1] described the response of human fibroelastic tissue of the disc when subjected to loading forces. This study and others that would follow would form the foundation of an area of investigation which would continue to develop over the ensuing decades.

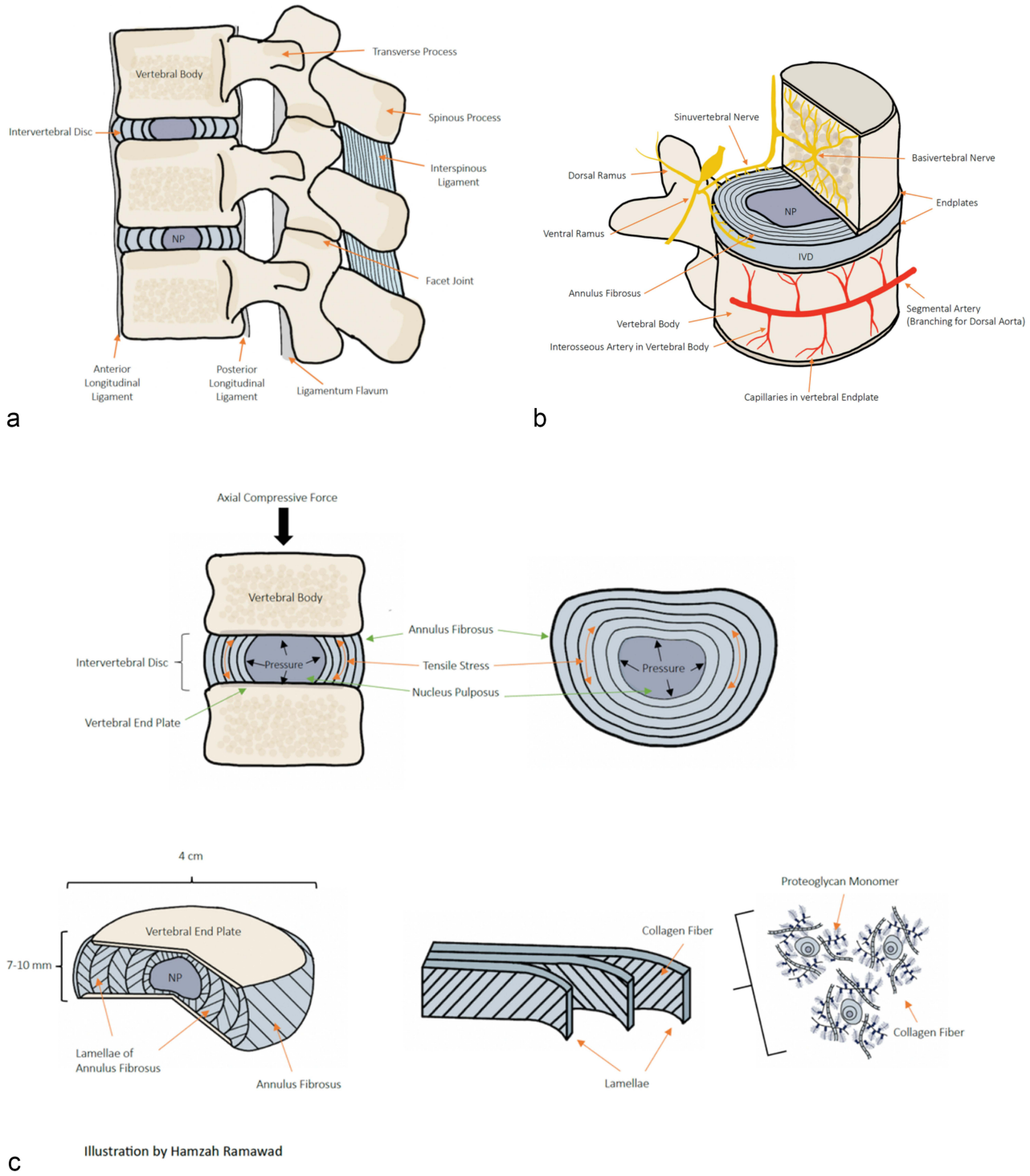


Figure 1 (**a**) The Functional Spinal Unit (FSU) with structures of the anterior column, middle and posterior columns illustrated as described in the text. (**b**) Normal anatomy, innervation and blood supply of the anterior column structures. (**c**) Illustration of disc lamellar structure, effect of compressive forces and aggrecan networking.

Disc disruption was first described by Crock in the 1970's but it would be several years before clinical focus on the disc would become more widespread.[2] During the ensuing decades, physical diagnosis has been the primary diagnostic tool coupled with advances in imaging (CT and MRI). Conservative treatment such as medications and physical therapy have been and are still widely recommended as initial treatments for patients suffering from low back pain of discogenic and spondylitic origin. For those not responding to conservative measures, spine surgery in the form of microdiscectomy has been present for decades and percutaneous interventions such as discography with injection, intradiscal electrothermography and radiofrequency annuloplasty were early candidates to treat pain of anterior column origin. While spinal surgery and microdiscectomy are still widely performed, many of the less invasive techniques did not reach widespread acceptance for a variety of reasons such as lack of coverage by payers and perceived variability in outcomes.[3] Recently, advances in minimally invasive spine procedures such as basivertebral nerve ablation and intradiscal restoration in the form orthobiologics and polymeric hydrogels have created a wide array of treatment options available to interested clinicians.[4] These techniques however carry the requisite obligation for the clinician to understand the anatomy of the anterior column, the mechanisms under which degeneration occurs, the diagnostic criteria involved and the correct application of modality to disease process in order optimize the outcomes for the patient.

The current review was commissioned by the American Society of Pain and Neuroscience (ASPN) to serve as a comprehensive reference with regard to educating around the topics of normal and pathological anterior column anatomy, the biophysics of the anterior column and the interaction of the functional spinal unit, a survey of surgical and interventional treatment options as well as emerging technologies and their mechanisms of action.

Finally, we endeavor to create a future state synthesis of the current information to serve as a discussion point for further study in the multimodal treatment of patients who may have complex interactions between anterior column pain and posterior column pain generators (ie consideration of the complex interaction of the FSU). In addition, we will consider potential radiological or other systemic identifying characteristics or biomarkers that may create a signal to develop focused best outcome predictions.

Methods

ASPN Guideline Clinical Committee and Multidisciplinary Collaboration

The ASPN clinical guideline committee is comprised of a diverse group of physicians representing the specialties most commonly involved in the provision of interventional treatments of spinal pain. This includes physicians from the core specialties of anesthesiology, neurosurgery, orthospine, physical medicine and rehabilitation, and radiology, as well as a pain psychologist/medical ethicist with many years of experience in consulting with interventional physicians. Committee members were selected based on clinical experience, research, and previous publication history. This group commissioned the creation of the current primer which serves as a narrative review of the anatomy, biophysics and imaging of FSU. Many in the interventional pain, interventional radiology, physical medicine and rehabilitation and even spine surgical communities are unfamiliar with the the anterior column of the spine and the interplay of the anterior, middle and posterior column as sources of pain and dysfunction. As such, a multidisciplinary group with special expertise was convened by the ASPN Back Guideline Committee to from the ASPN Discogenic, Intervertebral and Spinal Column (DISC) workgroup. It is envisioned this manuscript and group will continue to update this primer periodically creating a living document educating the interventional spine space about topics within the charter based upon clinical evidence and expert opinion. As a primer the intent of this manuscript is educational and not to create guidelines as many of the burgeoning areas of research are in their beginning stages; as such the intent is to highlight emerging clinical therapies and where possible outline the evidence that supports these modalities.

Individual topics were searched using PubMed and Web of Science to identify and compile the evidence for intervertebral disc anatomy, pathology and interventional therapies for the treatment of pain. Search words were created specific to the topics for each major section of this primer. Given the rapidly emerging nature of much of this work, this manuscript does not serve as a systematic review of the literature rather as an educational living document that can serve society to ensure the membership is kept informed of emerging trends in the pathophysiology and treatment of anterior column lumbar spinal dysfunction and pain.

Disc Anatomy and Biophysics

Normal Disc Morphology

Intervertebral discs (IVDs) are responsible for one-third of the height of the spinal column, ranging from 7 to 10 mm in thickness depending on their location within the spine (Figure 1b).[5] The IVD is an avascular structure and is therefore reliant on concentration gradients for the diffusion of nutrients and oxygen from the adjacent endplates.[6] Aggrecan (Figure 1b), a large protein (proteoglycan found in cartilaginous tissues as part of the extracellular matrix lending resistance to compressive forces) is largely responsible for the retention of water within the nucleus pulposus (NP); a healthy NP is made of 66% to 86% water.[7]

The NP functions as an inner gel-like center to absorb and uniformly redistribute the load stresses to the periphery, avoiding excessive pressure on the annulus fibrosus (AF). The AF is a ring-shaped disc of fibrous connective tissue which consists of 15 to 25 stacked sheets of stratified elastic tissue surrounding the NP (Figure 1b and c). Type I collagen, the primary form of collagen in the AF, is arranged in concentric rings called lamellae, which are uniformly aligned in a parallel orientation and interconnected through translamellar bridges.[8] The outer lamellae continue into the longitudinal ligaments and vertebral bodies. The AF central part is composed of an extracellular matrix enriched by chondrocytes and a series of protein fibers (mainly type II collagen) arranged in an alternate pattern, therefore not oriented vertically, allowing for greater effective resistance. In general, AF's structure contains the NP and prevents the development of stress concentrations which could cause damage to the underlying vertebrae or their endplates.[9]

The vertebral endplate (Figure 1b and c) consists of an upper and a lower cartilaginous endplate (CEP) approximately 0.6 mm thick, covering the superior and inferior part of the disc, with calcified cartilage adjoining the bone. The endplate permits diffusion and provides the main source of nutrition for the disc.[10]

With degeneration, the most significant biochemical change to occur is the loss of proteoglycans, which results in the subsequent loss of glycosaminoglycans and the reduction in osmotic pressure within the disc matrix. This has a major effect on the disc's load-bearing behavior, which is evident by a degenerative disc's tendency to bulge under pressure.[11–13]

Normal Disc Morphology Under Load Bearing

The IVD plays a critical role in maintaining mobility of the spine by distributing mechanical loads. This enables flexibility of the spine while protecting the adjacent vertebral bodies. The IVD is uniquely adapted to withstand complex, often superimposed forces such as axial compression, torsion, and shear. These forces are transmitted through the disc's composite structure, which includes the NP, AF, and the cartilaginous endplates.[14–16]

Forces acting in multiple planes of action (axial, compressive forces, rotation and shear, (Figure 2a) impact the FSU during normal movements of the spine and the IVD is subject to a variety and complex combination of mechanical forces (Figure 2b). These forces are redistributed across the disc's structure to reduce focal stress and potential injury.

The NP functions as a hydrostatic pressure reservoir. Compressive forces cause an increase in intradiscal pressure which is redistributed to the AF. The concentric lamellae of collagen fibers in the AF provide tensile strength to withstand both torsional and compressive forces.[15,16] The AF also exhibits a biphasic mechanical response during loading: the inner annulus acts as a viscoelastic shock absorber, while the stiffer outer fibers convert compressive loads into hoop stresses that resist bulging.[17] The disc's ability to withstand axial compression depends on hydration and proteoglycan content of the NP, which confer the ability of the IVD to resist deformation.[16,18] Axial loads are also transmitted both superiorly and inferiorly through the cartilaginous endplates to the vertebral bodies reducing focal stress in the motion segment.[14,15] Shear forces occur during anterior-posterior translation or lateral bending. These forces are resisted by the concentric collagen lamellae of the AF. The layers of the AF are anchored to fibers of the vertebral body, providing structural integrity and resisting translational movement that could disrupt disc alignment.[15,18]

Cartilaginous Endplate

The cartilaginous endplates (Figure 1b and c) are thin layers of hyaline cartilage between the intervertebral disc and the adjacent vertebral bodies. The CEP serves two key functions:

1.Mechanical load distribution: the endplates anchor the disc to the vertebrae, enabling even mechanical load transfer from the disc to the bony vertebral bodies and reducing focal stress that could increase risk of injury.[14,15]

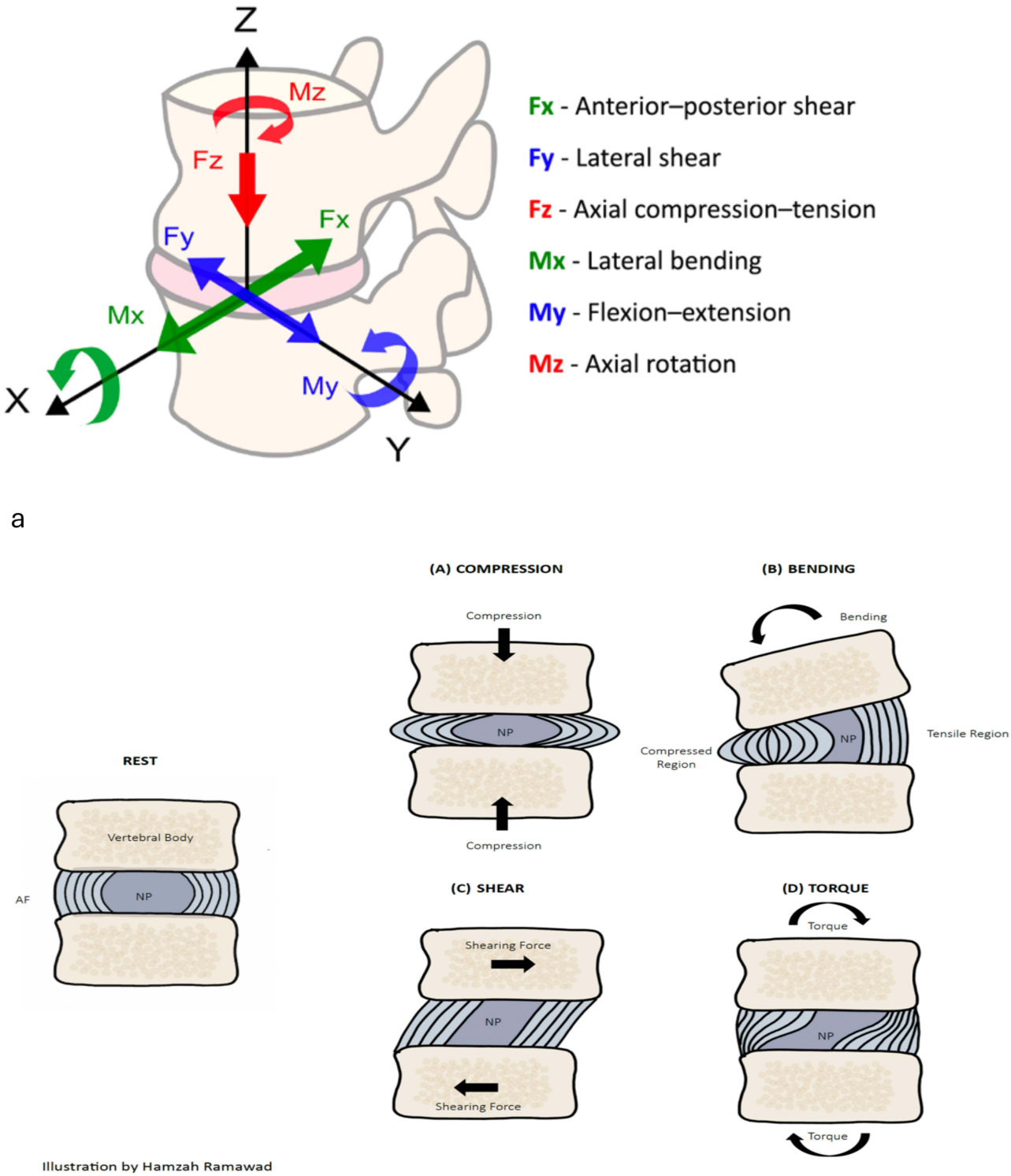


Figure 2 (**a**) Summary of all the force vectors that impact the FSU. (**b**) Illustration of the planes of motion that are characteristic at the IVD/CEP junction.

2.Nutrient transport: as the disc is avascular, nutrient and metabolite diffusion occur through the CEP.[15,17]

Degeneration or calcification of the endplates can cause uneven load distribution and impair nutrient transport which can accelerate disc degeneration.[14–16] Additionally, defects in the CEP may permit the migration of proinflammatory mediators into the disc space, potentially contributing to discogenic or vertebrogenic pain. Alternatively, Schmorl's nodes

can occur which are protrusions of the intervertebral disc material into the adjacent vertebra through a defect in the vertebral endplate (Figure 3).[17,18]

Biochemical Properties of Normal Disc Function

Histochemical Appearance and Function of Normal Disc Tissue

The NP has a fiber network that is up to 85% collagen type II.[19] Proteoglycans attract water through high osmotic pressure. Constituents include chondroitin-6-sulphate, keratan sulphate, hyaluronic acid, and chondroitin-4-sulphate.[20] The NP can vary in shape, ranging from ovular to bilocular.[21,22]

Furthermore, there is not always a clear-cut border between the AF and the NP. Rather, the greatest distinction is fibrillar density. The NP has large extrafibrillar spaces that accommodate glycosaminoglycans that can retain fluids. Generally, the NP is more central in the cervical levels and most posterior in the lower lumbar levels. The AF is much denser anteriorly and posteriorly and less so in the lateral regions.

One percent of the disc volume consists of chondrocytes that are spread throughout the extracellular matrix (ECM).[23] A substructure of the ECM is the pericellular matrix (PCM) which is composed of collagen type III and VI and proteoglycans. The PCM is thought to play a role in mechanoprotection of the chondrocytes from overload.[24]

The CEP is thickest at the periphery with decreasing thickness approaching the center.[25] A complex proteoglycan matrix lends a glasslike appearance and a soft, pliable structure. A thin layer of calcified material on the endplate attaches to the trabeculae of the vertebrae. It is believed that nutrients flow to the disc via contact between the CEP and the marrow. There are also regions between lamellae called the inter-lamellar matrix (ILM).[26] The ILM is less than 30 μm in thickness and is made up of a high density of elastic fibers. It is thought that the dense elastic network in the ILM allows relative sliding of adjacent lamellae. This allows for recovery after deformation and contributes to the structural integrity of the disc.[27] As discussed previously, each individual lamella is also divided by dense structures of elastic fibers (ie translamellar fibers). Elastic fibers, less than 1.5 μm thick, are made up of core elastin proteins surrounded by microfibrils, less than 0.01 μm thick.[24] The microfibrils are mostly fibrillin and amyloid and forms bundles around the elastin core. They are thought to serve as anchoring fibers to the surrounding ECM. Elastin provides passive recoil and control of elasticity, while microfibrils lend strength.

Within the NP, the ECM is made up of collagens and proteoglycans that have been a focus of studies on biomechanical properties. Collagen fibers are 1–20 μm wide and are of a cord or tape-like shape. Thin collagen fibrils,

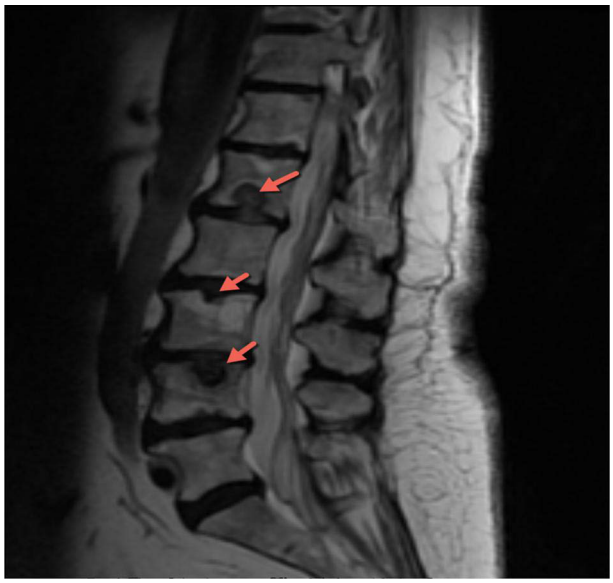


Figure 3 Sagital T2 weighted MRI depicting invagination of the CEP and intervertebral disc material into the vertebral body (Schmorl's nodes) (red Arrows).

30–100 nm thick, are closely packed to form fibers and form a three-dimensional network.[24] Elastin fibers are also present in the NP as a three-dimensional lattice that penetrates the vertebrae as Sharpey's fibers.[25]

There are localized differences as well. Less microfibrils surround elastin cores in the inner AF as compared to the outer AF. There is a honeycomb structure of elastic fibers in the transition zone (TZ) between the AF and NP.[26] The elastic network density is lower in the posterolateral region of the TZ as compared to the anterolateral area of the TZ.

Fluid Dynamics of Normal Disc Tissue

The NP, depending on age, may contain up to 70 to 90% water by weight.[27] This is made possible by the polar hydroxyl group of the glycosaminoglycan chondroitin sulfate which allows it to bind water. Disc mechanical function is influenced by the changes in fluid content and pressure in the disc that vary throughout the day based on loading history due to muscle activation, upper body weight, and external/inertial loads, posture, and internal osmotic pressure.[27] Disc volume, height, hydration, and nucleus pressure are highly dynamic and dependent on fluid content and flow. Multiple factors influence the fluid content and swelling pressure within the disc, including tension in collagen fibril networks, osmolarity of surrounding media, and the fixed charge density of the nonfibrillar matrix composition. The disc pressure is 3–5 times larger when standing as compared to lying flat.[28]

The IVD is predominantly an avascular tissue that obtains its blood supply from branches of metaphysical arteries located in the outer fibers of the annulus fibrosus.[29,30] These perivascular fibers are responsible for the delivery of oxygen and nutrients as well as removal of metabolites from the adjacent CEP and the peripheral AF.[31] Both perivascular annulus branches as well as blood vessels near disc-bone junction supply the avascular regions by diffusion.[30] Nonetheless, this perfusion decreases with age. In spite of the NP remaining avascular throughout life, evidence has shown that regardless of the age, blood vessel growth may occur within the CEP or layers of AF in disrupted disc tissue.[31] Pathologic conditions that can affect the natural perfusion include alterations in blood flow or end plate calcification which can disrupt blood supply and ultimately result in cell death of NP due to its distant location from these vessels.[32] In regards to the IVD innervation, overall only the outer third of the AF is innervated and the NP has no nerve supply. The AF receives its nerve supply from the sinuvertebral nerves (SVN). This nerve is formed from the junction of the ventral ramus (providing the somatic root) and the grey ramus (providing the autonomic root).[33] In a systematic review, Groh et al found that overall neural elements are localized in the outer third of the annulus fibrosus in non-pathological states but pervade into the inner two-thirds of AF in pathological spinal conditions.[29] Neural infiltration into the inner AF was most commonly found in patients with fissures within the annulus fibrosus or painful IVD tissues than in those with no spinal pathologies.[29] Studies have identified nociceptive nerve endings expressing substance P and calcitonin-gene related peptide (CGRP) in the IVD which are implicated in discogenic pain.[34–39]

Imaging Modalities

Complete imaging evaluation of the IVD (and, importantly, the disc-endplate complex as a whole) relies on a multimodality approach. While noncontrast magnetic resonance imaging (MRI) serves as the gold standard, it is not without its own limitations. Important concepts pertaining to application of various imaging modalities such as computed tomography (CT), single photon emission computed tomography (SPECT), MR spectroscopy, fluoroscopy (discography), and even plain radiography, are key for the clinician to understand and are discussed.

Though ostensibly the least advanced modality, digital radiography (DR), can offer important insights into disc structure and function. Importantly, DR is widely available, inexpensive, and fast. The most common examination of the spine (cervical, thoracic, or lumbar) consists of standing frontal (posteroanterior, PA) and lateral projections which serve to assess coronal and sagittal alignment, respectively. Disc space height loss, intradiscal vacuum phenomenon, osteophyte formation, and endplate changes (erosive and sclerotic) provide important information about the degree of disc degeneration and indirect evidence of dynamic instability. The latter can be further assessed with the addition of lateral flexion and extension views, with 3 mm or greater difference in listhesis between positions generally considered indicative of instability. The primary limitations of DR lie in its planar nature (producing 2D summations of 3D structures) and poor soft tissue resolution.

While not optimized to assess the subtle differentials in fluid attenuation of the IVD, CT is the most frequently utilized cross-sectional modality for evaluation of the spine and provides excellent assessment of the bony anatomy, alignment, and

ancillary findings of DDD including osteophytes, calcified protrusions, and erosive or sclerotic endplate changes. It also provides sufficient soft tissue resolution between the disc and adjacent epidural and intrathecal spaces to demonstrate degenerative bulges and many discrete herniations. Narrowing of the spinal canal, lateral recesses, and neural foramina can corroborate clinical findings of radicular pain or radiculopathy, although MRI is more sensitive for these purposes.

Importantly, CT of the spine is typically performed in a supine position, and comparison to weight bearing imaging can reveal important differences in disc height and alignment giving insight into dynamic instability and disc degeneration. Intradiscal vacuum phenomenon consists of gas (primarily nitrogen) in the disc space drawn out of solution by passive negative pressure diffusion when axial load on a collapsed disc space is relieved. This occurs due to a differential in the volume of remnant NP and the volumetric capacity of the AF. It serves as an indirect indicator of vertical instability that may suggest axial pain and worsening of stenosis with axial loading.

Compared to radiographic modalities, MRI provides excellent soft tissue resolution and even assessment of chemical properties of the imaged tissues. While more expensive and slower than DR or CT, MRI is crucial in the evaluation of the discogenic pain patient. The most common MR examination of the lumbar spine consists of supine examination utilizing sagittal T1-weighted (T1W), T2-weighted (T2W), and fat-suppressed T2W (most commonly short tau inversion recovery (STIR)) sequences and T1W and T2W axial sequences, with a coronal T1 or T2W sequence. Thoracic MRI tends to follow a similar protocol, while many routine cervical protocols add or substitute a T2 GRE (gradient echo) axial sequence for enhanced evaluation of the thecal sac, neural foramina, and the spinal cord.

Importantly, MRI provides superior assessment of the endplates, especially the presence of Modic changes consisting of subchondral bone marrow edema (Modic I), fibrofatty changes (Modic II), or sclerosis (Modic III), generally indicating increased chronicity and decreased likelihood of pain generation in that sequence (Figure 4). It is important to note that categories of Modic change often coexist at a single interspace. Schmorl's nodes (intravertebral disc herniations), erosions, and other endplate irregularities are also well depicted. Despite prior thinking that these changes would precede only in one direction temporally and that fibrofatty change represents a quiescent state, reconversion from Modic II to I has been demonstrated.[40] Further, the conspicuity of Modic I change seems to be load-dependent, with

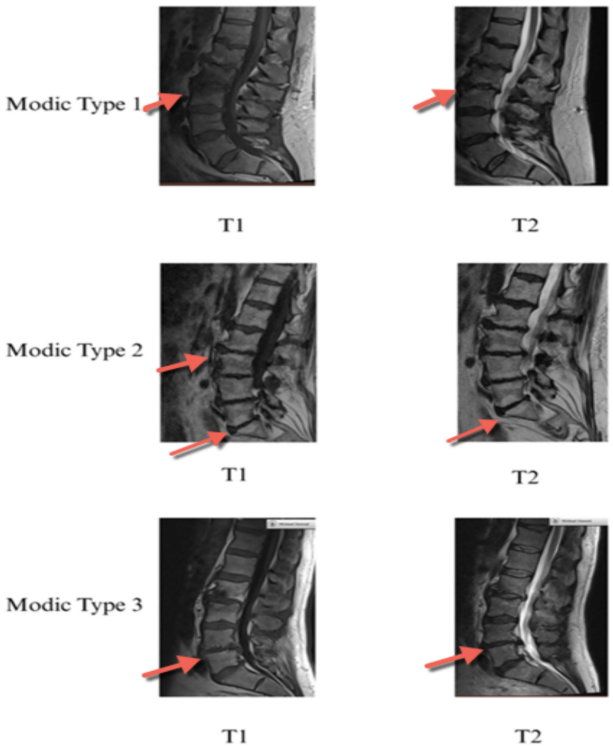


Figure 4 MRI examples of Modic Type 1,2, and 3 changes on sagittal T1 and T2 weighted images. Red arrows denote Modic change regions. Modic type description in text of manuscript.

anecdotal reports of lesions on weight-bearing MRI which were occult or less pronounced on supine MRI. These concepts will be further elucidated in subsequent sections on pathology of the anterior column.

Less frequently used variants of MRI include MR spectroscopy and weight-bearing MRI, both of which have shown promise in evaluation of the chemical and functional nature of DDD, respectively. Additionally, it should be pointed out that while anatomic changes on imaging must be clinically correlated with physical exam and possibly diagnostic testing (such as discogram) to determine of the pathological or degenerative structures are also pain generators in this particular patient. MRS provides spectroscopic evaluation of the biochemical properties of each disc, specifically the relative ratios of proteoglycan, lactate, alanine, and other molecules. Automated analysis of the spectral data can provide insight into potentially pain-generating discs and can help guide treatment.[41]

Weight-bearing MRI combines the advantages of standing imaging inherent to DR with the soft tissue and chemical resolving properties of MRI to produce an exam providing increased insight into the spine under physiologic conditions rather than the more static supine examination under which alterations in alignment, stenosis, and even Modic changes may be occult.

The use of SPECT has seen an increase in recent years in the assessment of lumbar discogenic pain and subsequent treatment planning. SPECT utilizes an intravenous radionuclide to produce cross-sectional functional imaging which is most often fused to a concurrent CT acquisition for anatomic localization. In the evaluation of chronic low back pain (CLBP), Tc99m-MDP (Technetium-99m methylene diphosphonate) is used to demonstrate areas of increased bone turnover and metabolic activity that may correlate with pain generation, particularly in the endplate and zygapophyseal joints (Figures 5a and b). The technique may help to distinguish painful segments as well as anterior and posterior column pain generators in an otherwise diffusely degenerated spine. Historically used more for planning interbody fusion surgery, the correlation of MDP uptake and painful Modic I changes indicates potentially additive utility versus routine MRI in the assessment of painful interspaces for treatment with basivertebral nerve ablation.

Fluoroscopic discography merits particular attention as both a modality of diagnostic imaging and potentially therapeutic intervention. Historically, intervertebral discography was performed with a provocative technique, attempting to replicate axial pain by pressurization of the disc using injection of contrast material. This modality has lost popularity over the years due to patient discomfort and perceived lack of benefit compared to MRI and SPECT. In addition, the discogram correlation of surgical prediction for discectomy was not sensitive or specific resulting in additional decline over the past two decades. In more recent years, the advent of therapeutic intradiscal injectables has led to increased interest in discography both for diagnostic and therapeutic purposes. Similar to any other intraarticular injection, the addition of anesthetic provides additional diagnostic information (the absence of reported pain following the injection serving as additional confirmation of the pain generating level or levels) and adds potential therapeutic benefit, which can be supplemented with the addition of liquid steroid.[42]

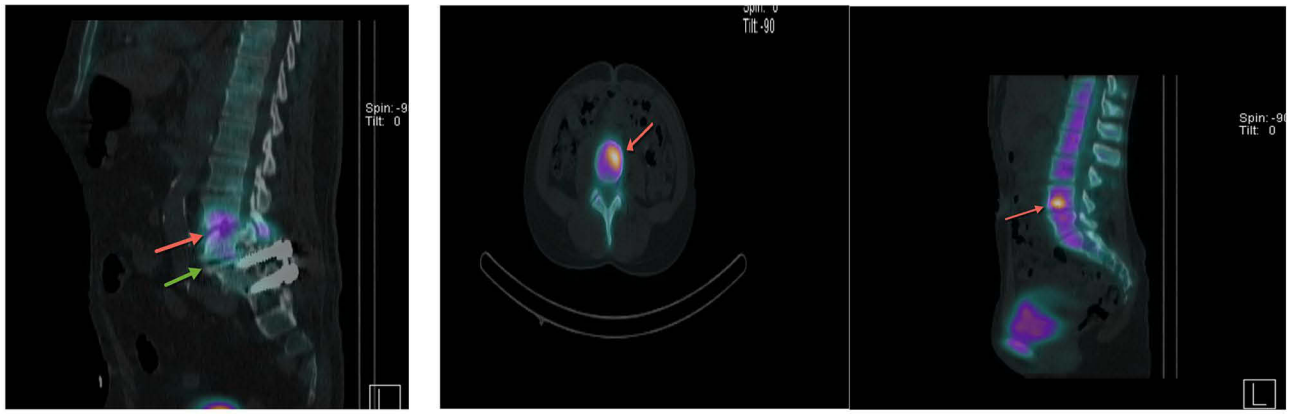


Figure 5 (**a**) SPEC CT image identifying area of pain generation due to disc degeneration. This was ruled out as infection by biopsy and subsequently treated with basivertebral nerve ablation the level above and below the disc with degenerative endplate change and radiotracer uptake (red arrow) generally associated with pain generator. Green arrow is an example of vacuum phenomena. (**b**) Use of SPECT CT to determine radiotracer uptake consistent with a pain generator (red arrows) in a patient concordant with mild Modic change on MRI (not shown) and treatment failure of posterior column interventions. Red arrow denotes uptake of tracer and suggesting highly metabolic zone consistent with potential pathology.

https://doi.org/10.2147/JPR.S553033

Aside from pain response, which has a false positive rate of 6.0% for individual disc, discography assesses the internal structure of the NP and degree and morphology of annual tearing. Post-discogram CT (CT discography) provides excellent 3D anatomic resolution of annular tears and fissures superior to the planar fluoroscopic discogram, graded with the modified Dallas classification,[43] in addition, these procedure can elucidate large tears and epidural contrast extravasation that may preclude candidacy for certain intradiscal injectable therapies.

In addition, intradiscal access must be treated with care requiring a wide prep zone, wide draping and notably, routine IV antibiotic prophylaxis is recommended with any disc access, given the concern for potential discitis. Although discitis is a rare complication with an estimated prevalence of 0.24% even without antibiotics, available cohorts studying discography with prophylactic antibiotics demonstrate a lower incidence between 0 and 0.016%.[44,45]

Another reported concern is possible chronic progression of imaging findings of DDD secondary to disc access, with this notion becoming popularized by Carragee et al[46] The clinical significance of these findings remains unclear, and notably the study only included patients asymptomatic at baseline. Nevertheless, the hypothetical risk of iatrogenically increased degeneration indicates the need for judicious use of discography, particularly in younger patients. Most patients undergoing discography, whether therapeutic or merely diagnostic, have failed to benefit durably from more conservative treatments including activity modification, physical therapy, medications, and epidural injections. Propagation of the outsized purported risks of infection and degeneration and the historical dearth of effective therapeutic treatments of anterior column pain (until recently) have contributed to a marked decrease in discography over the years, but the emergence of myriad potential therapies for anterior column pain suggests the renewed utility of discography incorporating safe practices to maximize patient benefit.

Pathology

Annular Structure-Transition from Normal to Degeneration

As described previously, each vertebral body is separated by a fibrous intervertebral disc that is composed of two elements. The NP comprises the inner core of the disc, is made up of roughly 80% water as well as collagen and protein fibers and has a gelatinous consistency. Its relative malleability allows each disc to serve as a shock absorber and distribute pressure for the spine. It is superiorly and inferiorly bound by cartilaginous endplates and surrounded by a thick outer ring of fibrous cartilage, the AF.[10,47] It is made up of a series of multiple concentric layers of type 1 and type 2 collagen fibers.[8,48] The inner annulus contains primarily rounded type 2 collagen, while the outer annulus contains type 1 collagen produced by elongated fibroblast cells. The AF not only serves to surround and protect the nucleus pulposus but provides traction and structural disc support. The IVD, in the most basic biophysical sense, distributes compressive force but also moves in much more complex planes of motion. The NP has fluid like dynamics when healthy in that it distributes compressive forces in a radial fashion. This fluid dynamic-radial distribution of force to the outer annulus is in a relatively uniform fashion when there is not disc degeneration. The annular lamellae are arranged concentrically, and with time and exposure to degenerative forces, the lamella begin to disrupt as will be discussed subsequently.

With increasing age, annular fibers breakdown and can separate, making the boundary between the annulus and nucleus more obscure.[49,50] This degeneration can lead to reduced structural support, which compromises disc integrity as well as the containment of the NP. When the nucleus extends beyond its previously defined boundaries and bulges or protrudes posteriorly or posterolateral, it can encroach on the spinal canal and its contents leading to various symptoms including pain, weakness, and paresthesias, depending on the interspinal level and severity of pressure on the nerves.[12,51,52] It should be noted that disc degeneration is a continuum along which clinicians can describe deterioration from normal to abnormal. The point at which clinical dysfunction develops requires clinical correlation however for the purposes of this discussion degeneration describes the anatomical degradation while pathologic recognizes both the anatomical change correlated with clinical dysfunction.[12] Nordberg et al conducted a study to investigate positional biomechanical changes in lumbar disc herniations. While overt flexion or a seated position was not part of the study, they found that lumbar herniated discs increased in size in the axial plane while standing, leading to higher nerve root compression grades for para-centrally encroaching discs. They concluded that lumbar disc derangements exhibited

dynamic behavior with morphological changes in the standing position vs other positions, and that weight-bearing MRI's may improve the diagnostic sensitivity in nerve root compression.[53]

Annular Tears

In order to consistently discuss morphological findings as well as apply and compare treatments, grading systems are needed to assess findings across different observers. Classifications systems must be reproducible with both interobserver and intraobserver reliability.[54] Prior to MRI, CT discography utilizing Quinnell's description was the original system for interpreting discography findings.[55] However, the Dallas Discogram Description (Figure 6) supplanted Quinnell's description to become the common grading system for interpreting lumbar discograms.[56] The Dallas system utilizes anteroposterior, lateral and the axial views available for CT discography. Utilizing these views, the Dallas system describes both disc degeneration and annular disruption as separate entities. Degeneration is evaluated in the axial view, grading from zero to 3 based upon morphological findings. The more common portion of the Dallas system grading scale is used to describe the degree of annular disruption based upon contrast extravasation between layers of the AF and describes the location and degree of protrusion (Figure 6). Unique to the Dallas system, while performing the radiologic procedure, a clinical element is also added to the grading system to give a more concordant picture of the morphological findings and their comparative clinical relevance. During contrast injection, a pain score is elicited from the patient as well as a subjective correlation of how this pain relates to their typical pain.

MRI is now the best imaging modality for assessment of disc pathology, with the T-2 weighted sequence most reflective of disc changes.[57] In addition to demonstrating disc dehydration, collagen breakdown and proteoglycan loss, MRI imaging can also provide valuable information about other structures that are also part of IVD degeneration such facet joints and endplates.[58] With the rapid adoption of MRI and newer fast spin-echo sequencing to image the IVD, a classification system was developed to reliably characterize disc degeneration morphology.

To give common nomenclature to the degree and extent of degeneration of an individual IVD, the Pfirrmann classification was created. The original Pfirrmann classification was developed utilizing three blinded observers of different experience and clinical relevance to MRI interpretation (musculoskeletal radiologist, senior staff radiologist

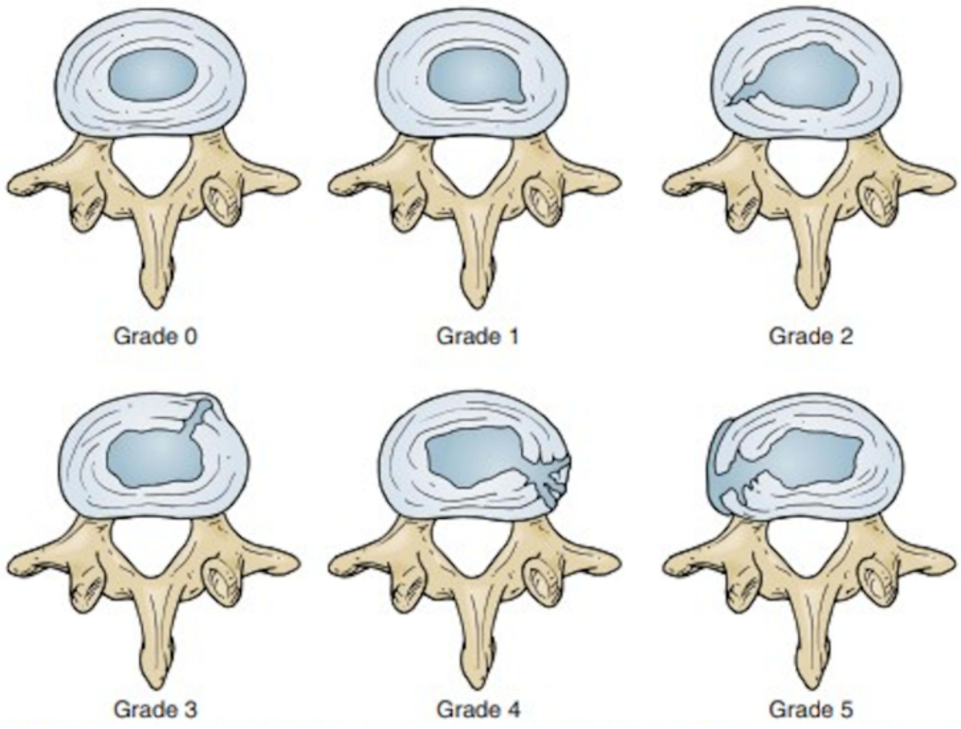


Figure 6 Modified Dallas Discogram scheme for the classification of annular tears by CT-discography (From modified From Sachs BL, Vanbaramata H, Spivy MA, et al. Dallas Discogram description. A new classification of CT/Discography in low back disorders. Spine. 12(3):287–94;1987).

https://doi.org/10.2147/JPR.S553033

and an orthopedic surgeon). Evaluation of the disc was preformed utilizing the T2-weighted mid-sagittal images. A 5-grade system was developed based upon disc structure, disc height, signal intensity and difference between the NP and AF. The intensity of signal is related to the histological findings and chemical composition of the disc.[59] Loss of signal at the disc on T2 weighted images is indicative of degenerative changes.[60] Proteoglycan concentration is directly correlated with NP brightness but is not correlated with collagen or water content. The Pfirrmann classification proved repeatable and reliable, however, the most frequent disagreements between observers were between Grade 1 and 2 likely owing to the description of homogenous vs inhomogeneous nucleus and Grade III and IV for NP and AF differentiation. One other pitfall noted by the authors were situations where a hypoplastic disc from a partially sacralized segment might be grade 5 but has actual disc morphology of a grade 2.

Ultimately, the five grade Pfirrmann system lacked discrimination when evaluating the disc in more elderly patients.[61] The mean age of patients in the original study was 40 years. Griffith et al[61] expanded the original classification system to a total of 8 grades, utilizing patients with a mean age of 73. With this expanded grading system, the modified Pfirrmann classification has been the gold standard for non-invasive classification of DDD (Figure 7).

Subchondral and vertebral endplate damage results in inflammation, edema and bone marrow changes which are visualized on MRI as Modic changes.[62] These changes are classified based upon signal intensity, with Modic type I, seen as iso-intense or decreased intensity of T1 and bright or increased signal on T2 and represents acute edema or inflammation of the vertebral endplates and the vertebrae. Modic type 2 as seen on MRI with increased signal on T1 and iso-intense to increased T2-weighted images.[57] These signal changes are consistent with fatty replacement of normal bone marrow.[60] Decreased signal on both T1 and T2 weighted images, consistent with osteosclerosis are Modic type 3 (Table 1) (Figure 4).[63]

Pain Pathology of Annular Tears

The NP and AF are mostly avascular structures depending upon diffusion at the periphery of the disc to supply nutrients and oxygen and remove metabolic waste.[63] The degeneration of an IVD may be thought of initially as an imbalance

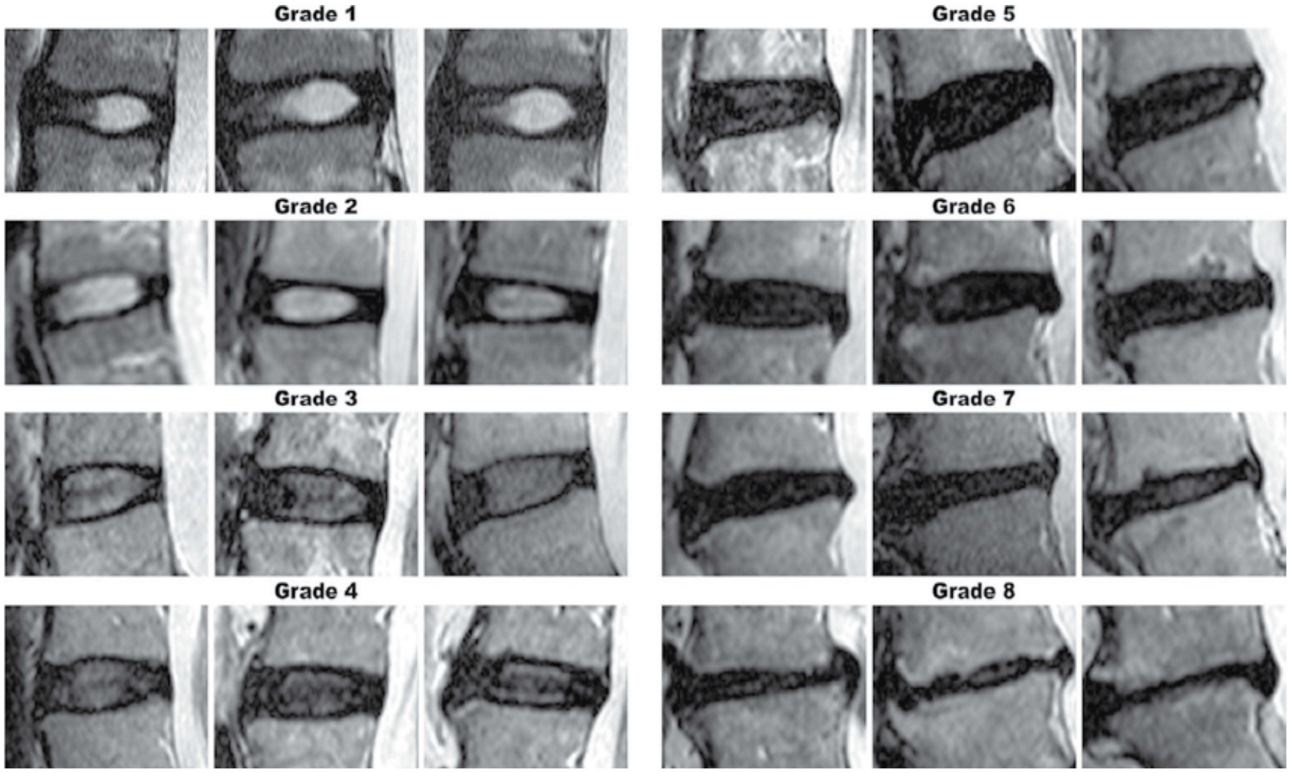


Figure 7 Modified Pfirrmann Classification (Permission via https://creativecommons.org/licenses/by/ 4.0/-from García Ramos, Carla & Reyes-Sanchez, Alejandro. (2018). Alteration of pelvic parameters in adjacent segment degeneration. Coluna/Columna. 17. 99–102. 10.1590/s1808-18512018170218944 2).

Table 1 Modic Changes on MRI by MRI Sequence Classification

Type 1	Iso/Hypointense	Hyperintense
Type 2	Hyperintense	Iso/Hypointense
Type 3	Hypointense	Hypointense

Notes: T1 = Time 1-weighted classification T2 = Time 2-weighted classification. The intensity classification refers to the way the Modic change appears when imaged using different scan time-weighted classifications. For example, Type 1 Modic changes appear hypointense (darker) on T1 weighted sequences and hyperintense (lighter) on T2 weighted sequences. The converse is true for Type 2 changes (lighter on T1-weighted sequences and darker on T2-weighted sequences) while Type 3 changes appear darker on both T1 and T2-weighted sequences.

between anabolic and catabolic processes within the disc.[64] This results in neovascularization, neoinnervation and extracellular matrix degradation of the disc. There are modifiable risks factors which can increase the likelihood of degeneration including smoking, obesity, aging, metabolic and oxidative stress, indolent infection and occupational exposure. In addition, there are studies documenting a strong genetic component with polymorphisms in gene coding for matrix and cytokine components.[65] With mechanical factors playing a large role, prevalence of disc degeneration is higher in the lower lumbar spine. Regardless of causes, the potential for degeneration begins early in life as the low-density cells of the NP derived from notochord become chondrocytes by the age of 5.[66] With this transition, the disc losses cells which play a role in the capacity to repair the IVD.

While there are multiple causes of disc degeneration, there is still a high prevalence of morphological disc degeneration in an asymptomatic population. There is thought to be a combination of the above factors in addition to the presence of inflammation which results in a painful degenerated IVD. Higher levels of cytokines such as TNF-alpha and interleukin 1, 4, 6, 8, and19 have all been isolated in both the serum and disc tissues of patients with DDD. In the pro-inflammatory environment, gradual degradation of both NP and AF matrix results through increase enzyme production.[67] Similarly, vascular supply and permeability is reduced at the endplate resulting in hypoxia, lower pH, impeded nutrient supply further inducing inflammation promoting degeneration. Ultimately, the pro-inflammatory state leads to dysregulation of the normal extracellular matrix, replacement of type II collagen with type I and proteoglycan loss in the NP resulting in dehydration and loss of turgor pressure. The disc loses the ability to resist compression and results in disc height loss and development of fissures in the AF and herniation of NP.[67]

Low back pain as a result of DDD occurs with disc herniation and compression or irritation of an existing or traversing nerve root. The fibrous ring of the AF is thickest in anterior portion, as measured radially as compared to the posterior. This difference in robustness of different parts of the disc is consistent with the typical failure occurring in the posterolateral aspect of the disc.[68] This disruption of the AF and herniation of the NP also allows nerve tissue ingrowth and vascularization that is responsible for discogenic low back pain.

However, low back pain and radicular pain can occur as a direct result of changes within the disc. Disruption of the AF occurs as it detaches from the insertion at the vertebral body. This disruption can be identified on T2 weighted images as an area of high signal. In a healthy disc, blood supply is provided by branches of the anterior spinal and basivertebral vessels, these vessels supply the cartilaginous end plate and the outermost portion of the AF. Likewise, only the outer portions of the AF are innervated by the sinuvertebral nerves (Figure 1b), however with loss of normal ECM and hydrostatic pressure which is normally inhibitory, neuronal ingrowth occurs penetrating deeper into the AP and NP and is responsible for discogenic pain.[32,63,64] The nociceptive fibers invading the inner AF and NP are an important factor in the pain pathogenesis of low back pain.[69] In addition to the disc being a source of pain, with the loss of biomechanical properties of the disc height, there is progressive stress on muscles, ligaments and the posterior facet joints which can also cause pain.[70]

Loss of Disc Height

Effect on Posterior Column

In 1978, Kirkaldy-Willis et al described the mechanical connection between the intervertebral disc and the facet joint using dissected cadavers and samples from laminectomy patients.[71,72] They postulated that there is a "three joint complex" composed of the two posterior facet joints and the disc itself. This suggests changes in either the disc, facet joints or both can alter the load transfer, and have direct mechanical consequences on the other. Over time, repeat rotational strain and minor compression injuries lead to microtrauma causing degeneration of the discs and facet joints.[71]

As the discs degenerate and lose height either by internal disruption, resorption, chemonucleolysis, and/or discectomy the resulting effects occur on the posterior column: 1) subluxation of the posterior joints, 2) upward and forward displacement of the superior articular process, and 3) narrowing of the lateral recess. In the early stages, degeneration is typically confined to one level (most commonly L4-5 or L5-S1).[71]

End Plate Degeneration, Inflammation and Modic Changes

Physiologically, an intact CEP acts as a biological barrier to prevent the transport of inflammatory mediators and bacteria between the disc nucleus and the vertebral body.[73] In patients with DDD, the CEP undergoes structural changes including ossification and increased porosity which reduces transport of essential nutrients to the discs. These changes can be seen histologically and radiographically.[64] As degeneration progresses, a hypoxic environment within the disc develops shifting the metabolism from aerobic to anaerobic. Due to the increased production of lactic acid, the intra-discal environment becomes more acidic. Over time these factors compromise disc integrity impairing compression, torsion, and tension. This further accelerates the degenerative process.[73] The resulting degenerated CEPs perpetuate a cycle of endplate damage, catabolic responses of disc cells, neovascularization, neoinnervation, reduced water binding by the disc matrix, and further overloading and damage to the endplate.[64,73]

Type 1 Modic changes show decreased signal intensity on T1-weighted spin-echo (SE) images (short repetition time [TR]/short echo time [TE]) and increased signal intensity on T2-weighted images (long TR/long TE). Type 2 Modic changes show increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2- weighted images.[57] Type 3 Modic changes show decreased signal intensity on T1-wigheted images and T2-weighted images.[74] The extent of Modic changes should be measured on the sagittal T1- and T2- weighted images. These marrow changes can be present on one or both adjacent vertebral bodies (with cranial or caudal extent). In most cases, the intervertebral disc will demonstrate signs of degenerated disc (Pfirrmann grade $\geq$ 2).[75]

Nucleus Pulposus

As previously mentioned, healthy NP is a gelatinous structure, primarily comprised of proteoglycans and water.[10] The major proteoglycan of the disc is aggrecan, which has an anionic character, providing the disc with the osmotic properties needed to resist compression.[76]

The most significant change in the degenerative cascade of the disc is the imbalance of proteoglycan turnover and consequently, loss of normal proteoglycan content in the NP. This process is multifactorial, attributed to age, recurrent mechanical stress, inadequate metabolite transport, and trauma.[77] With loss of proteoglycan, the osmotic pressure and thus, water content, of the disc diminishes. This translates to a reduced load-bearing ability of the disc, particularly within the NP. As disc degeneration and desiccation progress, the mechanical load is passed from the NP to the AF and endplates, potentially leading to compromised structural integrity of the annulus. This can ultimately lead to disc herniation in the degenerative disc.[77]

"Disc herniation" is broadly defined as a localized or focal displacement of disc material beyond the limits of the intervertebral disc space.[51] A localized, or focal displacement is defined as less than 25% (or 90°) of the disc circumference. In contrast, a "disc bulge" involves greater than 25% (or 90°) of the circumference of disc and typically will typically only extend a short distance (usually less than 3mm) from the margins of the apophysis.

A disc herniation can be classified as a disc protrusion or extrusion. A protrusion indicates that the greatest distance between any two ends of the displaced disc material is less than the distance between the edges of the base of the disc material (Figure 8). An extrusion indicates that the greatest distance between any two ends of the displaced disc material

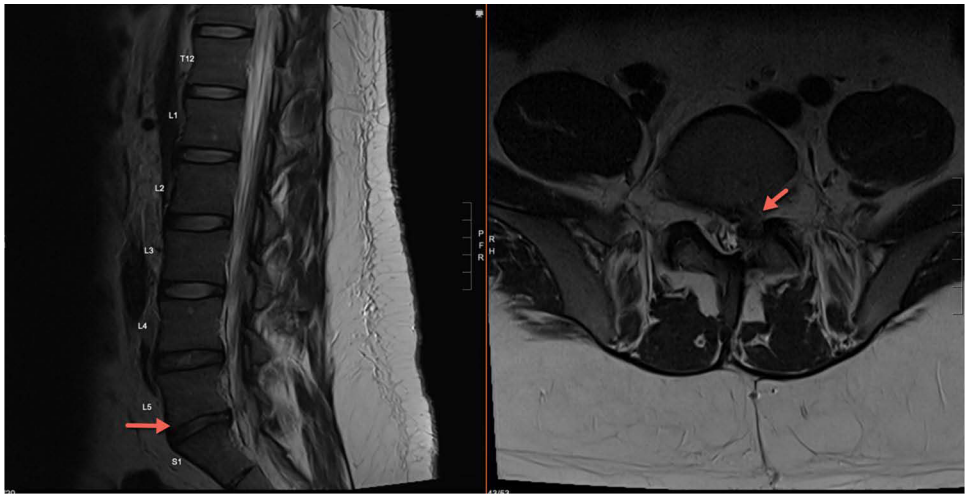


Figure 8 MRI T2 Sagital and Axial section (left) demonstrating L5 disc (red arrow) with annular disruption (sagital) and herniation/extrusion (right) in lateral recess (red arrow).

is greater than the distance between the edges of the base of the disc material. In the event the extrusion involves disc material that is no longer in continuity with the disc space, this would be classified as a disc extrusion with sequestration.[51] Furthermore, significant displacement of disc material away from the site of extrusion is classified as migration. These pathologies may be further characterized by location, size, and content of disc material. Of note, there is some accepted variability with use of this nomenclature. For example, some may prefer to simply use the more general term of "disc herniation" without further distinction between protrusion versus extrusion; "free fragments" are synonymous with "sequestrated fragment", etc. (Figure 8).

Regarding pain transmission from a disc herniation, there are key pathologic changes in a degenerated disc to first consider. While nociceptive nerve fibers normally only penetrate the outer layers of the annulus in a healthy disc, individuals with intervertebral disc degeneration have been found to have increased incidence of nerve ingrowth and vascularity to the inner layers of the annulus as well as the NP. These nerves were found to express pro-inflammatory neuropeptides such as substance P.[36,78] In other words, degenerated intervertebral discs exhibit elevated concentrations of proinflammatory and pronociceptive mediators compared to healthy discs.[36,78,79] Consequently, the herniation of disc material, particularly this pathologic NP, results in an inflammatory and immune response at the disc-neural interface. This phenomenon, in addition to the actual mechanical compression of spinal cord or nerve root, ultimately generates the pain response characteristic of a disc herniation.

There are several downstream effects thought to be due to the exposure of the nerve root, dorsal root ganglia, and/or spine to the NP. Cumulatively, these effects lead to nerve hypersensitization, increased ectopic discharge, and increased sensory transmission.[80] The presence of pro-inflammatory mediators released from cells of the NP, such as the cytokine TNF-α, prostaglandin E2, IL-6 and IL-10, are critically involved in this process. Glial cells, including microglia and astrocytes, also play a central role in this by producing inflammatory and neurotrophic factors in response to nerve injury.[81,82] In lumbar disc herniation and intervertebral disc degeneration models, activation of microglia and astrocytes is upregulated. Finally, elevated levels of pro-nociceptive neuropeptides such as substance P and CGRP, as well as increases in ion channels such as voltage-guided sodium channels have been demonstrated to play a central role as well.[83]

Furthermore, mechanical compression of the spinal cord or nerve roots by herniated discs also induces functional alterations in the affected nerves. This includes myelin sheath swelling, impaired microcirculation, demyelination, and axonal degeneration.

Pathologic and Degenerative Discs Relative to Normal Physiologic Load Bearing

The anatomical load bearing structures within the anterior column consist of elements referred to commonly as the FSU. The FSU components are the NP, the AF, the CEP, and the bony endplate (BEP) and the longitudinal ligaments (anterior and posterior) while the component structures of the posterior column are noted as the facet complex, the interspinous

 https://doi.org/10.2147/JPR.S553033

and supraspinous ligaments (Figure 1a and b).[15] Figure 2 demonstrates the positioning of the disc structure at rest and in isolation the planes of motion that can be applied to the IVD. These individual planes of motion (compression, shear stress, torsion and side bending) function in a complex amalgamation that is demonstrated in Figure 2a. The planes of motion relate to shear stress in the AP and lateral zones, compression, rotation about the central axis and lateral bending or central bending (flexion/extension) Figure 2b.[84] The neural arch in the central zone is mainly load bearing in lumbar extension as are the articular components of the posterior column.

Compressive overload of the IVD appears to damage the BEP first and has been linked to the creation of invagination into the vertebral body known as Schmorl's nodes (Figure 3).[85] For the purposes of this discussion we will refer to BEP herniation as BEP-h; otherwise the term herniation will be used to denote annular encroachment most typically in the posterior direction toward the spinal canal. Typically lumbar flexion and concomitant overload in multiple planes of motion are required for herniation with high rates of loading, (ie sudden loading) impacting the NP to the greatest extent.[86] Recent animal models have suggested that torsion applied to the IVD results in increased elastin production in response to torsion and shearing stress. This is in contrast to compressive forces which have been shown to activate multiple anabolic pathways.[87] While the IVD in experimental settings may receive isolated compressive forces, shearing/torsional forces or rotational forces to study physiochemical reactions, the in vivo situation is clearly more complex to understand.

The posterior AF is most vulnerable during axial rotation resulting in significantly less compressive force needed to produce IVD damage.[87] As the NP undergoes reactive stress (ie the tissue content of hydrated proteoglycan and Type II collagen declines and the production of Type I collagen production increases), the hydration and disc height begin to degrade. This results in the viscoelastic properties of the disc converting from fluid-type dynamics with greater force absorption to that resembling solid-type dynamics. This change in viscoelastic property results in a more rigid structure and several pathological processes leading to breakdown of the CEP, the BEP and creating reactive changes on MRI (Modic changes).[64] Numerous studies have suggested that with compressive and shear stress the CEP increases in porosity resulting in less nutrient transport and increased calcification. Innervation begins to convert from the normal presence of nociceptors in the outer third to the pathological neogenesis of nociceptors and proprioceptors within the AF. The presence of substance P overexpressing in degenerating disc tissue also is a feature of increased nociception. Finally, the presence of cytokines and pro inflammatory mediators result in upregulation of degrative enzymes further resulting in breakdown of the proteoglycan matrix. This loss of proteoglycan matrix is what ultimately reduces hydration of the NP leading to characteristic appearance on imaging and loss of disc height.[64]

Epidemiological Factors

Though traditionally viewed as a mechanical disorder, degeneration of the IVD is now understood as a multifactorial condition shaped by biological aging, genetic predisposition, and impaired nutrient diffusion. Clinical, epidemiologic, and molecular perspectives highlight how these key factors interact to drive the structural failure of the IVD and to guide future prevention and therapeutic strategies.[12]

Aging is the strongest risk factor for disc degeneration. By the third decade of life, disc cells begin to show senescence, and water content in the NP starts to decline.[88] Imaging studies reveal degenerative changes in over 80% of adults over 60, even when asymptomatic. With age, the NP becomes less gelatinous and loses its proteoglycan-rich matrix, impairing its ability to absorb axial loads. The AF also undergoes fissuring and collagen disorganization. Histologically, this transition involves the loss of large vacuolated notochordal cells—key players in maintaining matrix integrity—which are replaced by smaller chondrocyte-like cells.[89] On a molecular level, aging suppresses anabolic signaling pathways, including sonic hedgehog (Shh) and Brachyury, while promoting catabolic factors like matrix metalloproteinases (MMPs). These changes compromise ECM turnover and create a pro-degenerative environment. Still, not all aging discs are symptomatic. This suggests that aging primarily creates a permissive background, amplifying the effects of other risk factors.

Genetic predisposition plays a substantial role in determining who develops disc degeneration and how early it occurs. Twin studies reveal that genetics may explain 29–66% of variance in disc degeneration severity.[90] Genes involved in collagen structure (eg, *COL9A2*, *COL11A1*), aggrecan production, and inflammatory regulation have all been implicated. For instance, Zielinska et al[88] report that individuals who suffer lumbar disc herniation before age 21

often have a strong family history of spine pathology. Kalb et al[91] discuss how these genetic variants may alter structural resilience or modulate immune responses to disc injury.

Moreover, pro-inflammatory polymorphisms—particularly in *IL-1β* and *TNF-α*—may lead to exaggerated inflammatory responses following disc injury, promoting pain and matrix degradation.[92] Koroth et al[93] have shown that macrophage infiltration and chronic immune activation are common in degenerated discs, suggesting that genetically driven immune dysregulation may contribute to progressive tissue damage.

Because the disc is avascular, its cells depend on diffusion through the CEP for oxygen, glucose, and waste removal.[10] Aging and degeneration often impair this process. Endplate calcification, sclerosis, and compositional changes (eg, loss of glycosaminoglycans) can severely limit nutrient delivery.

Bonnheim et al[94] used advanced MRI techniques to demonstrate that poor CEP composition strongly correlates with reduced NP hydration and proteoglycan content, even in patients with intact vascular supply. Their findings suggest that intrinsic endplate quality—rather than systemic circulation, governs metabolic viability of the disc. Ito and Creemers further explain that reduced nutrient influx leads to localized hypoxia and acidosis, which in turn promotes cell death and inflammatory mediator release.[95] This triggers a cycle of degeneration that even regenerative therapies struggle to reverse.

Recognizing disc degeneration as a biologically active, multifactorial condition opens new doors for personalized care. While aging is non-modifiable, the rate and extent of degeneration may be influenced by early screening, genetic risk profiling, and preserving endplate health.

Disc morphologic degeneration reflects more than time and wear—it is the product of complex, interacting forces. Aging lays the groundwork by reducing regenerative capacity and mechanical strength. Genetics determine how susceptible the disc is to degradation or inflammation. And metabolic transport governs the disc's ability to sustain itself and recover. Together, these forces not only explain the wide variability in patient presentation but also point to future avenues for targeted therapy and prevention.

Vertebral Reaction to Disc Degeneration

Compression Fractures

Several factors influence the motion and stability of a FSU, including age, sex, height, weight, bone mineral density, intervertebral disc integrity, endplate changes, ligamentous and muscular support. The vertebrae themselves are composed of two types of bone: a thin, dense cortical shell approximately 0.35 mm thick, which encloses the more porous trabecular bone.[96]

The vertebral body is a known source of spine pain in conditions such as intraosseous tumors, infarcts, and vertebral compression fractures (VCFs).[97] The sinuvertebral nerve, which carries both somatic and autonomic fibers, transmit pain signals from the vertebral body and the AF.[98] The sinuvertebral nerve is formed by the convergence of a somatic root from the ventral ramus and an autonomic root from the grey ramus communicans. It then divides into superficial and deep branches. The superficial branch innervates the posterior AF and in the degenerative disc may penetrate deeply into the NP.[98]

Another branch of the sinuvertebral nerve is the basivertebral nerve which enters the posterior aspect of the vertebra via the basivertebral foramen providing innervation to the vertebral body.[97,99,100] Histological studies by Antonacci et al have shown that the basivertebral nerve fibers contain Substance P indicating nociceptive potential.[99]

In the standing position, the spinal column is subjected to gravitational forces that create anterior bending moments. The forward bending moments result in compressive forces across the FSUs, while the posterior ligamentous complex and paraspinal muscles experience tension to compensate. Vertebral compression fractures occur when a bending force exceeds the strength of the vertebral body, leading to structural failure of the bone.[101]

Such fractures alter spinal biomechanics, thus shifting the center of rotation posteriorly from its normal position at the ventral aspect of S1 to the level of the affected segment, increasing the moment arm and mechanical load on the compromised vertebral body.

VCFs not only result in mechanical instability but also in activation of nociceptive pathways within the vertebral body. The structural deformation and endplate disruption trigger a cascade of local inflammation, edema, and microstructural damage stimulating the basivertebral nerve. The importance of the basivertebral nerve as a conduit for vertebrogenic/anterior column pain is further supported by clinical interventions that target it directly. Basivertebral

nerve ablation (BVNA) has emerged as a treatment for chronic axial low back pain, attributed to vertebral endplate changes, specifically Modic type 1 and type 2 changes on MRI. The theory behind BVNA is the neuroanatomic understanding of basivertebral nociception.[100]

While BVNA is being used in the lumbar spine (specifically L3-S1), anatomic studies by Antonacci et al[99] have confirmed the presence of the basivertebral nerve throughout the spine, including thoracic levels. Given this, it stands to reason that in the context of a VCF, the same neuroanatomic pathways in degenerative vertebrogenic/ anterior column pain are implicated in a portion of the pain generation from VCF's.

Thus, following a compressive load that exceeds the structural capacity of the vertebral body or by direct trauma, endplate integrity is compromised. The resulting inflammation and altered loading patterns stimulate the basivertebral nerve. Once activated, the afferent signals from the basivertebral nerve travel through the sinuvertebral nerve to the dorsal root ganglion, then project centrally to the spinal cord and brain, where they are processed as pain.

In summary, the vertebral body as part of a functional unit in the spine is a critical structure within the anterior column that can generate pain through well-defined biomechanical and neuroanatomic mechanisms. In VCFs, disruption of the vertebral endplates and trabecular architecture activates signals via the basivertebral nerve eventually to the brain, making it a contributor to the pain resulting from a vertebral fracture.[102]

Infectious Factors in Disc Degeneration

Emerging evidence suggests that infectious processes—both overt and subclinical—may contribute to vertebral body and disc degeneration in a subset of patients with chronic low back pain. One proposed model describes a progressive cascade in which disc injury creates a permissive environment for bacterial colonization. In some cases, a chronic, low-grade infection may develop within the disc space. Although non-pyogenic, this localized infection is believed to provoke inflammation in the adjacent vertebral endplates, resulting in Modic type 1 changes seen on MRI. These changes have been linked to persistent axial pain and functional limitation. The hypothesis remains controversial, with ongoing debate about the significance of bacteria in disc tissue, the reproducibility of antibiotic trials, and broader concerns around antimicrobial resistance.[103]

Intra-Discal Vacuum Phenomenon

CT imaging of the spine is uncommonly obtained as a primary imaging study in the evaluation of back pain, largely due to the superiority of MRI imaging. MRI imaging offers more pronounced detail of vital soft tissues of the spine, without the radiation burden of CT imaging. However, CT imaging is far more likely to demonstrate the intradiscal vacuum phenomenon (IDVP) (Figure 5a). IDVP is defined as visible air within the intervertebral disc space on radiographs.[104] The prevalence of IDVP in the general population is around 2%, and up to 20% in the elderly with disc degeneration.[105]

The phenomenon is often, but not ubiquitously, found on imaging of patients with advanced disc degeneration. Its pathogenesis is poorly understood but may be explained by gaseous (primarily nitrogen) accumulation within degenerated disc fissures due to a reduction in intradiscal pressures from distractive micromotion forces between adjacent vertebrae.[104] Based on this theory, its finding is most closely correlated to the presence of segmental movement.

Moreover, there is growing evidence associating its presence with DDD. Cawley et al[106] compared the lumbar CT and MRI scans of 65 patients and concluded that worsening severity of IDVP on CT scans correlated with increased disc degeneration and reduced disc height on MRI. In a similar study, Eksi et al[107] compared the scans of 219 patients and found that IDVP was closely associated with severe intervertebral disc degeneration, Modic changes, and subchondral sclerosis. In a separate study by Cawley et al,[108] the authors analyzed individual lumbar segments and demonstrated an increasing severity of IDVP in segments closer to the lumbosacral junction. It is likely that IDVP is a static finding in what is a dynamic physical continuum between vacuum phenomenon, gas, and fluid, dependent on the opening of an anatomic cavity, the surrounding structures, and perfusion. D'Anastasi et al[109] studied 20 patients with IDVP on CT imaging with 2 prospective MRIs on each patient, one performed after bed rest, and one performed after mobilization. The authors concluded that the replacement of IDVP by intradiscal fluid is a time and position-dependent dynamic process and is related to Modic type 1 degenerative changes. Kanna et al[104] analyzed IDVP presence in 342 patients and concluded that pathways for the passage of peri-discal gases may include Modic disc-endplate contacts, anterior longitudinal ligament disruption, and coronal

translation. Furthermore, they proposed that the pathogenesis of IDVP may be dependent on the presence of these pathways in the setting of advanced disc degeneration and angular/coronal instability.

Cawley et al[108] found that IDVP was more likely to occur at the level of isthmic spondylolisthesis, adjacent to a previous fracture or suprajacent to a lumbosacral transitional vertebra. While it has not been conclusively proven, it is reasonable to hypothesize that IDVP may be associated with low back pain. Kasai et al[110] found increasing pain levels in patients subjected to a reduction of atmospheric pressure, which is able to induce expansion of IVDP gasses, stretching annulus fibers and causing pain.[105] The finding of IDVP is associated directly with well-recognized pain generators, such as advancing degenerative disc disease and endplate Modic changes. Furthermore, its formation is associated with segmental instability, which can indirectly lead to other spinal pathologies that are recognized pain generators, such as spinal stenosis or facet arthropathy.[109] Currently, the presence of IDVP is largely not considered in the evaluation of low back pain. However, a better understanding of its association with low back pain may one day transform this currently overlooked image finding into a biomarker for specific pain generators.

Low-Grade Infection and Disc Degeneration

In addition to overt infections, there is growing interest and controversy in the role of low-grade, subclinical bacterial colonization as a contributing factor to disc degeneration. Studies have isolated bacterial DNA, most frequently from skin flora, from excised disc specimens in patients undergoing surgery for disc herniation or chronic low back pain.[111,112] While contamination cannot be excluded, the strong association with Modic type 1 changes has prompted the hypothesis that such infections may initiate a localized inflammatory reaction resulting in disc and endplate degeneration.

This hypothesis may have important implications for interventional pain management, particularly in patients with chronic discogenic or vertebrogenic pain and Modic changes on imaging. These patients may not respond predictably to standard interventions such as epidural steroid injections or intradiscal therapies, highlighting the need to consider underlying pathophysiology when choosing treatment strategies. Additional work and evaluation of this tissue post mortem may be required to further clarify this conundrum. In the interim, prospective studies have attempted to clarify this issue.

Two randomized trials have examined the impact of antibiotic therapy in this population. Albert et al[113] found that 100 days of amoxicillin-clavulanate improved pain and function in patients with Modic type 1 changes, suggesting that infection might contribute to pain in selected patients. However, the larger AIM trial failed to replicate these results at a clinically significant level.[114] The heterogeneity of the results of these studies highlights the need for additional studies. Further investigation is required to determine if certain phenotypes of chronic anterior column back pain patients may be most likely to benefit from antibiotic therapy to maximize patient benefit as well as antibiotic stewardship. Interventional pain physicians should recognize the emerging concept of chronic low-grade vertebral body and/or intervertebral disc infections when evaluating patients with refractory anterior column pain, particularly when imaging demonstrates Modic changes without clear mechanical pathology. While the causal role of infection remains under investigation, a history of prior infection, discitis, or spinal procedures may raise suspicion for post-infectious degeneration as a pain generator.[103]

Transitional Vertebral Segments and Anterior Column Pain

Highly conserved over most mammalian species are somite-derived homeotic genes (HOX) that encode proteins responsible for vertebral body patterning, segmentation, and numbering.[115,116]

However, transitional vertebral segments may occur and are relatively common, particularly in the lumbosacral spine. Lumbosacral transitional vertebrae (LSTV) are reported to have a prevalence of 4–30% in the general population.[117] There are many variations of LSTVs, which can be divided primarily into varying sacralization morphologies of L5 and lumbarization morphologies of S1. Sacralization of L5 is likely more common than lumbarization of S1 (7.5% v 5.5%, respectfully).[116] These variations were described by Castellvi et al[118] and classified into 4 morphological types and 2 lateral variations, dependent on the degree of dysplasia and fusion of the lumbar and sacral vertebrae. Furthermore, O'Driscoll et al classified 4 types of disc morphologies existing between S1 and S2 vertebral segments, with type 4 having a well-formed disc extending the entire AP diameter of the sacrum. The authors described an association between a type 4 disc morphology and the incidence of LSTV.[116]

While there is a growing body of evidence to suggest that LSTVs are associated with increased low back pain, this remains a debated and unproven proposition. However, studies suggest that patients with LSTV have associated altered spinal biomechanics.[117,119] Becker et al[120] compared flexion-extension lumbar radiographs of patients with LSTV to age and sex matched controls and noted that the range of motion was significantly decreased in the transitional segment and increased in the adjacent cranial segment in patients with LSTV. Griffith et al[121] examined abdominopelvic CT examinations of patients with LSTV compared to non-LSTV patients and concluded that patients with LSTV had increased vertebral body cross-sectional areas throughout their lumbar spines, as well as an increase in lumbar disc and facet degeneration. Desai et al[122] compared patients with Bertolotti syndrome to controls in a population of patients with low back pain and found that Bertolotti patients had a 9.83° greater pelvic incidence and greater disc degeneration at L4-L5, but no significant difference in sacral slope, spondylolisthesis, facet grade, or spinal stenosis grade.

These altered biomechanics of the lumbosacral spine may lead to degenerative changes at the spinal level immediately cranial to the transitional level. Intuitively, these changes may arise in a similar fashion to the degenerative processes that occur in adjacent segment disease after spinal fusion surgery. Like surgical fusion, LSTV may be considered a non-iatrogenic fusion of the spine, reducing motion in the fused segments and subsequently increasing stress on the disc and posterior elements of the cranially adjacent level. Vergauwen et al[123] did not find a significant difference in overall incidence of degenerative spine changes between patients with LSTV and controls, but did note a different distribution pattern of degenerative changes in those with LSTV that involved a greater occurrence of disc protrusion/extrusion, disc degeneration, facet degeneration and nerve root canal stenosis at the suprajacent level than at the same level in patients without LSTV. In a separate study by Hanhivaara et al,[124] the authors concluded that Castellvi types II, III, and IV were associated with greater lumbar degeneration, including disc degeneration and facet joint degeneration in patients with LSTV compared to age-and sex- matched controls. Luoma et al[125] also found that LSTV was associated with increased risk of disc degeneration in suprajacent discs, but that these effects were obscured by age-related changes in middle-aged patients. Interestingly, the disc within an LSTV may be associated with less degeneration than a normal L5-S1 level.[126,127] It is postulated that there may be protective effects at the level of an LSTV, presumably from the reduced motion in the setting of fusion-like properties of the LSTV. Again, the disc degeneration at the suprajacent level has not conclusively been proven to be associated with a greater incidence of low back pain. Similarly, the protected and preserved disc within an LSTV segment has not been specifically studied as a pain-generating source.

Vertebral Osteomyelitis and Discitis

Vertebral osteomyelitis and discitis are classically considered rare, acute conditions, yet their long-term sequelae are increasingly recognized as contributors to chronic spinal pain.

Pyogenic spinal infections present acutely with axial back pain that is unrelieved by rest and often associated with neurologic compromise and classic "red flag symptoms."[128,129] Diagnosis is based on elevated inflammatory markers, imaging studies, and positive blood cultures in a patient with a history consistent with vertebral osteomyelitis or discitis.[128,129] While these patients often have a history of intravenous drug use, immunocompromise, or recent spinal instrumentation, idiopathic cases are well documented in the literature.[130] These infections frequently involve the lumbar spine and may initially mimic mechanical back pain. As the infection progresses, destruction of the endplates and narrowing of the disc space ensues, producing long-lasting biomechanical instability and nociceptive signaling even after antibiotic therapy has resolved the active infection.[131]

Contrast-enhanced MRI is the imaging gold standard for early diagnosis and typically demonstrates endplate erosion, vertebral marrow edema, and enhancement of the disc and adjacent structures.[132] These findings may be difficult to distinguish from Modic type 1 changes in patients without systemic symptoms. For interventionalists, this overlap presents a diagnostic challenge, particularly in cases of persistent axial pain where typical degenerative etiologies fail to explain the severity or chronicity of symptoms. A thorough review of systems would elucidate fevers, unintentional weight loss, or perhaps a history of being immunocompromised or IV drug use that would increase the likelihood of a patient being diagnosed with a spinal infection.[128]

Due to the relative lack of vascularity of the intervertebral discs and, to an extent, the lumbar vertebral bodies, treatment of acute vertebral osteomyelitis and discitis centers on prolonged antimicrobial therapy. However, despite long-

term intravenous antibiotic administration, patients often experience chronic pain.[103] Structural compromise of the anterior column, especially in cases where the vertebral body becomes collapsed or fused, may alter spinal loading patterns and contribute to ongoing pain even after infection is cleared.[133]

Postoperative Changes

Microdiscectomy

Lumbar microdiscectomy is generally considered a safe and effective surgical procedure for treating symptomatic herniated lumbar discs. It is minimally invasive and typically has a high success rate ranging from 80–90%.[134–136] However, like all surgical procedures there are some risks and potential complications.

Recurrent disc herniation is the most common complication with rates reported between 5–15% and is the most common indication for reoperation.[137,138] Recurrence most commonly occurs at the same level and on the same side as the original herniation and usually within the first 1–2 years after surgery. Risk factors for reherniation include younger age (under 55), smoking, obesity, inadequate disc removal, and larger size of the annular defect. Reoperation which occurs after about 10% of lumbar microdiscectomies, may be more challenging than the index surgery but conveys similar positive outcomes and low complication rates risks as the original surgery.[139] Incidental durotomy has been reported in 0.1–7% of cases.[140,141] Most dural tears are recognized intraoperatively and repaired immediately, with minimal long term consequences. However, in rare cases, durotomy may lead to persistent CSF leak, postural headaches, meningitis, arachnoiditis, pseudomenigocele formation, and the need for additional surgical interventions.

Wound complications such as superficial or deep infection are also rare following lumbar discectomy. The incidence of superficial wound infections is <2% while deep infections occur in <1%.[142] Discitis and epidural abscess are exceedingly rare but often necessitate additional surgery and lead to significant loss of disc height and potentially spinal instability.

Nerve root injury is an uncommon complication occurring less than 1%.[143] As lumbar discectomy is often an elective procedure performed in younger, healthier patients, medical complications are rare. The reported incidences of post-operative pulmonary embolism, deep vein thrombosis, pneumonia, UTI, myocardial infarction are all <1%.[143]

Fusion

Fusion Lumbar spine fusion surgery is a commonly performed procedure aimed at alleviating pain and restoring stability in patients suffering from degenerative disc disease, spinal instability, or other pathology affecting the lumbar region. While fusion can provide significant relief and improve function, it is also associated with a range of postoperative changes and complications that can affect patient outcomes.

One of the most frequently observed complications is adjacent segment disease (ASD), sometimes described as adjacent segment pathology, which refers to the development of degeneration in the segments adjacent to the fused levels. Studies have shown that the incidence of ASD can be about 20% to 30% within ten years post-surgery, largely due to altered biomechanical stressors on adjacent segments.[144] Another notable complication is pseudoarthrosis, characterized by a failure of the fusion to heal, which occurs in approximately 5% to 35% of patients and can lead to persistent pain and the need for additional surgeries.[145] Surgical technique, the use of bone grafting material, and patient factors such as tobacco use and vitamin D deficiency have been identified as contributing factors to this complication.[146]

Postoperative infections, while less common, can lead to significant morbidity, with reported rates of wound infection around 1% to 5%.[146] Another complication includes neurologic deficits, which can result from surgical trauma to neural tissues or hematoma formation postoperatively. The reported incidence of such deficits ranges widely, but serious complications occur in approximately 0.46% to 17% of cases.

Patients may also experience chronic pain post-surgery, with conditions such as complex regional pain syndrome (CRPS) or failed back surgery syndrome (FBSS), more recently described as persistent spinal pain syndrome (PSPS), emerging in a subset of individuals, thereby complicating recovery and rehabilitation.[147] Reports have stated that FBSS can occur in 10–40% of patients undergoing back surgery. Psychosocial factors, including anxiety and depression, have also been linked to worse outcomes, emphasizing the importance of a multidisciplinary approach to postoperative care.[148] Additional postoperative changes, such as changes in spinal alignment and residual back pain, can persist long term, influencing the overall success of the procedure and patient satisfaction.

Given these complexities, a thorough preoperative assessment, education about potential postoperative changes, and careful surgical technique are critical in minimizing complications and optimizing surgical outcomes for lumbar spine fusion patients.

Treatment

Intradiscal Treatment

Within the construct of medical treatment is should of course be acknowledged that lifestyle change, weight loss, medications, physical therapy, injection treatment and diet modification are staples of treatment of CLBP of any origin. Given the subspecialty nature of the discussion we wish to illuminate new and emerging interventional treatment options for the edification of the knowledge base of the proceduralist new to this area of focus.

Platelet Rich Plasma Injections

Platelet-rich plasma (PRP) injections, consisting of high amounts of patient's platelets, contain seven proteins and cytokines involved in regeneration and growth: platelet-derived growth factors (PDGF), transforming growth factor-B (TGF-B), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and adhesive proteins including fibrin, fibronectin, and vitronectin which all work to strengthen the extracellular matrix. PDGF, a glycoprotein, is released from platelets and stimulates cell membrane receptors to induce the development of high energy phosphate bonds, which promotes mitogenesis, angiogenesis, and macrophage activation. This then increases the production of TGF-B. TGF- B, typically generated by autologous platelets and macrophages, is a growth factor that targets fibroblasts, marrow stem cells, and pre-osteoblasts to promote healing, bone regeneration, and bone modeling and downregulates osteoclasts. VEGF is involved in upregulating vasculogenesis and angiogenesis and EGF prompts cell growth, proliferation, and differentiation upon binding to its receptor, EGFR.

In 2006, Chen et al demonstrated that the growth factors found in PRP, notably TGF-B, hold promise for treatment of disc degeneration through human nucleus pulposus proliferation and chondrogenic differentiation.[149]

Subsequently, many clinical trials have been carried out assessing the efficacy of PRP intradiscal injections. A double-blind, randomized, placebo-controlled trial of PRP intradiscal injection versus contrast agent (control) revealed significant differences in Functional Rating Index (FRI) and Numeric Rating Scale (NRS) scores in the treatment arm at 8 weeks post-injection compared to the control ($p = 0.03$ and $p= 0.02$).[150] At the 6-month and 1-year endpoints, significant improvements from baseline were observed in the FRI, NRS worst pain, and SF-36 pain scores for the treatment arm ($p < 0.01$, $p < 0.01$, and $p= 0.3$, and $p < 0.01$ respectively) but the differences between the treatment and control outcomes were not compared after the 8-week timepoint.[150] A long-term follow up study of those in the treatment arm was conducted, and showed differences in NRS and SF-36 pain scores from baseline ($p < 0.001$ and $p <0.001$), indicating clinically significant and sustained improvement in pain and function out to between five and nine years (average of 6.57 years to follow up) post-intradiscal PRP injection.[151] 72% of participants indicated significant improvements in pain and function at the last follow-up time point. The remaining 33% of the participants believed the intradiscal PRP injection delayed the need for surgery and underwent surgery after PRP injections approximately four years later.[151]

Single-arm studies have shown similar results. Analyzing six clinical trials, intradiscal PRP injections showed sustained improvement in pain levels over the course of 6 months. A decrease in pain scores by >30% was seen in 57% of patients at 1 month and 65.6% of patients at 6 months post injection. Concurrently, a decrease in pain levels by >50% was seen in 51.0% of patients at 1 month following injection and 51.9% at 6 months. There were no adverse events noted in any of the 6 studies.[152] A 2022 study conducted by Zhang et al[153] demonstrated that pain and lumbar function were significantly improved at the 48-week follow up visit ($p<0.05$, $n=31$). Twenty-two (71%) patients were classified as clinical successes after the intradiscal injection of PRP. Success was determined by meeting the minimally clinically important difference for FRI, NRS, SF-36 pain and physical function questionnaires.[153]

A triple-arm, blinded, randomized controlled trial was conducted comparing PRP intradiscal injection to an epidural steroid injection (ESI) of triamcinolone in those with lumbar disc herniations. Significant differences in leg pain VAS reduction between the two treatments ($p < 0.05$) were demonstrated at 6 to 24 weeks but back pain VAS scores did not show significant differences.[154]

A pilot study was conducted by Kawabata et al[155] to determine the feasibility of PRP intradiscal injections in treating Modic type 1 changes associated with low back pain. In 10 participants, significant differences were observed in the VAS after 1 week ($p = 0.008$), and in the ODI and Roland Morris disability questionnaire (RDQ) after 25 weeks ($p = 0.039$ and $p = 0.047$). Significant improvement in VAS was correlated with higher WBC in the PRP injection, and no changes were reported in type of Modic changes or Pfirrmann grade of the injected disc.[155]

Intradiscal PRP injections stimulate the proliferation of NP cells by promoting the release of key growth factors such as PDGF, TGF-β, VEGF, EGF, and various adhesive proteins. These bioactive molecules help stabilize the disc microenvironment, thereby enhancing its regenerative capacity. Clinical evidence supports the safety and efficacy of PRP injections, highlighting their potential to significantly alleviate symptoms and improve outcomes in patients suffering from chronic back pain.

Stem Cell Injections

Mesenchymal stem/stromal cells (MSCs) and mesenchymal progenitor cells (MPCs) are currently being utilized in clinical trials to treat DDD. MSCs are collected from autologous or allogeneic bone marrow (known as bone marrow aspirate concentrate or BMAC), adipose tissue, umbilical cord, and placental tissue, while MPCs are collected from mesenchymal allogeneic bone marrow or autologous intravertebral disc tissue.[156]

As demonstrated in previous in vivo studies conducted with rabbit models, MSCs allow self- renewal without differentiation.[157] Results have shown that after MSCs are transplanted into the IVD, the stem cells are differentiated into NP cells or chondrocytes.[157] This then induces production of extracellular matrix proteins and key molecules including Type II collagen as well as aggrecans and proteoglycans, which contribute to the water binding capacity and load bearing potential of the intervertebral disc.[158,159]

MPCs have been shown to secrete TGF-β1, further increasing matrix component production.[160] TGF-β1 also causes a shift towards M2 macrophage production. This shift results in decreased levels of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), increases in collagen production, and documented analgesic effects.[161]

Currently, autologous treatments such as BMAC, and adipose-derived stem cells (ASCs) are available therapeutic options. ASCs are harvested from a patient's own adipose tissue and processed through mechanical emulsification before being injected into the affected intervertebral disc. A previous ex vivo study highlighted that after obtaining the MSCs, exposing them to osteogenic factors and the disc environment stimulates the production of osteoblastic gene markers and strengthens the extracellular matrix.[162] Animal studies (conducted in rabbit models) have shown that ASCs typically facilitate regeneration by stimulating chondrogenesis and NP-like cells, thereby producing cell proliferation, similar to MSCs.[163] As such, adipose-derived stem cell therapy represents a promising and effective treatment option for appropriate patients.

BMAC consists of MSCs and growth factors which may help to promote healing within the discs. In a prospective, multicenter cohort study, thirty-two patients received the BMAC procedure. Early outcomes revealed significant reduction in VAS (59.4%) and ODI (56.3%) from baseline to 12 months and a 43.8% reduction in the VAS leg pain.[164] These findings suggest that BMAC is a viable and effective option for patients seeking regenerative treatment for discogenic back pain.

Therefore, both adipose-derived stem cell therapy and the BMAC are potentially effective and available options for patients that may become more prevalent as research continues to advance the field.

Current clinical studies are utilizing MPCs or MSCs and expanding the number of cells used for the injection as the density of cells injected may play an important role in the efficacy of the disc treatment. Various cellular densities are being introduced to the disc environment, which contains only about 5.8×10^3 cells/mm^3, and the expansion of these cells is being done under hypoxic or normoxic conditions. Carriers or scaffolds are also being employed to ensure cellular localization within the disc and to optimize the cells' survival and function in the hostile disc environment which lacks a direct blood supply and maintains low oxygen tension.[165–168] These cells demonstrate a strong ability to differentiate into chondrocytes and NP cells, aiding in the development and reconstitution of the extracellular disc matrix.

As an example, use of allogeneic mesenchymal precursor cells combined with hyaluronic acid (HA) to create rexlemestrocel-L. This product is then injected into the intervertebral disc to repair the degenerated disc and generate a healthier disc environment through the TGF-β1, and macrophage shift mechanisms mentioned previously. In its Phase II trial, Mesoblast determined safety and efficacy of rexlemestrocel-L in 100 subjects, expanded in a normoxic

environment to 6 million and 18 million MPCs with a 1% HA carrier vs both a vehicle control (1% HA) and a saline placebo. Through the 12-month, 24-month and 36-month endpoints, the 6 million MPC group showed significant decrease in VAS scores when compared to the saline placebo (p=0.018, p=0.005, and p=0.047). At the 12-month endpoint, the 6 million MPC group showed the greatest percentage of patients with a 50% or more decrease in VAS (48.2% of patients, $p \leq 0.05$) and a 15-point ODI improvement (50.0%, p=0.05) when compared to the 18 million cell group and the control groups. A significant decrease in VAS scores was also seen when compared to the HA vehicle control at the 3-month and 6-month endpoints (p=0.005, p=0.032). Their first Phase III trial continued with the 6 million cell expanded product, and tested this in 404 subjects, both with and without the 1% HA carrier against a saline placebo. At the 6-month, 12-month and 24-month endpoints, significant decrease in pain was observed, but usage of the intradiscal saline placebo rendered the results insufficient.[169] Mesoblast is currently conducting a second Phase III trial of the 6 million rexlemestrocel-L product mixed with 1% HA versus a sham procedure, with a target of 300 subjects. The study began enrolling in 2025, with expected data completion by 2027.

Another approach utilizes an autologous approach, where subjects' bone marrow cells were harvested, expanded to 40×10^6 cells, and are then injected at the affected disc level. The investigational product, BRTX-100, is composed of a platelet lysate- carrier and bone marrow mononuclear cells cultured in a hypoxic environment and nourished in MSCs, activating chondrocyte-like cells, osteoblasts, and adipocytes. BRTX-100 aims to reduce disc inflammation, increase extracellular matrix remodeling and to promote angiogenesis. The study is in its Phase II, currently being evaluated for safety and efficacy.

A randomized controlled trial was conducted to investigate differences in autologous approaches assessing intradiscal PRP, BMAC, or a saline trigger point placebo. Results showed that both PRP and BMAC intradiscal injections showed significant differences in NRS pain scores compared to control ($p < 0.001$).[170] All participants in the placebo group crossed over into one of the treatment arms after the 3-month follow-up time point.

Another emerging concept is the use of allogeneic disc progenitor cells from donated adult human intervertebral disc tissue. With a sample size of 60 subjects across 13 sites, it was found that there was a 62.8% decrease (p=0.0005) in the VAS at the 1-year follow-up visit in patients that received a high dose, whereas there were no significant changes in the low-dose group or the placebo group. The high-dose group also experienced a significant increase in disc volume (mean increase of 249.0 mm^3 at 52 weeks and 402.1 mm^3 at 104 weeks (p=0.028).

Recent clinical studies indicate that injecting MPCs and MSCs into degenerated intervertebral discs holds strong promise for enhancing the proliferation of native disc cells.[164–169] These studies also report substantial improvements in patient-reported outcomes, including reduced pain levels as measured by VAS and ODI scores. These clinical benefits are accompanied by evidence from animal models of increased extracellular matrix remodeling, angiogenesis, and collagen synthesis within the disc environment. Ongoing research is focused on further confirming the safety and therapeutic efficacy of these cell-based interventions.

Hydrogels and Collagen Matrix Polymers

Relatively recent advancements in augmentation and restoration of the IVD architecture utilize synthetic hydrogel and collagen matrix technologies to restore disc height and load bearing capacity. Given these are relatively new technologies they are highlighted here as emerging concepts for awareness for the interested clinician.

Hydrogels

Augmentation of the intervertebral disc with hydrogel materials has been investigated due to the biomechanical similarities of many hydrogels to the native NP tissue and to the desire to develop a functional treatment for intradiscal tissue lost to DDD.[171–176] The implication of being able to inject the gel as a liquid has changed the utility of the procedure from that of a nucleus replacement to that of intradiscal augmentation. Intradiscal augmentation is placing hydrogel with similar properties to the native tissue into the NP and into the annular tears that accompany the degenerated IVD (Figure 9).

A number of injectable hydrogel materials have been previously investigated for intervertebral disc augmentation including poly N-isopropyl acrylamide (PNIPAAM) and dimethylacrylamide (DMAc) copolymer hydrogels in addition

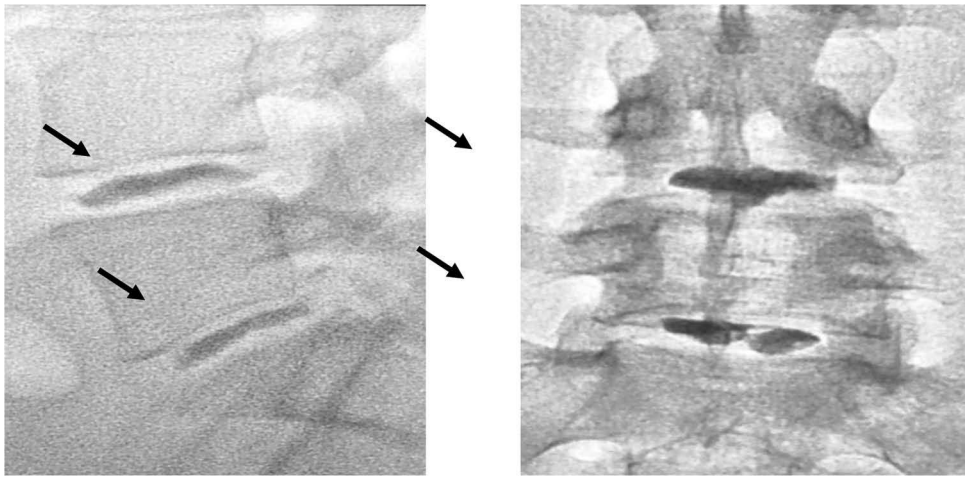


Figure 9 Lateral (left) and anteroposterior (right) fluoroscopic images demonstrate hydrogel (black arrows) within the L4-5 and L5-S1 intervertebral disc.

to polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) copolymers.[175] Polyethylene glycol was also combined with PVA hydrogels using the theta-gel method which also utilized PEG as the gelling agent which successfully produced an injectable hydrogel that was able to form a cohesive implant.[177,178]

The implant is a viscoelastic composite that is hydrophilic and able to absorb and retain water, mimicking the osmotic and mechanical properties of a healthy nucleus pulposus. Prior to injection the copolymer gel is heated to 65°C and delivered intradiscally via a 17G needle under local anesthesia and fluoroscopic guidance. Upon cooling to just above body temperature (approximately 42°C), the material solidifies in situ, forming a cohesive mass that augments the intervertebral disc (Figure 9) and supports axial load distribution. The hydrogel is designed to function within the physiological pressure ranges of the intervertebral disc and to resist mechanical fatigue under cyclic spinal loading.

Functional and Pain Improvements. Substantial and significant clinical improvements were noted in both disability and pain scores. Mean ODI decreased from 57.4 ± 1.5 at baseline to 11.2 ± 2.0 at 12 months ($p < 0.001$) (Figure 10a and b). NRS scores for back pain improved from 7.3 ± 0.2 to 2.2 ± 0.3, and leg pain from 5.5 ± 0.4 to 1.4 ± 0.3 over the same period ($p < 0.001$). Improvements were evident as early as one month and sustained through all follow-up intervals.

More than 93% of patients achieved the minimum clinically important difference (MCID) for both ODI and NRS back pain, reflecting meaningful improvements in daily functioning and pain.

The findings of this study demonstrate that injectable hydrogel implants represent a promising minimally invasive approach for the treatment of symptomatic DDD. By augmenting the IVD, the implant appears to restore disc biomechanics and potentially seal annular fissures, thereby limiting the release of inflammatory mediators implicated in discogenic pain. Importantly, the implant does not preclude future surgical intervention. In cases of migration, the material was easily removed via endoscopy. The observed reduction in back and leg pain suggests that biomechanical restoration may have broader effects on pain modulation, including a possible anti-inflammatory benefit through containment or reduction of the cytokines within the disc.

Collagen Matrix Restoration: Intradiscal Collagen

Collagen matrix restoration of the IVD refers to the process of repairing or rebuilding the collagen network within the disc, which is important for maintaining its structural integrity and function. The AF of the intervertebral disc is primarily composed of highly arranged collagen fibers arranged in lamellae of mostly type I collagen that forms a matrix that resists multidirectional movements.[8] The NP center of the disc is made of 70–90% water with the remainder consisting of primarily type II collagen and proteoglycans.[30]

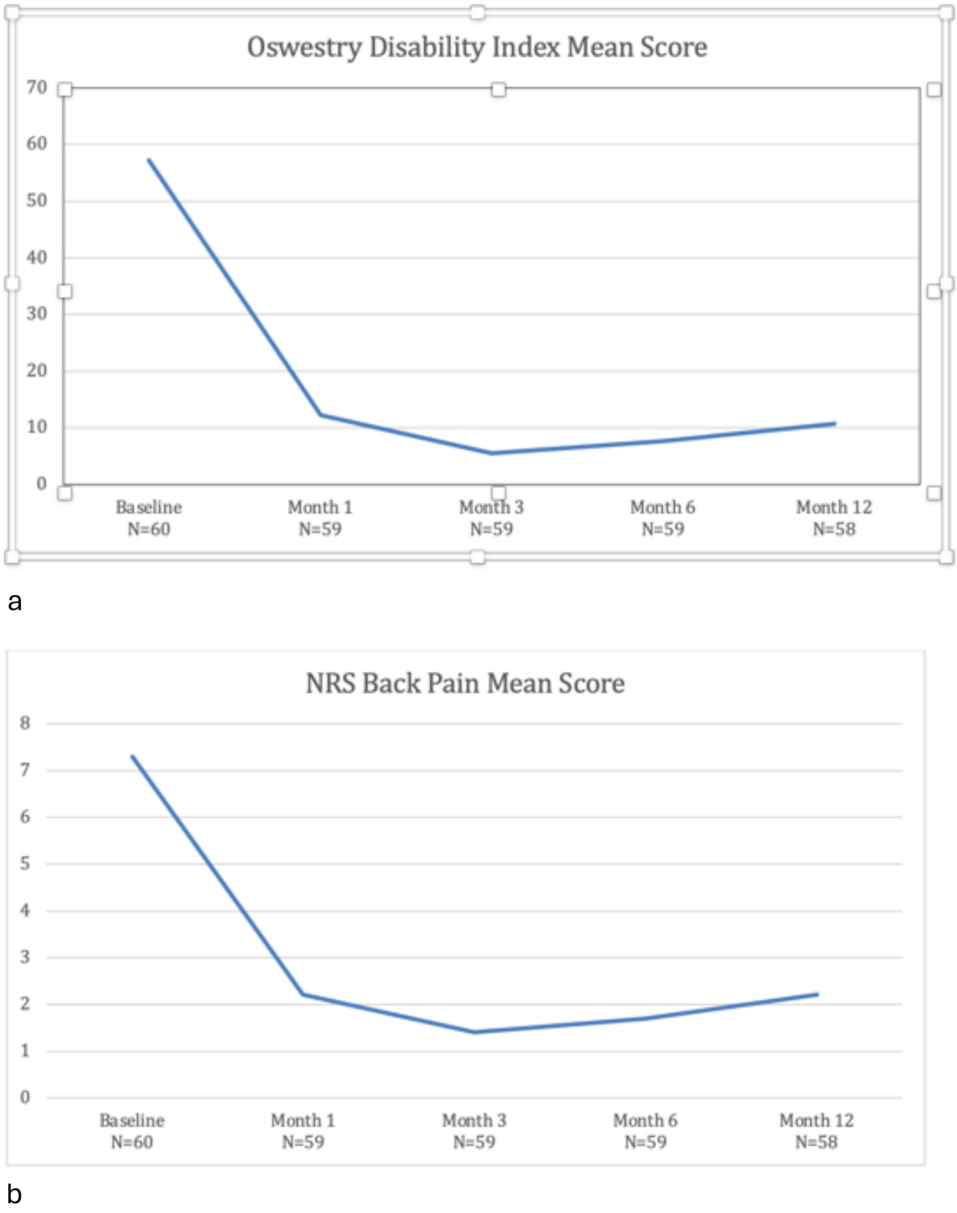


Figure 10 Results of Hydrafil implant. (**a**) Line graph demonstrating the Oswestry Disability Index (ODI) at baseline, one month, three months, and six months' time points. Data shows a 41% improvement in the patients function at the six-month follow-up time point. (**b**) Line graph demonstrating the Numerical Rating Scale (NRS) pain scores obtained at baseline, one month, three months and six months for the patient's back pain. Data shows a 5.2 point reduction in back pain at the six-month follow-up time point.

Degeneration and Restoration

In cases of degeneration or injury, the type I and II collagen fibers can become weakened, damaged, or degraded, leading to loss of disc height, structural instability, pain, and other complications.[179–181] Restoration of the collagen matrix involves repairing or replacing damaged fibers to strengthen the structure of the disc and improve its mechanical properties.[182] This restoration can potentially slow or reverse disc degeneration, constrain aberrant joint motions, enhance the disc's ability to withstand stress, and help to prevent further damage or disc herniation.

Therapies aimed at collagen matrix restoration typically involve promoting collagen synthesis or using biomaterials such as genipin-based polymers to mechanically reinforce the disc and improve mechanotransduction responses.[16]

Genipin Intradiscal Stabilization

Early studies have explored genipin polymers which are injectable as a non-biologic, self-polymerizing treatment for DDD.[182] Genipin is a biocompatible organic compound that forms bonds between the terminal ends of the polymer and amines on proteins in the disc tissue and can be injected into the IVD utilizing fluoroscopic-guided delivery of the self-forming genipin polymers directly to the damaged AF (Figure 11).[183]

The therapeutic effect of this treatment likely arises from the mechanical properties of the genipin polymers, which collectively stabilize the compromised collagen matrix of the disc.[184–187] This action limits abnormal deformations and helps to support a portion of the disc's load, ultimately providing mechanical stabilization to the intervertebral joint (Figure 12). Referred to as Intralink (Spinal Simplicity, Kansas City, MO, USA), this genipin-based treatment has the potential to address the root causes of degenerative disc disease by targeting disc mechanical insufficiency and joint instability, two of the contributors to discogenic pain.[188–190] Genipin polymers have shown promise in reducing joint instability, excessive disc bulging, tissue overload, and annular tearing, indicating that this novel approach can not only alleviate discogenic pain but also restore joint stability and resist further tissue degradation.

Initial Clinical Data

Early clinical results seen in a 20 subject multi-site, single arm feasibility study for evaluating the safety and efficacy of an injectable genipin-based nano-tethering device showed that the joint-stabilizing effects observed in ex vivo experiments can be successfully replicated in a clinical setting.[188–190] The treatment evaluated in this trial led to clinically meaningful improvements in pain and disability scores for at least 80% of patients, with benefits persisting from two weeks to two years post-treatment.[182] In patients with more severely unstable joints, the Injectable Disc Stabilization Device (IDSD) significantly reduced instability scores, bringing them from an average of 2.4 standard deviations above the mean for an asymptomatic population down to the asymptomatic mean. The treatment efficacy did vary according to the patient's weight.

Additional studies will be needed prior to regulatory approval of genipin. A post-injection inflammatory response can be seen 2–3 days after leakage of the IDSD outside the disc. This inflammatory change is completely treatable by an epidural steroid injection but is the main source of adverse events associated with this therapy and subsequent clinical trials will likely be indicated for patients with degenerated symptomatic IVDs that have the ability to retain the injectate. A watertight disc is not identifiable on imaging so discography may be necessary for patients prior to treatment with the IDSD.

While this non-biologic nano-tethering approach effectively reinforces spinal discs and stabilizes joints across all stages of disc degeneration, the injectable genipin polymers may be best used to address the currently unmet need in

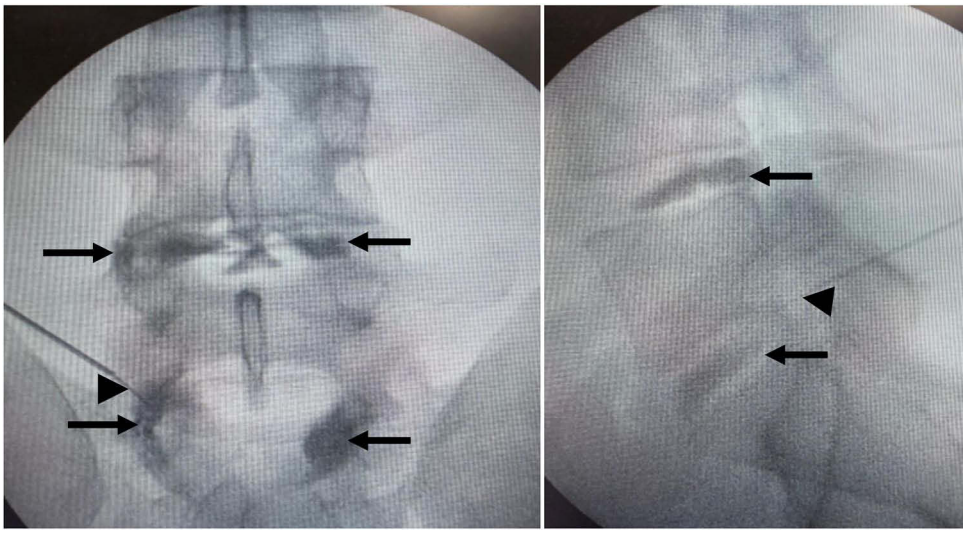


Figure 11 Anteroposterior (left) and lateral (right) fluoroscopic views of the lower lumbar spine with injections of genipin and contrast into the posterolateral annulus fibrosis (black arrows) of the L4-5 and L5-S1 intervertebral discs via a needle (black arrowheads) placed through Kambin's triangle and into the annulus of the disc.

https://doi.org/10.2147/JPR.S553033

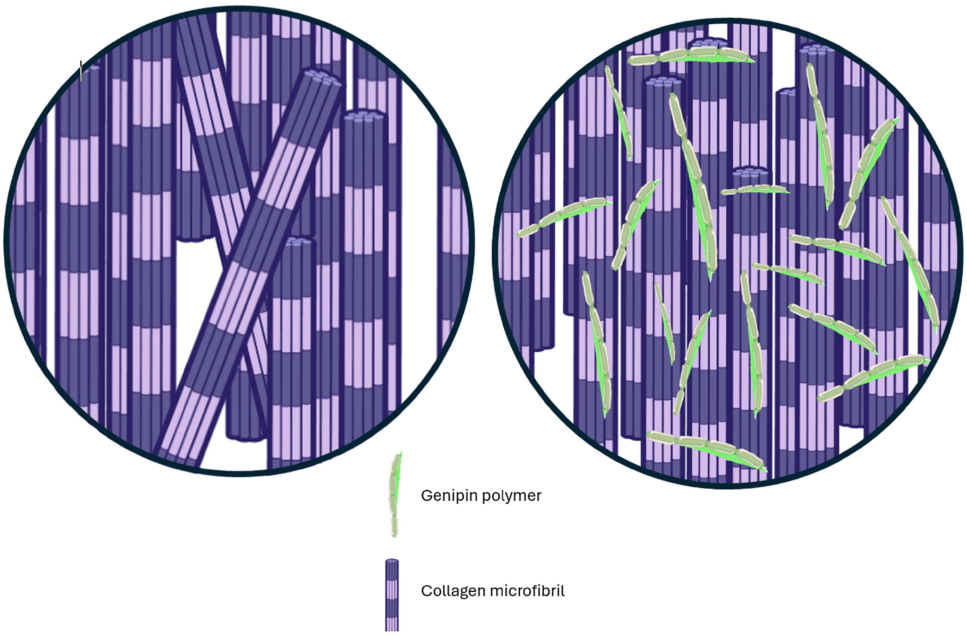


Figure 12 Image representation of the structural arrangement of collagen microfibrils within a subfibril of the annulus fibrosus matrix. The left side shows the native collagen structure and the right side shows the reinforced structure after addition of the genipin polymers.

early to mid-stage discogenic pain patients. By reducing mechanical degradation, this has the potential to slow disease progression and prevent decades of pain and disability. Its ability to provide additional mechanical support may counteract the mechanically induced aspects of degeneration that trigger a cascade of harmful changes in the disc and surrounding tissues. In doing so, injectable genipin could help lower the risk of subsequent disc failures and associated radiculopathy.

There is no clinical evidence currently that confirms whether treatment with genipin polymers provides sufficient load support to effectively resist the degenerative process. The recently published early-stage feasibility study is limited by its small sample size, which could overestimate treatment effects. Additionally, as a single-arm study, it lacks a control group for direct comparison with standard treatments or for assessing potential placebo effects. Further validation is needed through larger, controlled follow-up trials before an IDSD can be brought to the market.

Allograft Augmentation

One of the current clinical approaches to treating disc degeneration is derived from experience in orthopedics, wound healing, and transplantation in regard to the use human tissue to compensate for anatomical deficiencies and there is growing evidence for its use in managing painful DDD (Figure 13).[191–193] Clinically, the use of allograft or homologous tissue is well-established for addressing tissue loss or deficiency. In the context of disc degeneration, a NP allograft may offer a biologic supplement to reinforce tissue loss and restore the disc's mechanical function. Key attributes that make biologic tissue suitable for disc repair include its ability to provide mechanical support, maintain viscoelastic properties, and distribute axial loads during movement. The mechanical role of the disc is also crucial for facilitating the transport of soluble biochemical factors throughout the disc and its surrounding tissues. This transport is intimately connected with cellular responses, influencing matrix turnover and metabolic activity.[194]

In degenerative discs, the loss of proteoglycans significantly impairs the disc's load-bearing function. This reduction leads to decreased osmotic pressure and impairs the disc's capacity to retain hydration under load.[12,195] Replacing the NP with appropriately hydrated biological tissue may help restore disc structure and function. Allogeneic disc materials, both with and without viable cells, have been used successfully to treat lumbar discogenic pain associated with DDD.[191,196,197] Early clinical data supports the potential of biologic supplementation to relieve pain and improve functional outcomes in affected patients.[196–198]

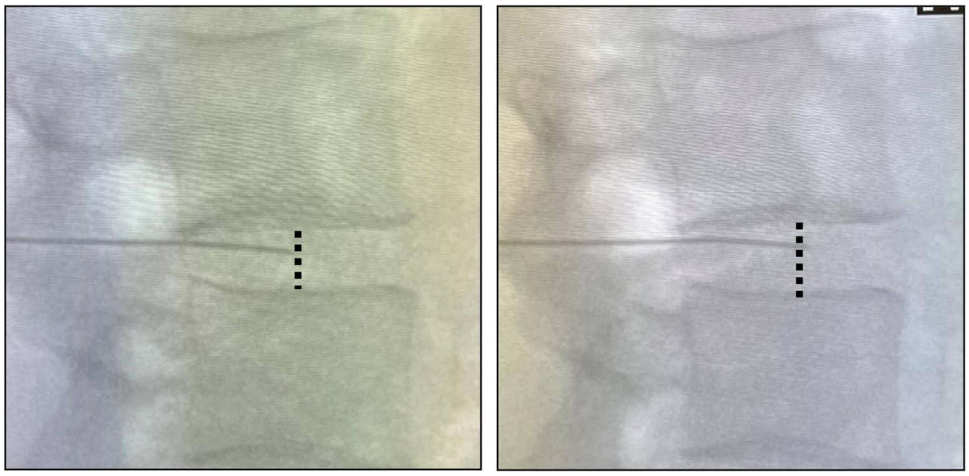


Figure 13 Lateral fluoroscopic views of the L3-4 intervertebral disc show the difference in disc height (dotted black line) before (left) and after (right) injection of allogeneic nucleus pulposis allograft.

Effectiveness at Six-Month Follow-Up

At the six-month assessment, patients demonstrated significant improvements in back pain severity, as measured by the NRS, and in functional disability, assessed using the ODI.[192] A clinically meaningful reduction in pain and disability was observed, with many patients surpassing the minimal clinically important difference (MCID) threshold of ≥ 30% improvement over baseline values. The results at this stage provided a foundation for an assessment of whether these benefits would persist or diminish over an extended period.

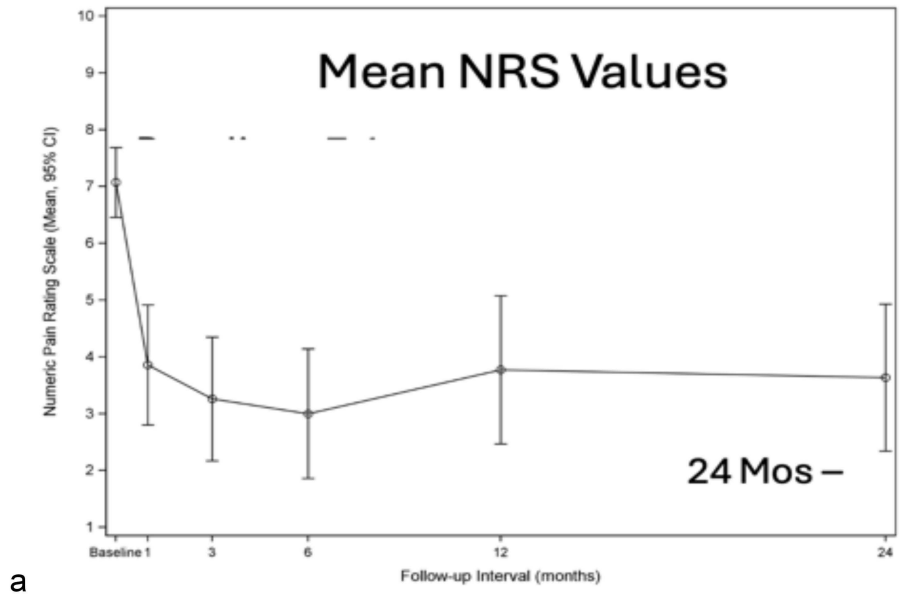
Patients reported an average reduction in NRS scores from 7.1 at baseline to 3.6 at twenty- four months, reflecting a statistically and clinically significant 49% improvement ($p<0.001$) (Figure 14a). Additionally, ODI scores demonstrated a 60% reduction, with nearly three-quarters of participants achieving MCID levels of functional improvement (Figure 14b). Notably, the percentage of patients reporting severe or crippled back impairment dropped from 82% at baseline to 18% at 24 months, further demonstrating the impact of the intervention. These findings are particularly important given that chronic low back pain is notoriously difficult to treat, and conventional non-surgical treatments often fail to provide sustained benefits.[199–201]

The initial clinical data presents robust evidence that NP allograft supplementation is a promising therapeutic approach for managing chronic lumbar discogenic pain. The consistent improvements in pain and function observed at 6, 12, and 24 months post-procedure highlight the durability and clinical relevance of this intervention. While additional research is needed to validate these findings in larger populations, the results suggest that allogeneic NP supplementation may play a crucial role in transforming the landscape of non-surgical spine care, providing a much-needed alternative for patients with treatment-resistant discogenic pain.

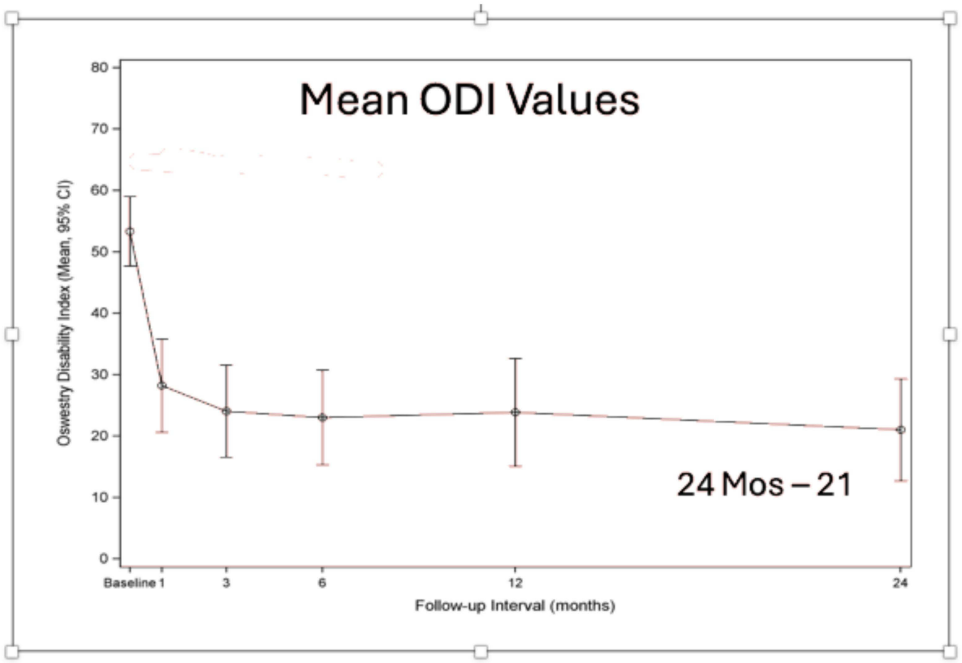
Discectomy

The role of discectomy in addressing intervertebral disc-related pain syndromes, including both posterior disc herniations and anterior vertebral column dysfunction, has garnered significant attention in the field of spinal surgery. Discectomy, a surgical procedure that involves the removal of part of the intervertebral disc, aims to alleviate pain by decompressing the affected nerve roots and restoring spinal function. This procedure is particularly indicated for patients whose symptoms are refractory to conservative treatment options. Literature suggests that discectomy can lead to substantial pain relief and improved functional outcomes in patients with herniated discs.[202,203] A study by Buttermann et al[202] showed increased motor function after microdiscectomy compared to patients treated with epidural steroid injections at one and three months post-operatively.

Furthermore, discectomy has been shown to be effective in alleviating radicular pain associated with herniated lumbar discs by directly addressing the mechanical compression of nerve roots faster than conservative care alone.[204] Weinstein



a



b

Figure 14 (**a**) Graph demonstrating mean longitudinal improvement of 43% in back pain severity scores to 24 months of follow-up (p<0.001). Mean NRS scores are 7.1 (baseline, n=28), 3.9 (1 month, n=28), 3.3 (3 months, n=27), 3.0 (6 months, n=28), 3.8 (12 months, n=22) and 3.6 (12 months, n=22). (**b**) Graph demonstrating mean improvement of 53% in back function scores through 12 months of follow-up (p<0.001). Mean ODI values are 53 (baseline, n=28), 28 (1 month, n=28), 24 (3 months, n=27), 23 (6 months, n=28), 24 (12 months, n=22) and 21 (24 months, n=22).

et al, in the SPORT trial, reported results of a prospective comparative study including 743 patients comparing surgical and medical/interventional treatment of lumbar intervertebral disc herniations.[204] The surgically treated group consisted of 528 patients and the medical/interventional group consisted of 191 patients. Outcomes were assessed for up to two years using SF-36, ODI, patient self-reported improvement, work status and satisfaction. At 3 months, patients in the surgical group had statistically significant improvement in measures of bodily pain, physical function and ODI.[204] The differences between the surgically treated group and those treated without surgical intervention narrowed at 2 years but remained statistically significant.

Studies suggest that surgical intervention for disc herniation prior to 6 months is associated with faster recovery and improved long-term outcomes.[205] Despite the positive outcomes associated with discectomy, it is essential to acknowledge the potential risks, such as infection, bleeding, and the development of recurrent disc herniation. Addressing these complications through comprehensive preoperative assessment and postoperative care strategies can mitigate risks and improve patient safety. Additionally, ongoing research into adjunct therapies, such as regenerative medicine approaches, aims to complement discectomy by promoting disc healing and enhancing long-term outcomes.

In summary, discectomy remains a pivotal intervention for managing intervertebral disc pain syndromes, especially in patients with persistent symptomatology despite conservative measures. While discectomy provides significant pain relief and functional improvement, careful patient selection and consideration of evolving techniques and adjunct therapies are crucial for optimizing outcomes in this patient demographic.

Endplate Treatments

The endplates form a continuous interface between the disc and the vertebral body and are composed of semi-porous cancellous bone and hyaline cartilage. This complex has a thickness of up to 0.8 mm. Painful endplate degenerative changes can include fissuring of the endplates with development of vascular granulation resulting in bone marrow edema (Modic type 1 lesions) and appearance of yellow fatty marrow that replaces the normal bone marrow (Modic type 2 lesions), both of which can result in chronic low back pain. The first MRI description of those changes and the correlation between the endplate MR signal change and low back pain was described by Michael Modic et al in 1988.[57] Three types of endplate signal change have been described; however, only Modic changes type 1 and type 2 have been associated with more severe back pain, higher levels of disability, worse outcomes, and increased healthcare costs.[206,207] The overall population prevalence of painful endplates is estimated at 5.8%,[206–208] representing a major cause of low back pain and disability.

Other painful endplate findings seen on imaging include: avulsions of the outer annulus at the attachment to the vertebral body rim; erosions of the cartilaginous endplate and/or underlying endplate bone; changes to the cartilage matrix (calcification, dehydration, and loss of matrix protein); fissuring and fracture of the bony endplate; herniation of the NP through the endplate (Schmorl's nodes) with disc depressurization; avulsion of the cartilage endplate at the inner annulus–endplate junction. The endplates' innervation and vascularity enter via the basivertebral foramen, a channel located along the mid to posterior portion of the vertebral body, equidistant between endplates. This foramen contains an artery, a vein, and a nerve (the basivertebral nerve).

The apex of this nerve, located just proximal to the halfway point from the posterior vertebral body wall to the anterior wall, branches out with neural arborization terminating adjacent to the endplate cartilage. This deep and posteriorly positioned neural apex leads to technical procedural challenges for interventionalists.

The pain arising from the basivertebral nerve is referred to as vertebrogenic pain, and distinguishing vertebrogenic from discogenic pain can be difficult clinically. Painful endplates are also highly associated with accelerated disc degeneration.[209–211] No current diagnostic test allows for reliable and complete differentiation between vertebrogenic and discogenic back pain, but MRI is the diagnostic modality of choice to differentiate these two causes of back pain with the identification of Modic changes as the primary indicator of vertebrogenic back pain.

Platelet-Rich Plasma (PRP)

As discussed previously, PRP is a concentrate of whole blood that is centrifuged to obtain plasma rich in platelets and growth factors. This concentrate contains numerous growth factors (PDGF, TGF-β, VEGF, EGF, FGF, IGF-1) that can be injected in various tissues to downregulate inflammatory mediators (IL-1, TNF-α) and upregulate anti-inflammatory effects providing the ability to decrease pain.[212–215] PRP also has also shown in-vitro evidence of tissue regeneration, with upregulation of proteoglycan synthesis, collagen synthesis, and reduced antiapoptotic effects, with fibrinogen acting as a scaffold.[216] However, no study to date has demonstrated macroscopic changes suggestive of in-vivo disc regeneration.

Various PRP preparation protocols have been described, with leucocyte-rich PRP (LR-PRP) and leucocyte-poor PRP (LP-PRP) being the two most common injectable concentrates. The addition of high-density fibrin networks to LR-PRP and LP-PRP is not commonly used for musculoskeletal or spine procedures. Most intradiscal injection protocols use 1–2 cc of PRP per disc.

Most of the anterior column pain PRP studies focus on discogenic back pain treated with intradiscal injections. A review of the current literature, including four randomized controlled trials and four observational studies, evaluated PRP in patients without Modic changes.[217–219] Systematic reviews and meta-analyses confirmed that PRP was effective in controlling pain, though without significant macroscopic disc healing evidence on imaging.[217] Only limited data exist evaluating PRP's efficacy in treating patients with vertebrogenic pain and/or Modic-type imaging phenotypes. Kawabata et al[155] reported two cases of painful Modic type 1 lesions in which LR-PRP injection reduced endplate edema on 24-week follow-up MRI. This was followed by a prospective pilot study of 10 patients with Modic type 1 vertebrogenic back pain, showing a significant VAS pain decrease (from 70.0 ± 13.3 to 39.0 ± 28.8), improved ODI and RMDQ scores, and reduced endplate T2-weighted signal intensity (from 10.1 to 7.90 mm^2) at 24 weeks. No adverse events were reported.

Early evidence from intraosseous PRP in knee osteoarthritis and subchondroplasty for osteonecrosis appears promising but intraosseous PRP applications for the treatment of painful vertebral endplates remain in the early stages of clinical development without a direct correlation to treat Modic type 1 degenerative endplate pathology at this time.[220] A single case report documented decrease in size of a disc herniation and a Schmorl's node following intraosseous and intradiscal LP-PRP injection with plasma-rich growth factors (PRGF-Endoret). Further studies are required to validate the clinical efficacy and radiologic outcomes of intradiscal and/or intraosseous PRP injections in patients with vertebrogenic pain and Modic type 1 degenerative changes.

Intradiscal Steroids

Intradiscal steroid injections aim to reduce pain and inflammation of the intervertebral disc and adjacent endplate regions. Prior data has demonstrated elevated levels of proinflammatory cytokines in degenerated discs contributing to nociception and disease progression. Seven randomized clinical trials have been published evaluating the performance of glucocorticoids in painful degenerated discs against control substances (bupivacaine, saline, lidocaine, or discography).[221–227] In the treatment group, both particulate and non-particulate glucocorticoids were used (methylprednisolone, betamethasone, dexamethasone). A meta-analysis of these studies demonstrated statistically significant improvements in pain (NRS) and function (ODI) compared to the control groups at early (<3 months) and intermediate (3–6 months) follow-up timepoints.[42] Outcomes were not statistically significant at long-term follow-up (≥6 months).

Interestingly, two studies demonstrated safe and effective use of intradiscal glucocorticoids in patients with discogenic or vertebrogenic back pain related to disc degeneration, with or without Modic type 1 changes.[224,227] Both groups benefited from steroid injections for an intermediate period of time (3–6 months).

A retrospective study of 66 patients who received intradiscal injections of steroids and local anesthetic for low back pain showed a statistically significant difference between the pre-injection and follow-up NRS scores ($p < 0.001$) and a significant difference between pre-injection and maximum relief NRS scores ($p < 0.001$). All patients had MRI findings of Modic type 1 or 2 changes and degenerative disc disease of grade 4 or above on the modified Pfirrmann scale. In addition to the significant reduction of low back pain at the time of follow-up (mean of 19.4 days), more than 71% of the patients met the MCID.[42] The authors concluded that for patients with chronic low back pain and Modic changes, intradiscal steroid injections provided significant short term pain relief. The safety profile of intradiscal steroids is excellent, with no serious adverse events reported.[228] Accelerated disc degeneration after intradiscal interventions and discograms has been a concern for decades ever since the introduction of provocative discography as a diagnostic test for discogenic back pain. However, a 7-year matched cohort study demonstrated that low-pressure provocative discography, using a protocol consistent with the Spine Intervention Society/International Association for the Study of Pain standards (≤3 mL intradiscal volume, ≤50 psi above opening pressure), does not cause accelerated disc degeneration.[229] In summary, intradiscal injection of glucocorticoids is a safe and effective treatment for up to 6 months in patients with Modic type 1 changes and is effective, at least in the short term for patients with both Modic type 1 and type 2 degenerative endplate changes. Symptoms may recur after six months and no study to date has demonstrated radiologic phenotype improvement of the Modic type 1 endplate but the data on this subject is still quite limited.

Basivertebral Nerve Ablation (BVNA)

The basivertebral nerve is a structure located within the mid to posterior portion of the vertebral body, equidistant between the endplates. The apex of this structure in the posterior portion of the vertebral body may be difficult to reach but can be accessed through specialized image-guided interventional techniques and curved access cannulas prior to ablation. Thermal destruction of the nerve plexus leads to pain reduction and functional improvement. Modic type 1 and 2 changes, alongside clinical evidence of vertebrogenic pain, remain the most relevant criteria for determining wether the patient is a candidate for BVNA.[230–232] Interest in BVNA has increased substantially in the past decade and is now considered an essential procedure in comprehensive pain practices.

A total of 41 articles has assessed BVNA for the treatment of vertebrogenic pain. Seventeen of these studies report patient-related outcomes, all showing significant improvement in VAS and/or ODI scores that are sustained over time. A 5-year aggregate paired dataset analysis from three prospective trials with similar inclusion criteria (SMART,[233] INTRACEPT,[234] CLBP prospective single-arm[235]) showed significant pain and functional improvement: mean pain score improved by 4.3 ± 2.5 points, and ODI improved by 28.0 ± 17.5 points. At five years, 33% of patients were pain-free, 68.7% resumed pre-CLBP activity levels, 65.2% discontinued opioids and spinal injections were decreased by 58.1%.[236] Although the overall safety profile is excellent, rare adverse events have been reported including transient motor/sensory deficits, incisional pain, nerve root injury, radiculopathy, and urinary retention. VCFs, particularly in elderly populations, occurred in 12% of cases.[97] These fractures may be underrecognized and seems to be associated with more advanced osteoporosis.[237] A separate multicenter study confirmed BVNA's safety and long-term durability, with high patient satisfaction. BVNA represents a paradigm shift in managing vertebrogenic chronic low back pain, with accumulating evidence supporting its efficacy and durability. Technical access challenges to the basivertebral nerve apex are being addressed with advanced interventional tools and techniques.

Mixed Pain Syndromes

Anterior Column Pain Coupled with Intermittent or Subacute Radicular Pain from Positional Disc Bulging

Anterior column pain may occur in isolation or exist in combination with radicular pain. The degenerative cascade begins with internal disc disruption and then disc herniation and/ or progressive degeneration that may create anterior column pain acutely, subacute or chronically. As previously discussed, this chronic low back pain related to DDD is often described as discogenic pain. The posterior annulus of the intervertebral disc is innervated with nociceptors from the sinuvertebral nerve that enters the disc via annular tears and may produce back pain or lead to a referred pattern of buttock or leg pain. A disc protrusion or extrusion may also cause an inflammatory response around the adjacent nerve root thus causing nociception in the distribution of that nerve which can result in both anterior column and radicular pain. This condition may persist from acute to subacute phases and can be treated with epidural steroid injections until the radicular pain component abates.

The anterior column pain may also respond to injection of epidural steroids, but the damage done to the disc may have initiated a degenerative sequence that results in disruption to the endplate with subsequent exposure to the vasculature within the vertebral body. This situation can result in a cascade of inflammatory cytokines and upregulation of nociceptors along the endplates with resulting pain signals that travel to the dorsal root ganglion via the basivertebral nerve and the more proximal sinuvertebral nerve afferently.[238]

As degeneration advances, anterior column pain may shift from discogenic (via sinuvertebral nerve) to vertebrogenic (via basivertebral nerve). Disc height may decrease as the degeneration continues and further cause irritation on the nerve roots in the foramina. Additional degeneration may lead to osteophyte formation, ligamentum flavum thickening and facet joint hypertrophy resulting in lateral recess stenosis causing intermittent radicular pain or leg weakness.[239]

The nonspecific innervation of the paravertebral autonomic neural plexus surrounding the lumbar vertebral bodies may contribute to referred pain patterns that mimic radicular pain. These nerves surround the lumbar vertebral bodies periosteum, annulus fibrosis, and anterior longitudinal ligament. These afferent sympathetic nerves may enter the sympathetic ganglia and transmit to the ventral ramus of the somatic spinal nerve by way of the gray rami communicants and then to the dorsal root ganglia before ascending up the spinal cord either by way of the dorsal horn or the lateral

spinothalamic tract. Activation of these nerves of the neural plexus may lead to nonspecific localization of pain. The pain may be referred to the somatic distribution of the spinal nerve where the impulse entered and result in referred pain to a distant area of the body. Thus, discogenic and vertebrogenic pain may naturally be anterior column pain with a referred radicular pain to the lower extremities or pain referred in a somatic pattern.[240]

Anterior Column Pain Coupled with Posterior Column Pain

The existence of both anterior and posterior vertebral column pain is a clinically common scenario in which physicians are faced with determining the primary pathology based on the patient presentation and symptoms. Without question, the care plan is predicated on the physicians' understanding of the differential pathology as well as a concise grasp of diagnostic strategies and an awareness of "red flag" concerns.[241,242] Anterior column pain is sourced predominantly from vertebrogenic pain and discogenic pain as well as pain emanating from supportive connective tissues (ie, longitudinal ligaments, etc). Posterior column pain is predominantly related to degenerative changes of the zygapophyseal joints, but pain may emanate from supportive connective tissues locally as well.[243–245]

Pain emanating from anterior column structures such as the vertebral bodies and intervertebral discs may present similarly in pattern and characteristics in the clinical setting, but choice of treatment is distinctly different especially when spinal stability is considered. When spinal instability is noted and when neurological compromise is present or imminent, spinal stabilization is indicated in most scenarios. Other diagnostic scenarios when arthrodesis is commonly indicated include scoliotic deformity, traumatic fracture or other sources of spinal instability that compromise the neural contents of the spine.

Autoimmune disorders, neoplasms and infections provide special circumstances that require tailored clinical judgment on a case-by-case scenario. Nonetheless, the prevailing standard of care in these scenarios is often spinal arthrodesis that may be done via the anterior or posterior approach.[246] Of note, cervical arthrodesis is done both anteriorly and posteriorly with the anterior cervical discectomy and fusion (ACDF), a commonly performed surgery. Thoracic fusion is mostly done using the posterior approach and the lumbar spine can be fused using the anterior, posterior, lateral and oblique approaches. The common techniques of fusion in the lumbar spine include an anterior lumbar interbody fusion (ALIF), a transforaminal lumbar interbody fusion (TLIF), and a lateral lumbar interbody fusion (LLIF). An extensive discussion of arthrodesis is beyond the scope of this manuscript but has been widely established by expert consensus.[247–249]

Vertebrogenic pain treatment is well documented in the case of fractures through vertebral augmentation as well as through basivertebral nerve ablation in the case of vertebrogenic pain emanating from the vertebral endplates in patients where the MR imaging study shows the presence of Modic changes. These scenarios are described earlier in this document.

Discogenic axial spine pain may arise from a variety of causes within the disc itself. Natural degenerative changes over time results in morphological changes exhibited on MRI and most commonly graded by the Pfirrman or modified Pfirrmann scale.[54,247–250] Interventional testing and diagnosis of discogenic back pain has been done with provocative and/or anesthetic discography, but the reliability of this technique remains not been well defined by high level clinical studies.[251,252] Discogenic low back pain and the physical evaluation and documentation of five main components of discogenic back pain have been recently described.[253] In addition, regenerative techniques such as the injection of MSCs, PRP, and allogenic NP are supported by a growing body of evidence.[253,254] In other cases, surgical intervention or spinal cord stimulation may serve as an alternative to intradiscal treatments.

Posterior column pain is most notably related to advancement of zygapophyseal joint disease (facet joint disease) as well as pain from closely associated structures such as myofascial sources and connective tissues. Patient history, direct visualization through advanced imaging and physical examination key points provide substrate for the diagnosis of facet related spinal pain. It is widely accepted, however, that the standard for diagnosis of facet pain is the use of diagnostic medial branch blocks or a combination of medial branch block and facet joint injection with local anesthetic.[255]

Development of spondylosis in the lumbar spine may be an isolated phenomenon, but more recently it has been recognized that multifidus degeneration may contribute to the progression of facet and disc degeneration.[256] Diagnosis of multifidus dysfunction is commonly done through the prone instability test, or the multifidus lift test and multifidus atrophy can be assessed through magnetic resonance imaging and graded accordingly.[257,258] Restorative stimulation through implanted peripheral neuromodulation leads overlying the medial portion of the third lumbar transfers processes has gained attention recently with treatment results contributing to the resolution of low back pain symptoms and multifidus dysfunction.[259,260]

Combined mixed anterior and posterior column pain commonly exists where degenerative processes are more advanced. As such, patients with multiple pain generators are well suited to undergo management through pharmacological options as well as through biomechanical treatments such as physical therapy. Both ventral and dorsal muscle strengthening and improvement in flexibility are paramount to sustain the integrity of the sagittal balance of the spine. When conservative measures have failed, minimally invasive choices provide a viable option in the absence of a well-founded surgical indication for arthrodesis. Physical exam findings and history should direct initial action, and preliminary diagnostic interventions may be chosen. In the case of axial loading symptoms, discography at the suspected levels of disc disease may be chosen, whereas in the case of physical exam findings consistent with facet joint pain, diagnostic medial branch blocks would be indicated. When cervical or thoracic disc disease is suspected as the primary cause of symptoms, there are more limited treatment options in these areas. Epidural steroid injections are often done although there is limited literature support for the use of epidural steroid injections in the absence of radicular pain. Intradiscal treatments of the thoracic and cervical spine are technically more difficult to perform and may necessitate learning new techniques or the referral to a center with this capability. When injections fail to produce symptom resolution cervical neuromodulation may be chosen for axial neck pain but there are no significant studies to support the use of neuromodulation for axial thoracic back pain related to the anterior column.

If a preponderance of pain exists in the anterior column following discography, intradiscal treatments are indicated. Spinal cord stimulation for discogenic pain is also a viable option as studies have shown the effectiveness of high frequency stimulation in cases of non- surgical low back pain. In the case of pain related to the posterior elements, radiofrequency rhizotomy of facet mediated pain is indicated for the cervical, thoracic and lumbar spine. In addition, there is strong evidence to support the use of peripheral neuromodulation for restorative therapy if multifidus dysfunction exists with or without the presence of facet mediated pain.[259,260]

Discogenic Pain with Persistent Spinal Pain Syndrome or Post-Laminectomy Pain Syndrome

Among the multiple etiologies of Persistent Spinal Pain Syndrome (PSPS) or Post-Laminectomy Pain Syndrome (PLPS), discogenic pain due to adjacent segment disease (ASD) with internal disc disruption and accelerated disc degeneration is a leading cause. Advanced interventional strategies have emerged to address this complex pathology, especially when conservative approaches fail.

Surgical intervention alters spine biomechanics, often accelerating degeneration at spinal levels adjacent to fusion, with an incidence of up to 26% of ASD after fusion surgery.[261] Approximately one-quarter to one-third of adjacent segment disc degeneration cases progress to ASD. The true rate of adjacent segment disc degeneration and disc-related ASD remains unclear, as many studies use only disc height loss on radiographs as a proxy for disc degeneration. Disc height reduction, however, is a late-stage radiological finding, while painful discs may maintain normal height.

Moreover, adjacent disc degeneration, epidural scarring, nerve root compression, and pain pathway sensitization contribute to chronic pain in ASD. Interventions described for discogenic or vertebrogenic back pain (eg, PRP, stem cell therapy, corticosteroid injection, BVNA) may be considered, but PSPS and PLPS often require multimodal treatment strategies.

Vertebral Compression Fracture Treatment

VCFs demonstrate a bimodal distribution, with younger patients sustaining these injuries secondary to high-energy mechanisms.[262] The most common etiology of compression fractures, however, is osteoporosis.[262] They often occur at the midthoracic (T7 to T8) spine and the thoracolumbar junction (T12 to L1). Functional impairment from compression fractures is often comparable with that related to hip fracture.[263,264]

Height loss from osteoporosis is typically asymptomatic and gradual. In addition to osteoporotic compression fractures, height loss can be caused by disc desiccation and resultant disc space narrowing or scoliosis.[265,266] In one study, height loss of more than six centimeters had a specificity and sensitivity of ninety-four and thirty percent, respectively, for the detection of a compression fracture.[267] Kyphosis is often an indicator of multiple vertebral compression fractures, especially wedge fractures. It may, however, occur independently of vertebral abnormalities. Each complete compression fracture causes approximately one centimeter or more loss in height. Loss of more than four cm in height can be associated with as much as fifteen degrees of kyphosis.[268]

A history of a previous compression fracture is a risk factor for subsequent fractures. Approximately nineteen percent of patients who have a vertebral compression fracture will have another fracture in the next year.[269] In one analysis of the literature, women with preexisting vertebral fractures had approximately four times greater risk of subsequent vertebral fractures than women without prior fractures.[270] The presence of VCFs also predicts future nonvertebral fractures, particularly hip fractures. This risk increases with the number and severity of prior fractures.[271]

From a radiographic standpoint, characteristics of compression fractures include vertebral endplate irregularity, general demineralization, and anterior wedging of one or more vertebrae with vertebral collapse.[271] The presence of posterior wedging is uncommon. If present, it may indicate an underlying destructive lesion. One can assess the severity of vertebral fractures by way of radiographic staging. The most commonly used grading criteria used in epidemiology studies and clinical trials is Genant's semi-quantitative (GSQ) criteria that divides the vertebral body deformity into four grades with Grade 0 categorized as no deformity.[272] A Grade 1 compression fracture would result in a 20–25% height deformity, while Grade 2 and 3 compression fractures cause a 25–40% and > 40% height deformity, respectively.[272]

Both vertebroplasty and kyphoplasty involve the percutaneous injection of bone cement under image guidance into a fractured vertebra. During kyphoplasty, inflatable bone tamps are placed into the fractured vertebral body to create a cavity in which bone cement is placed to reduce the fracture and thus to improve kyphotic deformity.[273] The optimal timing of the vertebral augmentation procedures related to fracture acuity is unclear and should be based on the patients symptoms rather than an arbitrary designation of time.[274] The potential short-term benefit of both procedures is improvement in pain. The long-term benefits include improved functional capability, prevention of recurrent pain at the treated level, avoidance of prolonged medication use, and the limitation or reversal of height loss and spinal deformity and decreased mortality.

Patient selection is a critical factor for both the decision to perform vertebral augmentation and the selection of the type of procedure. Vertebral augmentation is not indicated for those patients with mild to moderate pain that responds to medical management.[275] Those patients with incapacitating pain who are unable to taper parenteral opioids and those who are not improving with or are intolerant of oral opioids are good candidates for vertebral augmentation.[276]

Kyphoplasty is generally performed more frequently than vertebroplasty.[277] Vertebroplasty is performed when there is little to no compression of the vertebral body, but MRI shows bone marrow edema consistent with fracture. Kyphoplasty relies on the use of a balloon tamponade system that may partially restore vertebral height. Vertebroplasty, on the other hand, takes less time to perform, does not rely on the performance of a balloon system, and is less expensive.

Three meta-analyses examined the best quality data and have come to very similar conclusions.[278–280] They all show that KP and VP are significantly better than nonsurgical management (NSM) for improving patients pain and function and that KP has comparatively better than VP at improving pain and function.[264] Comparing effects of kyphoplasty, vertebroplasty, and nonsurgical management in a systematic review of randomized and non-randomized controlled studies.

When comparing efficacy and safety of vertebroplasty versus sham treatment, VERTOS V, VOPE, and the VAPOUR trial and other randomized control trials (RCTs) demonstrated that VP significantly reduces pain and improves quality of life over active control (anesthetic infiltration) in subacute and chronic OVCFs.[281,282] These trials have added clarity to the efficacy of VP since the 2009 sham trials published in the New England Journal of Medicine.

The data comparing KP versus NSM shows that KP provides statistically significantly better pain relief, functional improvement, and lower complication rates (1.72% vs 15.5%) compared to NSM.[283–286]

The third generation implant augmentation has been developed since the advent of balloon KP and has shown promise for treating patients with more challenging VCFs. Devices such as the SpineJack have been shown to improve vertebral height and sagittal balance with promising pain and functional outcomes and the ability to decrease the number of additional and adjacent level fractures.

In summary, vertebral augmentation, including vertebroplasty, balloon kyphoplasty, and implant augmentation, is an effective and safe treatment for back pain due to osteoporotic vertebral compression fractures. It provides rapid pain relief, functional recovery, and a mortality benefit when performed timely, aligning with evidence-based care pathways for osteoporotic VCFs.

Advanced Treatments

Percutaneous Cement Discoplasty (PCD)

In cases of severely degenerated adjacent-level discs, PCD has been used worldwide. Polymethyl methacrylate (PMMA) has been applied as a stand-alone intervertebral spacer in elderly patients with severe spondylosis, vertical instability, dynamic foraminal stenosis, and multiple comorbidities precluding surgical intervention.[284–286] Severe spondylosis is an important hallmark to recognize as condition that may warrant the consideration of PCD.

This condition is characterized by disc narrowing, vacuum phenomenon, fissuring, endplate erosions, and reactive vertebral changes (ie Modic changes). Those findings contribute to instability and dynamic central canal and foraminal stenosis. Injecting PMMA into vacuum discs increases stability and decompresses the central canal and foramina indirectly. In well-selected patients with severe spondylosis and dynamic stenosis the clinical outcomes of PCD are excellent.

Biomechanical studies have confirmed that PCD enhances foraminal dimensions while preserving motion. It improves flexion-extension and lateral bending stability.[284–286] A recent safety analysis of 344 patients treated with PCD reported a 30.4% cement leakage rate which is similar to that seen in vertebral augmentation. Most leaks were asymptomatic and only 1.2% resulted in motor deficits.[284–286] Twelve clinical series and four meta-analyses support PCD for patients unable to undergo surgery, citing short recovery, brief hospitalization and an acceptable safety profile.

Epidural Adhesiolysis

In patients with epidural fibrosis or discogenic pain from PSPS/PLPS, percutaneous epidural adhesiolysis can be effective.[287] This procedure targets ventral epidural fibrosis using catheter-guided injection of contrast, steroids, hypertonic saline, and hyaluronidase. Level I evidence and strong recommendations support its use in patients with failed conservative and epidural injection therapies.

Spinal Cord Stimulation (SCS)

SCS is a well-established treatment for PSPS and PLPS, and growing evidence supports its role in treating discogenic pain. By modulating dorsal column and dorsal horn activity, SCS reduces neuropathic and mixed axial pain. A systematic review confirmed significant VAS and ODI improvements with SCS.[288] The SENZA-RCT and additional subsequent studies showed that 10 kHz high-frequency stimulation offers additional benefit and significant pain relief for axial low back and leg pain. Intrathecal Drug Delivery Systems (IDDS) IDDS is an essential technology to manage intractable pain in PSPS/PLPS. Medications such as hydromorphone and bupivacaine reduce pain, and the overall amount of opioids used. Though dose escalation is observed, it occurs at a slower rate than historically reported for patients taking systemic opioids. Other drugs such as morphine, clonidine, fentanyl and ziconotide can be used intrathecally to manage intractable pain. A rigorous trialing and implant algorithm is critical to optimizing outcomes when utilizing this therapy.

Conclusions

Intradiscal and vertebrogenic sources of pain are now well established clinically as significant pain generators in patients suffering from chronic low back pain. Heretofore, the lack of available treatment options has led to less emphasis on anterior column pain generators and a concomitant lack of awareness of these entities as targets for treatment. It will be incumbent upon any practitioner treating these patients to become conversant in the anatomy, biophysics and imaging of both normal and pathologic segments. Further, in this rapidly evolving area of treatment, understanding the entirety of the FSU and interplay of the anterior, middle and posterior columns and how they interact will be key to practicing cutting edge evidence-based spinal medicine.

Acknowledgments

Financial support for this work was provided, in part, by Vivex Biologics (Miami, FL, USA). The authors appreciate the thorough review by Jon E. Block, Ph.D. and the manuscript preparation by Malahki Thorn. Hamzah A. Ramawad M.D contributed the original illustrations in Figures 1a and 1b and 2b.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The following Authors have no relevant conflicts of interest for this work: Jacob Fleming, Mark Malinowski, Rose Garcia, Anuj Shah, Hamzah Ramawad, Iden Cowan, Kristin Jarzombek, Kas Amirdelfin, Marcin Karcz, Kas, Brian Durkin, Matthew Green. Jay Grider: Original Shares in Spinal Simplicity and on original Medical Advisory for Interalink Spine purchased by Spinal Simplicity. Timothy Deer: Relevant conflicts: Consultant for Vivex. Consultant for Spinal Simplicity. Douglas Beall: Relevant conflicts: Consultant/Receipt of grants/research supports: ReGelTec, Orthoson, Vivex, Discgenics, Mesoblast, Discure, Tissue Tech, Smart Soft, Medtronic, Merit Medical, Johnson & Johnson, IZI, Techlamed, Peterson Enterprises, Medical Metrics, Avanos, Boston Scientific, Simplify Medical, Stryker, Lenoss Medical, Piramal, Nanofuse, Spinal Simplicity, Spark Biomedical, Bronx Medical, Smart Soft, RayShield, Stayble, Thermaquil, Vivex, Stratus Medical, Genesys, Abbott, Eliquence, SetBone Medical, Amber Implants, Cerapedics, Neurovasis, Spine Biopharma; Receipt of honoraria or consultation fees: ReGelTec, Vivex, Mesoblast, Discure; Research Funding: ReGelTec, Orthoson, Vivex, Discgenics, Mesoblast, Discure, Tissue Tech, Spine Biopharma, Kolon TissueGene. Melissa Murphy: Medtronic: speaking, consulting, research. Pacira Biosciences: speaking, consulting, research, Nervonik: advisory board, stockholders. Steven Falowski: Consultant-Abbott Shiratronics, Medtronic Saluda CornerLoc Equity-BackStop, Neural, SurgenTec, SynerFuse, Aurora Spine, Thermaquil, SPR Therapeutics, Saluda CornerLoc, PainTeq, Celeri. Nasir Khatri: Abbott, Brixton Biosciences (research grant only) Nalu (research grant only), Nevro/Globus, Saluda, Spinal Simplicity, SPR Therapeutics, WISE Srl. Mateusz Graca: Consultant for ViaDIsc and VIVEX Biologics. Jordan Tate: ReGeltec Research Grant, Saluda- Consultant, Research Grant, Commercial Advisory Board, Medtronic- Consultant, Stimwave- Consultant, Vertos- Consultant, Nevro- Consultant, Research Grants, Commercial Advisory Board, Styker- Consultant, Lab Faculty, Curonix- Consultant, Lab Faculty, Mainstay- Consultant, Research Grant, Lab Faculty, Vivex- Consultant, Research Grants, Abbott -Consultant, Lab Faculty, PainTeq -Consultant, Commercial Advisory Board. Usman Latif: is a consultant for Abbott, Brixton Biosciences, InFormed Consent, Nalu, Nevro, Saluda Medical, Spinal Simplicity, SPR, Stryker, Vertex Pharmaceuticals, Vertos Medical, Vivex Biologics, and WISE; an advisory board member for Abbott, InFormed Consent, Nalu, Nevro, Saluda Medical, Spinal Simplicity, Vertos Medical, and Vivex Biologics; has funded research with Mainstay Medical, Nalu, Spinal Simplicity, and Vivex Biologics; and has stock or stock options with InFormed Consent and Spinal Simplicity. Chau Vu: is a consultant for Saluda Medical and PainTEQ. Christopher Mallard: Medtronic grant recipient paid to the university and consulting fees for Johnson & Johnson. Kaku Barkoh: XoBiologix, Abbott, Spinal Simplicity, Intrinsic Therapeutics, Kuros Biosciences. Anne Christopher: Paid consultant Abbott, SI Bone, Boston Scientific. Michael Harned: Medtronic grant recipient paid to university. Raj Patel: is a consultant for Vivex. Tim Davis: consulting fees from Abbott, Boston Scientific, Biotronik; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott, Boston Scientific, Biotronik, research support from Vivex, Mesoblast, Spine Biopharma, Biorestorative Therapies, and SI BONE, outside the submitted work. Olivier Clerk-Lamalice: reports personal fees from Stryker, Medical Metrics, stocks/options from Regeltec, SpinaFx, and Beam Medical, outside the submitted work. Brian Durkin: reports personal fees from Boston Scientific, outside the submitted work. Dagmar Gross: reports personal fees from ReGelTec, outside the submitted work. Mark Malinowski: reports personal fees from Abbott, Biotronik and Nevro, outside the submitted work. Tom Hedman: an employee of Spinal Simplicity. He also reports intralink formulation patent issued to Spinal Simplicity LLC. Michael Dorsi: Biotronik, Abbott, Globus, Saluda, Painteq, Ferring, Stryker. Dawood Sayed: consultant for PainTeq, Abbott, Mainstay, Saluda and Surgentec. The authors report no other conflicts of interest in this work.

References

1. Koeller W, Funke F, Hartmann F. Biomechanical behavior of human intervertebral discs subjected to long lasting axial loading. *Biorheology*. 1984;21(5):675–686. doi:10.3233/bir-1984-21502
2. Crock HV. A reappraisal of intervertebral disc lesions. *Med J Aust*. 1970;1(20):983–989. doi:10.5694/j.1326-5377.1970.tb116676.x
3. Andersson GB, Mekhail NA, Block JE. Treatment of intractable discogenic low back pain. A systematic review of spinal fusion and intradiscal electrothermal therapy (IDET). *Pain Physician*. 2006;9(3):237–248.
4. Zhao Y, Dong H, Xia Q, et al. A new strategy for intervertebral disc regeneration: the synergistic potential of mesenchymal stem cells and their extracellular vesicles with hydrogel scaffolds. *Biomed Pharmacother*. 2024;172:116238. doi:10.1016/j.biopha.2024.116238
5. Roberts S, Menage J, Urban JP. Biochemical and structural properties of the cartilage end-plate and its relation to the intervertebral disc. *Spine*. 1989;14(2):166–174. doi:10.1097/00007632-198902000-00005
6. De Geer CM. Intervertebral disk nutrients and transport mechanisms in relation to disk degeneration: a narrative literature review. *J Chiropr Med*. 2018;17(2):97–105. doi:10.1016/j.jcm.2017.11.006
7. Nedresky D, Reddy V, Singh G. Anatomy, back, nucleus pulposus. *StatPearls*. Treasure Island (FL) ineligible companies. Disclosure: vamsi Reddy declares no relevant financial relationships with ineligible companies. Disclosure: Gurdeep Singh declares no relevant financial relationships with ineligible companies; 2025.
8. Marchand F, Ahmed AM. Investigation of the laminate structure of lumbar disc anulus fibrosus. *Spine*. 1990;15(5):402–410. doi:10.1097/00007632-199005000-00011
9. Fearing BV, Hernandez PA, Setton LA, Chahine NO. Mechanotransduction and cell biomechanics of the intervertebral disc. *JOR Spine*. 2018;1(3). doi:10.1002/jsp2.1026
10. Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. *Pain Pract*. 2008;8(1):18–44. doi:10.1111/j.1533-2500.2007.00171.x
11. Brown S, Rodrigues S, Sharp C, et al. Staying connected: structural integration at the intervertebral disc-vertebra interface of human lumbar spines. *Eur Spine J*. 2017;26(1):248–258. doi:10.1007/s00586-016-4560-y
12. Urban JP, Roberts S. Degeneration of the intervertebral disc. *Arthritis Res Ther*. 2003;5(3):120–130. doi:10.1186/ar629
13. Urban JPG, Fairbank JCT. Current perspectives on the role of biomechanical loading and genetics in development of disc degeneration and low back pain; a narrative review. *J Biomech*. 2020;102:109573. doi:10.1016/j.jbiomech.2019.109573
14. Galbusera F, van Rijsbergen M, Ito K, Huyghe JM, Brayda-Bruno M, Wilke HJ. Ageing and degenerative changes of the intervertebral disc and their impact on spinal flexibility. *Eur Spine J*. 2014;23 Suppl 3:S324–S332.
15. Newell N, Little JP, Christou A, Adams MA, Adam CJ, Masouros SD. Biomechanics of the human intervertebral disc: a review of testing techniques and results. *J Mech Behav Biomed Mater*. 2017;69:420–434. doi:10.1016/j.jmbbm.2017.01.037
16. Setton LA, Chen J. Mechanobiology of the intervertebral disc and relevance to disc degeneration. *J Bone Joint Surg Am*. 2006;88(Suppl 2):52–57. doi:10.2106/JBJS.F.00001
17. Walker MH, Anderson DG. Molecular basis of intervertebral disc degeneration. *Spine J*. 2004;4(6 Suppl):158S–166S. doi:10.1016/j.spinee.2004.07.010
18. Vergroesen PP, Kingma I, Emanuel KS, et al. Mechanics and biology in intervertebral disc degeneration: a vicious circle. *Osteoarthritis Cartilage*. 2015;23(7):1057–1070. doi:10.1016/j.joca.2015.03.028
19. Eyre DR, Muir H. Quantitative analysis of types I and II collagens in human intervertebral discs at various ages. *Biochim Biophys Acta*. 1977;492(1):29–42. doi:10.1016/0005-2795(77)90211-2
20. Bibby SR, Jones DA, Lee RB, Yu J, Urban JPG. The pathophysiology of the intervertebral disc. *Joint Bone Spine*. 2001;68(6):537–542. doi:10.1016/S1297-319X(01)00332-3
21. Lipson SJ, Muir H. Volvo award in basic science. Proteoglycans in experimental intervertebral disc degeneration. *Spine*. 1981;6(3):194–210. doi:10.1097/00007632-198105000-00002
22. Lipson SJ, Muir H. Experimental intervertebral disc degeneration: morphologic and proteoglycan changes over time. *Arthritis Rheum*. 1981;24(1):12–21. doi:10.1002/art.1780240103
23. Tavakoli J, Elliott DM, Costi JJ. Structure and mechanical function of the inter-lamellar matrix of the annulus fibrosus in the disc. *J Orthop Res*. 2016;34(8):1307–1315. doi:10.1002/jor.23306
24. Ushiki T. Collagen fibers, reticular fibers and elastic fibers. A comprehensive understanding from a morphological viewpoint. *Arch Histol Cytol*. 2002;65(2):109–126. doi:10.1679/aohc.65.109
25. Cyril D, Giugni A, Bangar SS, et al. Elastic fibers in the intervertebral disc: from form to function and toward regeneration. *Int J Mol Sci*. 2022;23(16):8931. doi:10.3390/ijms23168931
26. Tavakoli J, Diwan AD, Tipper JL. The ultrastructural organization of elastic fibers at the interface of the nucleus and annulus of the intervertebral disk. *Acta Biomater*. 2020;114:323–332. doi:10.1016/j.actbio.2020.07.021
27. Schmidt H, Reitmaier S, Graichen F, Shirazi-Adl A. Review of the fluid flow within intervertebral discs - how could in vitro measurements replicate in vivo? *J Biomech*. 2016;49(14):3133–3146. doi:10.1016/j.jbiomech.2016.09.007
28. Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE. New in vivo measurements of pressures in the intervertebral disc in daily life. *Spine*. 1999;24(8):755–762. doi:10.1097/00007632-199904150-00005
29. Groh AMR, Fournier DE, Battie MC, Seguin CA. Innervation of the human intervertebral disc: a scoping review. *Pain Med*. 2021;22(6):1281–1304. doi:10.1093/pm/pnab070
30. Waxenbaum JA, Reddy V, Futterman B. Anatomy, back, intervertebral discs. *StatPearls*. Treasure Island (FL) ineligible companies. Disclosure: Vamsi Reddy declares no relevant financial relationships with ineligible companies. Disclosure: Bennett Futterman declares no relevant financial relationships with ineligible companies. 2025.
31. Shirazi-Adl A, Taheri M, Urban JP. Analysis of cell viability in intervertebral disc: effect of endplate permeability on cell population. *J Biomech*. 2010;43(7):1330–1336. doi:10.1016/j.jbiomech.2010.01.023
32. Mohd Isa IL, Teoh SL, Mohd Nor NH, Mokhtar SA. Discogenic low back pain: anatomy, pathophysiology and treatments of intervertebral disc degeneration. *Int J Mol Sci*. 2022;24(1):208. doi:10.3390/ijms24010208

33. Ashton IK, Roberts S, Jaffray DC, Polak JM, Eisenstein SM. Neuropeptides in the human intervertebral disc. *J Orthop Res*. 1994;12(2):186–192. doi:10.1002/jor.1100120206
34. Brown MF, Hukkanen MV, McCarthy ID, et al. Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. *J Bone Joint Surg Br*. 1997;79(1):147–153. doi:10.1302/0301-620X.79B1.0790147
35. Coppes MH, Marani E, Thomeer RT, Groen GJ. Innervation of "painful" lumbar discs. *Spine*. 1997;22(20):2342–2349. doi:10.1097/00007632-199710150-00005
36. Freemont AJ, Peacock TE, Goupille P, Hoyland JA, O'Brien J, Jayson MI. Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet*. 1997;350(9072):178–181. doi:10.1016/S0140-6736(97)02135-1
37. Kokubo Y, Uchida K, Kobayashi S, et al. Herniated and spondylotic intervertebral discs of the human cervical spine: histological and immunohistological findings in 500 en bloc surgical samples. Laboratory investigation. *J Neurosurg Spine*. 2008;9(3):285–295. doi:10.3171/SPI/2008/9/9/285
38. Palmgren T, Gronblad M, Virri J, Kaapa E, Karaharju E. An immunohistochemical study of nerve structures in the anulus fibrosus of human normal lumbar intervertebral discs. *Spine*. 1999;24(20):2075–2079. doi:10.1097/00007632-199910150-00002
39. Roberts S, Eisenstein SM, Menage J, Evans EH, Ashton IK. Mechanoreceptors in intervertebral discs. Morphology, distribution, and neuropeptides. *Spine*. 1995;20(24):2645–2651. doi:10.1097/00007632-199512150-00005
40. Hutton MJ, Bayer JH, Powell JM. Modic vertebral body changes: the natural history as assessed by consecutive magnetic resonance imaging. *Spine*. 2011;36(26):2304–2307. doi:10.1097/BRS.0b013e31821604b6
41. Gornet MG, Peacock J, Ryken T, Schranck FW, Eastlack RK, Lotz JC. Establishing a gold standard for noninvasive identification of painful lumbar discs: prospective comparison of magnetic resonance spectroscopy vs low-pressure provocation discography. *Int J Spine Surg*. 2024;18(1):91–100. doi:10.14444/8574
42. Marcus JL, Westerhaus BD, Fleming J, et al. Intradiscal steroid injections for degenerative disc disease with Modic changes: a retrospective study of therapeutic and diagnostic features. *Cureus*. 2024;16(4):e58333. doi:10.7759/cureus.58333
43. Stretanski MF, Vu L. Fluoroscopy discography assessment, protocols, and interpretation. *StatPearls*. Treasure Island (FL) ineligible companies. Disclosure: ly Vu declares no relevant financial relationships with ineligible companies. 2025.
44. Pobiel RS, Schellhas KP, Pollei SR, Johnson BA, Golden MJ, Eklund JA. Diskography: infectious complications from a series of 12,634 cases. *AJNR Am J Neuroradiol*. 2006;27(9):1930–1932.
45. Willems PC, Jacobs W, Duinkerke ES, De Kleuver M. Lumbar discography: should we use prophylactic antibiotics? A study of 435 consecutive discograms and a systematic review of the literature. *J Spinal Disord Tech*. 2004;17(3):243–247. doi:10.1097/00024720-200406000-00013
46. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino J, Herzog R. 2009 ISSLS prize winner: does discography cause accelerated progression of degeneration changes in the lumbar disc. *Spine*. 2009;34(21):2338–2345. doi:10.1097/BRS.0b013e3181ab5432
47. Inoue H. Three-dimensional architecture of lumbar intervertebral discs. *Spine*. 1981;6(2):139–146. doi:10.1097/00007632-198103000-00006
48. Eyre DR, Muir H. Types I and II collagens in intervertebral disc. Interchanging radial distributions in annulus fibrosus. *Biochem J*. 1976;157(1):267–270. doi:10.1042/bj1570267
49. Antoniou J, Steffen T, Nelson F, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. *J Clin Invest*. 1996;98(4):996–1003. doi:10.1172/JCI118884
50. Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine*. 1995;20(11):1307–1314. doi:10.1097/00007632-199506000-00022
51. Fardon DF, Williams AL, Dohring EJ, Murtagh FR, Gabriel Rothman SL, Sze GK. Lumbar disc nomenclature: version 2.0: recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. *Spine J*. 2014;14(11):2525–2545. doi:10.1016/j.spinee.2014.04.022
52. Ito M, Incorvaia KM, Yu SF, Fredrickson BE, Yuan HA, Rosenbaum AE. Predictive signs of discogenic lumbar pain on magnetic resonance imaging with discography correlation. *Spine*. 1998;23(11):1252–1258. doi:10.1097/00007632-199806010-00016
53. Nordberg CL, Boesen M, Fournier GL, Bliddal H, Hansen P, Hansen BB. Positional changes in lumbar disc herniation during standing or lumbar extension: a cross-sectional weight-bearing MRI study. *Eur Radiol*. 2021;31(2):804–812. doi:10.1007/s00330-020-07132-w
54. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine*. 2001;26(17):1873–1878. doi:10.1097/00007632-200109010-00011
55. Quinnell RC, Stockdale HR, Harmon B. Pressure standardized lumbar discography. *Br J Radiol*. 1980;53(635):1031–1036. doi:10.1259/0007-1285-53-635-1031
56. Sachs BL, Vanharanta H, Spivey MA, et al. Dallas discogram description. A new classification of CT/discography in low-back disorders. *Spine*. 1987;12(3):287–294. doi:10.1097/00007632-198704000-00018
57. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166(1 Pt 1):193–199. doi:10.1148/radiology.166.1.3336678
58. Tonosu J, Oka H, Higashikawa A, Okazaki H, Tanaka S, Matsudaira K. The associations between magnetic resonance imaging findings and low back pain: a 10-year longitudinal analysis. *PLoS One*. 2017;12(11):e0188057. doi:10.1371/journal.pone.0188057
59. Schiebler ML, Camerino VJ, Fallon MD, Zlatkin MB, Grenier N, Kressel HY. In vivo and ex vivo magnetic resonance imaging evaluation of early disc degeneration with histopathologic correlation. *Spine*. 1991;16(6):635–640. doi:10.1097/00007632-199106000-00007
60. Tertti M, Paajanen H, Laato M, Aho H, Komu M, Kormano M. Disc degeneration in magnetic resonance imaging. A comparative biochemical, histologic, and radiologic study in cadaver spines. *Spine*. 1991;16(6):629–634. doi:10.1097/00007632-199106000-00006
61. Griffith JF, Wang YX, Antonio GE, et al. Modified Pfirrmann grading system for lumbar intervertebral disc degeneration. *Spine*. 2007;32(24):E708–712. doi:10.1097/BRS.0b013e31815a59a0
62. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. *Eur Spine J*. 2016;25(11):3723–3734. doi:10.1007/s00586-016-4459-7
63. Scarcia L, Pileggi M, Camilli A, et al. Degenerative disc disease of the spine: from anatomy to pathophysiology and radiological appearance, with morphological and functional considerations. *J Pers Med*. 2022;12(11):1810. doi:10.3390/jpm12111810
64. Kirnaz S, Capadona C, Wong T, et al. Fundamentals of intervertebral disc degeneration. *World Neurosurg*. 2022;157:264–273. doi:10.1016/j.wneu.2021.09.066

65. Williams FM, Bansal AT, van Meurs JB, et al. Novel genetic variants associated with lumbar disc degeneration in Northern Europeans: a meta-analysis of 4600 subjects. *Ann Rheum Dis*. 2013;72(7):1141–1148. doi:10.1136/annrheumdis-2012-201551
66. Purmessur D, Cornejo MC, Cho SK, Hecht AC, Iatridis JC. Notochordal cell-derived therapeutic strategies for discogenic back pain. *Global Spine J*. 2013;3(3):201–218. doi:10.1055/s-0033-1350053
67. Desmoulin GT, Pradhan V, Milner TE. Mechanical aspects of intervertebral disc injury and implications on biomechanics. *Spine*. 2020;45(8): E457–E464. doi:10.1097/BRS.0000000000003291
68. Virk S, Meyers KN, Lafage V, Maher SA, Chen T. Analysis of the influence of species, intervertebral disc height and Pfirrmann classification on failure load of an injured disc using a novel disc herniation model. *Spine J*. 2021;21(4):698–707. doi:10.1016/j.spinee.2020.10.030
69. Lama P, Le Maitre CL, Harding IJ, Dolan P, Adams MA. Nerves and blood vessels in degenerated intervertebral discs are confined to physically disrupted tissue. *J Anat*. 2018;233(1):86–97. doi:10.1111/joa.12817
70. Fine N, Lively S, Seguin CA, Perruccio AV, Kapoor M, Rampersaud R. Intervertebral disc degeneration and osteoarthritis: a common molecular disease spectrum. *Nat Rev Rheumatol*. 2023;19(3):136–152. doi:10.1038/s41584-022-00888-z
71. Kirkaldy-Willis WH, Wedge JH, Yong-Hing K, Reilly J. Pathology and pathogenesis of lumbar spondylosis and stenosis. *Spine*. 1978;3 (4):319–328. doi:10.1097/00007632-197812000-00004
72. Bashkuev M, Reitmaier S, Schmidt H. Relationship between intervertebral disc and facet joint degeneration: a probabilistic finite element model study. *J Biomech*. 2020;102:109518. doi:10.1016/j.jbiomech.2019.109518
73. Huang B, Liu J, Wei X, et al. Damage to the human lumbar cartilage endplate and its clinical implications. *J Anat*. 2021;238(2):338–348. doi:10.1111/joa.13321
74. Zhang YH, Zhao CQ, Jiang LS, Chen XD, Dai LY. Modic changes: a systematic review of the literature. *Eur Spine J*. 2008;17(10):1289–1299. doi:10.1007/s00586-008-0758-y
75. Udby PM, Samartzis D, Carreon LY, Andersen MO, Karppinen J, Modic M. A definition and clinical grading of Modic changes. *J Orthop Res*. 2022;40(2):301–307. doi:10.1002/jor.25240
76. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? *Spine*. 2006;31(18):2151–2161. doi:10.1097/01.brs.0000231761.73859.2c
77. Kushchayev SV, Glushko T, Jarraya M, et al. ABCs of the degenerative spine. *Insights Imaging*. 2018;9(2):253–274. doi:10.1007/s13244-017-0584-z
78. Freemont AJ, Watkins A, Le Maitre C, et al. Nerve growth factor expression and innervation of the painful intervertebral disc. *J Pathol*. 2002;197(3):286–292. doi:10.1002/path.1108
79. Peng B, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br*. 2005;87(1):62–67. doi:10.1302/0301-620X.87B1.15708
80. Chen C, Cavanaugh JM, Song Z, Takebayashi T, Kallakuri S, Wooley PH. Effects of nucleus pulposus on nerve root neural activity, mechanosensitivity, axonal morphology, and sodium channel expression. *Spine*. 2004;29(1):17–25. doi:10.1097/01.BRS.0000096675.01484.87
81. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: state-of-the-art review. *Pain Med*. 2013;14(6):813–836. doi:10.1111/pme.12082
82. Bogduk N, Tynan W, Wilson AS. The nerve supply to the human lumbar intervertebral discs. *J Anat*. 1981;132(Pt 1):39–56.
83. Goupille P, Jayson MI, Valat JP, Freemont AJ. The role of inflammation in disk herniation-associated radiculopathy. *Semin Arthritis Rheum*. 1998;28(1):60–71. doi:10.1016/S0049-0172(98)80029-2
84. Lazaro-Pacheco D, Mohseni M, Rudd S, Cooper-White J, Holsgrove TP. The role of biomechanical factors in models of intervertebral disc degeneration across multiple length scales. *APL Bioeng*. 2023;7(2):021501. doi:10.1063/5.0137698
85. Hamanishi C, Kawabata T, Yosii T, Tanaka S. Schmorl's nodes on magnetic resonance imaging. Their incidence and clinical relevance. *Spine*. 1994;19(4):450–453. doi:10.1097/00007632-199402001-00012
86. Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. *Spine*. 2000;25 (13):1625–1636. doi:10.1097/00007632-200007010-00005
87. Barbir A, Godburn KE, Michalek AJ, Lai A, Monsey RD, Iatridis JC. Effects of torsion on intervertebral disc gene expression and biomechanics, using a rat tail model. *Spine*. 2011;36(8):607–614. doi:10.1097/BRS.0b013e3181d9b58b
88. Zielinska N, Podgorski M, Haladaj R, Polguj M, Olewnik L. Risk factors of intervertebral disc pathology-a point of view formerly and today-a review. *J Clin Med*. 2021;10(3). doi:10.3390/jcm10030409
89. Mohanty S, Dahia CL. Defects in intervertebral disc and spine during development, degeneration, and pain: new research directions for disc regeneration and therapy. *Wiley Interdiscip Rev Dev Biol*. 2019;8(4):e343. doi:10.1002/wdev.343
90. Battie MC, Videman T, Kaprio J, et al. The Twin spine study: contributions to a changing view of disc degeneration. *Spine J*. 2009;9(1):47–59. doi:10.1016/j.spinee.2008.11.011
91. Kalb S, Martirosyan NL, Kalani MY, Broc GG, Theodore N. Genetics of the degenerated intervertebral disc. *World Neurosurg*. 2012;77 (3–4):491–501. doi:10.1016/j.wneu.2011.07.014
92. Le Maitre CL, Freemont AJ, Hoyland JA. Accelerated cellular senescence in degenerate intervertebral discs: a possible role in the pathogenesis of intervertebral disc degeneration. *Arthritis Res Ther*. 2007;9(3):R45. doi:10.1186/ar2198
93. Koroth J, Buko EO, Abbott R, et al. Macrophages and intervertebral disc degeneration. *Int J Mol Sci*. 2023;24(2). doi:10.3390/ijms24021367
94. Bonnheim NB, Wang L, Lazar AA, et al. The contributions of cartilage endplate composition and vertebral bone marrow fat to intervertebral disc degeneration in patients with chronic low back pain. *Eur Spine J*. 2022;31(7):1866–1872. doi:10.1007/s00586-022-07206-x
95. Ito K, Creemers L. Mechanisms of intervertebral disk degeneration/injury and pain: a review. *Global Spine J*. 2013;3(3):145–152. doi:10.1055/s-0033-1347300
96. Somovilla-Gomez F, Lostado-Lorza R, Corral-Bobadilla M, Escribano-Garcia R. Improvement in determining the risk of damage to the human lumbar functional spinal unit considering age, height, weight and sex using a combination of FEM and RSM. *Biomech Model Mechanobiol*. 2020;19(1):351–387. doi:10.1007/s10237-019-01215-4
97. Becker S, Hadjipavlou A, Heggeness MH. Ablation of the basivertebral nerve for treatment of back pain: a clinical study. *Spine J*. 2017;17 (2):218–223. doi:10.1016/j.spinee.2016.08.032
98. Shayota B, Wong TL, Fru D, et al. A comprehensive review of the sinuvertebral nerve with clinical applications. *Anat Cell Biol*. 2019;52 (2):128–133. doi:10.5115/acb.2019.52.2.128

99. Antonacci MD, Mody DR, Heggeness MH. Innervation of the human vertebral body: a histologic study. *J Spinal Disord*. 1998;11(6):526–531. doi:10.1097/00002517-199812000-00013
100. Sayed D, Naidu RK, Patel KV, et al. Best practice guidelines on the diagnosis and treatment of vertebrogenic pain with basivertebral nerve ablation from the American Society of Pain and Neuroscience. *J Pain Res*. 2022;15:2801–2819. doi:10.2147/JPR.S378544
101. Benzel EC, Kayanja M, Fleischman A, Roy S. Spine biomechanics: fundamentals and future. *Clin Neurosurg*. 2006;53:98–105.
102. Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral end plate in low back pain. *Global Spine J*. 2013;3(3):153–164. doi:10.1055/s-0033-1347298
103. Gilligan CJ, Cohen SP, Fischetti VA, Hirsch JA, Czaplewski LG. Chronic low back pain, bacterial infection and treatment with antibiotics. *Spine J*. 2021;21(6):903–914. doi:10.1016/j.spinee.2021.02.013
104. Kanna RM, Hajare S, Thippeswamy PB, Shetty AP, Rajasekaran S. Advanced disc degeneration, bi-planar instability and pathways of peri-discal gas suffusion contribute to pathogenesis of intradiscal vacuum phenomenon. *Eur Spine J*. 2022;31(3):755–763. doi:10.1007/s00586-022-07122-0
105. Cianci F, Ferraccioli G, Ferraccioli ES, Gremese E. Comprehensive review on intravertebral intraspinal, intrajoint, and intradiscal vacuum phenomenon: from anatomy and physiology to pathology. *Mod Rheumatol*. 2021;31(2):303–311. doi:10.1080/14397595.2020.1764744
106. Cawley DT, McDonnell A, Simpkin A, et al. Intra-discal vacuum phenomenon with advanced lumbar spine disc degeneration: complementary findings from both MRI and CT. *BMC Med Imaging*. 2025;25(1):94. doi:10.1186/s12880-025-01635-y
107. Eksi MS, Ozcan-Eksi EE, Akkas A, et al. Intradiscal vacuum phenomenon and spinal degeneration: a cross-sectional analysis of 219 subjects. *Curr Med Res Opin*. 2022;38(2):255–263. doi:10.1080/03007995.2021.1994379
108. Cawley DT, Simpkin A, Abrahim E, et al. Intradiscal vacuum phenomenon matches lumbar spine degeneration patterns in an ageing population. *Eur Spine J*. 2024;33(5):2014–2021. doi:10.1007/s00586-024-08174-0
109. D'Anastasi M, Birkenmaier C, Schmidt GP, Wegener B, Reiser MF, Baur-Melnyk A. Correlation between vacuum phenomenon on CT and fluid on MRI in degenerative disks. *AJR Am J Roentgenol*. 2011;197(5):1182–1189. doi:10.2214/AJR.10.6359
110. Kasai Y, Takegami K, Uchida A. Change of barometric pressure influences low back pain in patients with vacuum phenomenon within lumbar intervertebral disc. *J Spinal Disord Tech*. 2002;15(4):290–293. doi:10.1097/00024720-200208000-00005
111. da Rocha VM, Lima C, Candido GB, et al. Would Cutibacterium acnes be the villain for the chronicity of low back pain in degenerative disc disease? Preliminary results of an analytical cohort. *J Pers Med*. 2023;13(4):598. doi:10.3390/jpm13040598
112. Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS. Association between sciatica and Propionibacterium acnes. *Lancet*. 2001;357(9273):2024–2025. doi:10.1016/S0140-6736(00)05109-6
113. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*. 2013;22(4):697–707. doi:10.1007/s00586-013-2675-y
114. Braten LCH, Rolfsen MP, Espeland A, et al. Efficacy of antibiotic treatment in patients with chronic low back pain and Modic changes (the AIM study): double blind, randomised, placebo controlled, multicentre trial. *BMJ*. 2019;367:15654.
115. Ashley JW, Enomoto-Iwamoto M, Smith LJ, et al. Intervertebral disc development and disease-related genetic polymorphisms. *Genes Dis*. 2016;3(3):171–177. doi:10.1016/j.gendis.2016.04.006
116. Matson DM, Maccormick LM, Sembrano JN, Polly DW. Sacral dysmorphism and Lumbosacral Transitional Vertebrae (LSTV) Review. *Int J Spine Surg*. 2020;14(Suppl 1):14–19. doi:10.14444/6075
117. Konin GP, Walz DM. Lumbosacral transitional vertebrae: classification, imaging findings, and clinical relevance. *AJNR Am J Neuroradiol*. 2010;31(10):1778–1786. doi:10.3174/ajnr.A2036
118. Castellvi AE, Goldstein LA, Chan DP. Lumbosacral transitional vertebrae and their relationship with lumbar extradural defects. *Spine*. 1984;9(5):493–495. doi:10.1097/00007632-198407000-00014
119. Huang QQ, Liu SS, Liang GQ. Advances in the study of anatomy and biomechanics of lumbosacral transitional vertebrae. *Zhonghua Wai Ke Za Zhi*. 2019;57(2):156–160. doi:10.3760/cma.j.issn.0529-5815.2019.02.019
120. Becker L, Schonnagel L, Mihalache TV, et al. Lumbosacral transitional vertebrae alter the distribution of lumbar mobility-Preliminary results of a radiographic evaluation. *PLoS One*. 2022;17(9):e0274581. doi:10.1371/journal.pone.0274581
121. Griffith JF, Xiao F, Hilkens A, Griffith IHY, Leung JCS. Increased vertebral body area, disc and facet joint degeneration throughout the lumbar spine in patients with lumbosacral transitional vertebrae. *Eur Radiol*. 2022;32(9):6238–6246. doi:10.1007/s00330-022-08736-0
122. Desai A, McGrath K, Rao EM, et al. Examining degenerative disease adjacent to lumbosacral transitional vertebrae: a retrospective cohort study. *J Neurosurg Spine*. 2023;1:1–8.
123. Vergauwen S, Parizel PM, van Breusegem L, et al. Distribution and incidence of degenerative spine changes in patients with a lumbo-sacral transitional vertebra. *Eur Spine J*. 1997;6(3):168–172. doi:10.1007/BF01301431
124. Hanhivaara J, Maatta JH, Niinimaki J, Nevalainen MT. Lumbosacral transitional vertebrae are associated with lumbar degeneration: retrospective evaluation of 3855 consecutive abdominal CT scans. *Eur Radiol*. 2020;30(6):3409–3416. doi:10.1007/s00330-020-06691-2
125. Luoma K, Vehmas T, Raininko R, Luukkonen R, Riihimaki H. Lumbosacral transitional vertebra: relation to disc degeneration and low back pain. *Spine*. 2004;29(2):200–205. doi:10.1097/01.BRS.0000107223.02346.A8
126. Elster AD. Bertolotti's syndrome revisited. Transitional vertebrae of the lumbar spine. *Spine*. 1989;14(12):1373–1377. doi:10.1097/00007632-198912000-00015
127. Farshad-Amacker NA, Herzog RJ, Hughes AP, Aichmair A, Farshad M. Associations between lumbosacral transitional anatomy types and degeneration at the transitional and adjacent segments. *Spine J*. 2015;15(6):1210–1216. doi:10.1016/j.spinee.2013.10.029
128. Berbari EF, Kanj SS, Kowalski TJ, et al. Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61(6):e26–46. doi:10.1093/cid/civ482
129. Hall WA, Graeber A, Cecava ND. Vertebral osteomyelitis. *StatPearls*. Treasure Island (FL) ineligible companies. Disclosure: Adam Graeber declares no relevant financial relationships with ineligible companies. Disclosure: Nathan Cecava declares no relevant financial relationships with ineligible companies. 2025.
130. Kayani I, Syed I, Saifuddin A, Green R, MacSweeney F. Vertebral osteomyelitis without disc involvement. *Clin Radiol*. 2004;59(10):881–891. doi:10.1016/j.crad.2004.03.023
131. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362(11):1022–1029. doi:10.1056/NEJMcp0910753

132. Albert HB, Lambert P, Rollason J, et al. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J*. 2013;22(4):690–696. doi:10.1007/s00586-013-2674-z
133. Gupta A, Kowalski TJ, Osmon DR, et al. Long-term outcome of pyogenic vertebral osteomyelitis: a cohort study of 260 patients. *Open Forum Infect Dis*. 2014;1(3):ofu107. doi:10.1093/ofid/ofu107
134. Dewing CB, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: correlation by herniation type and level. *Spine*. 2008;33(1):33–38. doi:10.1097/BRS.0b013e31815e3a42
135. Shahi P, Vaishnav AS, Mai E, et al. Practical answers to frequently asked questions in minimally invasive lumbar spine surgery. *Spine J*. 2023;23(1):54–63. doi:10.1016/j.spinee.2022.07.087
136. Song J, Araghi K, Dupont MM, et al. Association between muscle health and patient-reported outcomes after lumbar microdiscectomy: early results. *Spine J*. 2022;22(10):1677–1686. doi:10.1016/j.spinee.2022.05.013
137. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the maine lumbar spine study. *Spine*. 2005;30(8):927–935. doi:10.1097/01.brs.0000158954.68522.2a
138. Keskimaki I, Seitsalo S, Osterman H, Rissanen P. Reoperations after lumbar disc surgery: a population-based study of regional and interspecialty variations. *Spine*. 2000;25(12):1500–1508. doi:10.1097/00007632-200006150-00008
139. Abdu RW, Abdu WA, Pearson AM, Zhao W, Lurie JD, Weinstein JN. Reoperation for recurrent intervertebral disc herniation in the spine patient outcomes research trial: analysis of rate, risk factors, and outcome. *Spine*. 2017;42(14):1106–1114. doi:10.1097/BRS.0000000000002088
140. Leven D, Passias PG, Errico TJ, et al. Risk Factors for reoperation in patients treated surgically for intervertebral disc herniation: a subanalysis of eight-year SPORT data. *J Bone Joint Surg Am*. 2015;97(16):1316–1325. doi:10.2106/JBJS.N.01287
141. Morgan-Hough CV, Jones PW, Eisenstein SM. Primary and revision lumbar discectomy. A 16-year review from one centre. *J Bone Joint Surg Br*. 2003;85(6):871–874. doi:10.1302/0301-620X.85B6.13626
142. Esfahani DR, Shah H, Arnone GD, Scheer JK, Mehta AI. Lumbar discectomy outcomes by specialty: a propensity-matched analysis of 7464 patients from the ACS-NSQIP database. *World Neurosurg*. 2018;118:e865–e870. doi:10.1016/j.wneu.2018.07.077
143. Pugely AJ, Martin CT, Gao Y, Mendoza-Lattes SA. Outpatient surgery reduces short-term complications in lumbar discectomy: an analysis of 4310 patients from the ACS-NSQIP database. *Spine*. 2013;38(3):264–271. doi:10.1097/BRS.0b013e3182697b57
144. Radcliff KE, Kepler CK, Jakoi A, et al. Adjacent segment disease in the lumbar spine following different treatment interventions. *Spine J*. 2013;13(10):1339–1349. doi:10.1016/j.spinee.2013.03.020
145. Chun DS, Baker KC, Hsu WK. Lumbar pseudarthrosis: a review of current diagnosis and treatment. *Neurosurg Focus*. 2015;39(4):E10. doi:10.3171/2015.7.FOCUS15292
146. Lim S, Edelstein AI, Patel AA, Kim BD, Kim JYS. Risk factors for postoperative infections after single-level lumbar fusion surgery. *Spine*. 2018;43(3):215–222. doi:10.1097/BRS.0000000000000608
147. Ghobrial GM, Williams KA Jr, Arnold P, Fehlings M, Harrop JS. Iatrogenic neurologic deficit after lumbar spine surgery: a review. *Clin Neurol Neurosurg*. 2015;139:76–80. doi:10.1016/j.clineuro.2015.08.022
148. Amaral V, Marchi L, Martim H, et al. Influence of psychosocial distress in the results of elective lumbar spine surgery. *J Spine Surg*. 2017;3(3):371–378. doi:10.21037/jss.2017.08.05
149. Chen WH, Lo WC, Lee JJ, et al. Tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-beta1 in platelet-rich plasma. *J Cell Physiol*. 2006;209(3):744–754. doi:10.1002/jcp.20765
150. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar intradiskal Platelet-Rich Plasma (PRP) injections: a prospective, double-blind, randomized controlled study. *PM R*. 2016;8(1):1–10;quiz10. doi:10.1016/j.pmrj.2015.08.010
151. Cheng J, Santiago KA, Nguyen JT, Solomon JL, Lutz GE. Treatment of symptomatic degenerative intervertebral discs with autologous platelet-rich plasma: follow-up at 5-9 years. *Regener Med*. 2019;14(9):831–840. doi:10.2217/rme-2019-0040
152. Peng B, Xu B, Wu W, Du L, Zhang T, Zhang J. Efficacy of intradiscal injection of platelet-rich plasma in the treatment of discogenic low back pain: a single-arm meta-analysis. *Medicine*. 2023;102(10):e33112. doi:10.1097/MD.0000000000033112
153. Zhang J, Liu D, Gong Q, Chen J, Wan L. Intradiscal autologous platelet-rich plasma injection for discogenic low back pain: a clinical trial. *Biomed Res Int*. 2022;2022:9563693. doi:10.1155/2022/9563693
154. Wongjarupong A, Pairuchvej S, Laohapornsvan P, et al. "Platelet-Rich Plasma" epidural injection an emerging strategy in lumbar disc herniation: a randomized controlled trial. *BMC Musculoskelet Disord*. 2023;24(1):335. doi:10.1186/s12891-023-06429-3
155. Kawabata S, Hachiya K, Nagai S, et al. Autologous Platelet-rich plasma administration on the intervertebral disc in low back pain patients with Modic type 1 change: report of two cases. *Medicina*. 2023;59(1):1.
156. Lorio MP, Tate JL, Myers TJ, Block JE, Beall DP. Perspective on intradiscal therapies for lumbar discogenic pain: state of the science, knowledge gaps, and imperatives for clinical adoption. *J Pain Res*. 2024;17:1171–1182. doi:10.2147/JPR.S441180
157. Feng G, Zhao X, Liu H, et al. Transplantation of mesenchymal stem cells and nucleus pulposus cells in a degenerative disc model in rabbits: a comparison of 2 cell types as potential candidates for disc regeneration. *J Neurosurg Spine*. 2011;14(3):322–329. doi:10.3171/2010.11.SPINE10285
158. Hohaus C, Ganey TM, Minkus Y, Meisel HJ. Cell transplantation in lumbar spine disc degeneration disease. *Eur Spine J*. 2008;17(Suppl 4):492–503.
159. Orozco L, Soler R, Morera C, Alberca M, Sanchez A, Garcia-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: a pilot study. *Transplantation*. 2011;92(7):822–828. doi:10.1097/TP.0b013e3182298a15
160. Chen G, Park CK, Xie RG, Ji RR. Intrathecal bone marrow stromal cells inhibit neuropathic pain via TGF-beta secretion. *J Clin Invest*. 2015;125(8):3226–3240. doi:10.1172/JCI80883
161. Amirdelfan K, Bae H, McJunkin T, et al. Allogeneic mesenchymal precursor cells treatment for chronic low back pain associated with degenerative disc disease: a prospective randomized, placebo-controlled 36-month study of safety and efficacy. *Spine J*. 2021;21(2):212–230. doi:10.1016/j.spinee.2020.10.004
162. Halvorsen YC, Wilkison WO, Gimble JM. Adipose-derived stromal cells--their utility and potential in bone formation. *Int J Obes Relat Metab Disord*. 2000;24 Suppl 4:S41–44. doi:10.1038/sj.ijo.0801503
163. Romaniyanto FNU, Mahyudin F, Prakoeswa CRS, et al. Adipose-Derived Stem Cells (ASCs) for regeneration of intervertebral disc degeneration: review article. *Stem Cells Cloning*. 2022;15:67–76. doi:10.2147/SCCAA.S379714

164. Haines CM, Bhatt FR, Orosz LD, et al. Low back pain, disability, and quality of life one year following intradiscal injection of autologous bone marrow aspirate concentrate. *Stem Cells Int*. 2022;2022:9617511. doi:10.1155/2022/9617511
165. Vadala G, Ambrosio L, Russo F, Papalia R, Denaro V. Interaction between mesenchymal stem cells and intervertebral disc microenvironment: from cell therapy to tissue engineering. *Stem Cells Int*. 2019;2019:2376172. doi:10.1155/2019/2376172
166. Vadala G, Ambrosio L, Russo F, Papalia R, Denaro V. Stem cells and intervertebral disc regeneration overview-what they can and can't do. *Int J Spine Surg*. 2021;15(s1):40–53. doi:10.14444/8054
167. Vadala G, Sowa G, Hubert M, Gilbertson LG, Denaro V, Kang JD. Mesenchymal stem cells injection in degenerated intervertebral disc: cell leakage may induce osteophyte formation. *J Tissue Eng Regen Med*. 2012;6(5):348–355. doi:10.1002/term.433
168. Yoshikawa T, Ueda Y, Miyazaki K, Koizumi M, Takakura Y. Disc regeneration therapy using marrow mesenchymal cell transplantation: a report of two case studies. *Spine*. 2010;35(11):E475–480. doi:10.1097/BRS.0b013e3181cd2cf4
169. Beall DP, Bae HW, DePalma MJ, et al. Efficacy and safety of allogeneic mesenchymal precursor cells with and without hyaluronic acid for treatment of chronic low back pain: a prospective, randomized, double blind, concurrent-controlled 36-month study. *Spine J*. 2025;25(9):1997–2013. doi:10.1016/j.spinee.2025.03.015
170. Navani A, Ambach M, Calodney A, et al. The safety and effectiveness of orthobiologic injections for discogenic chronic low back pain: a multicenter prospective, crossover, randomized controlled trial with 12 months follow-up. *Pain Physician*. 2024;27(1):E65–E77. doi:10.36076/ppj.2024.27.E65
171. Allen MJ, Schoonmaker JE, Bauer TW, Williams PF, Higham PA, Yuan HA. Preclinical evaluation of a poly (vinyl alcohol) hydrogel implant as a replacement for the nucleus pulposus. *Spine*. 2004;29(5):515–523. doi:10.1097/01.BRS.0000113871.67305.38
172. Bader RA. Synthesis and viscoelastic characterization of novel hydrogels generated via photopolymerization of 1,2-epoxy-5-hexene modified poly(vinyl alcohol) for use in tissue replacement. *Acta Biomater*. 2008;4(4):967–975. doi:10.1016/j.actbio.2008.02.015
173. Joshi A, Fussell G, Thomas J, et al. Functional compressive mechanics of a PVA/PVP nucleus pulposus replacement. *Biomaterials*. 2006;27(2):176–184. doi:10.1016/j.biomaterials.2005.06.003
174. Klara PM, Ray CD. Artificial nucleus replacement: clinical experience. *Spine*. 2002;27(12):1374–1377. doi:10.1097/00007632-200206150-00022
175. Thomas J, Lowman A, Marcolongo M. Novel associated hydrogels for nucleus pulposus replacement. *J Biomed Mater Res A*. 2003;67(4):1329–1337. doi:10.1002/jbm.a.10119
176. Vernengo J, Fussell GW, Smith NG, Lowman AM. Synthesis and characterization of injectable bioadhesive hydrogels for nucleus pulposus replacement and repair of the damaged intervertebral disc. *J Biomed Mater Res B Appl Biomater*. 2010;93(2):309–317. doi:10.1002/jbm.b.31547
177. Bodugoz-Senturk H, Choi J, Oral E, et al. The effect of polyethylene glycol on the stability of pores in polyvinyl alcohol hydrogels during annealing. *Biomaterials*. 2008;29(2):141–149. doi:10.1016/j.biomaterials.2007.09.015
178. Bodugoz-Senturk H, Macias CE, Kung JH, Muratoglu OK. Poly(vinyl alcohol)-acrylamide hydrogels as load-bearing cartilage substitute. *Biomaterials*. 2009;30(4):589–596. doi:10.1016/j.biomaterials.2008.10.010
179. Buckwalter JA, Woo SL, Goldberg VM, et al. Soft-tissue aging and musculoskeletal function. *J Bone Joint Surg Am*. 1993;75(10):1533–1548. doi:10.2106/00004623-199310000-00015
180. Butler D, Trafimow JH, Andersson GB, McNeill TW, Huckman MS. Discs degenerate before facets. *Spine*. 1990;15(2):111–113. doi:10.1097/00007632-199002000-00012
181. Zhao F, Pollintine P, Hole BD, Dolan P, Adams MA. Discogenic origins of spinal instability. *Spine*. 2005;30(23):2621–2630. doi:10.1097/01.brs.0000188203.71182.c0
182. Hedman T, Yu J, Singh H, Deer T. Early clinical results of intervertebral joint stabilization by injectable load-sharing polymers. *J Pain Res*. 2023;16:2777–2789. doi:10.2147/JPR.S413104
183. Slusarewicz P, Zhu K, Hedman T. Kinetic analysis of genipin degradation in aqueous solution. *Nat Prod Commun*. 2010;5(12):1853–1858.
184. Chuang SY, Odono RM, Hedman TP. Effects of exogenous crosslinking on in vitro tensile and compressive moduli of lumbar intervertebral discs. *Clin Biomech*. 2007;22(1):14–20. doi:10.1016/j.clinbiomech.2006.08.001
185. Kirking B, Hedman T, Criscione J. Changes in the interfacial shear resistance of disc annulus fibrosus from genipin crosslinking. *J Biomech*. 2014;47(1):293–296. doi:10.1016/j.jbiomech.2013.10.019
186. Kirking BC, Toungate JK, Hedman TP. The dose response relationship between intervertebral disc flexion-extension neutral zone metrics and injected genipin concentration. *J Appl Biomater Funct Mater*. 2013;11(2):e73–79. doi:10.5301/JABFM.5000151
187. Slusarewicz P, Zhu K, Kirking B, Toungate J, Hedman T. Optimization of protein crosslinking formulations for the treatment of degenerative disc disease. *Spine*. 2011;36(1):E7–13. doi:10.1097/BRS.0b013e3181cc3de9
188. Hedman TP, Chen WP, LC L, HJ L, Chuang SY. Effects of collagen crosslink augmentation on mechanism of compressive load sharing in intervertebral discs. *J Med Biol Eng*. 2017;37(1):94–101. doi:10.1007/s40846-016-0207-z
189. Hedman TP, Saito H, Vo C, Chuang SY. Exogenous cross-linking increases the stability of spinal motion segments. *Spine*. 2006;31(15):E480–485. doi:10.1097/01.brs.0000224531.49174.ea
190. Popovich JM Jr, Yau D, Chuang SY, Hedman TP. Exogenous collagen crosslinking of the intervertebral disc restores joint stability after lumbar posterior decompression surgery. *Spine*. 2011;36(12):939–944. doi:10.1097/BRS.0b013e3181e8b1d5
191. Beall DP, Davis T, DePalma MJ, et al. Viable disc tissue allograft supplementation; one- and two-level treatment of degenerated intervertebral discs in patients with chronic discogenic low back pain: one year results of the VAST randomized controlled trial. *Pain Physician*. 2021;24(6):465–477.
192. Beall DP, Davis TT, Amirdelfan K, et al. Nucleus pulposus allograft supplementation in patients with lumbar discogenic pain: initial 6-month outcomes from a prospective clinical pilot study. *Pain Physician*. 2024;27(8):E865–E871. doi:10.36076/ppj.2024.7.E865
193. Beall DP, Wilson GL, Bishop R, Tally W. VAST clinical trial: safely supplementing tissue lost to degenerative disc disease. *Int J Spine Surg*. 2020;14(2):239–253. doi:10.14444/7033
194. Lyons G, Eisenstein SM, Sweet MB. Biochemical changes in intervertebral disc degeneration. *Biochim Biophys Acta*. 1981;673(4):443–453. doi:10.1016/0304-4165(81)90476-1
195. Urban JP, McMullin JF. Swelling pressure of the lumbar intervertebral discs: influence of age, spinal level, composition, and degeneration. *Spine*. 1988;13(2):179–187. doi:10.1097/00007632-198802000-00009
196. Beall DP, Davis TT, Amirdelfan K, et al. Supplemental nucleus pulposus allograft in patients with lumbar discogenic pain: results of a prospective feasibility study. *BMC Musculoskelet Disord*. 2025;26(1):437. doi:10.1186/s12891-025-08701-0

197. Costandi S, Beall DP, Davis TT, et al. Durability of supplemental nucleus pulposus allograft in patients with lumbar discogenic pain. *J Pain Res*. 2025;18:1901–1908. doi:10.2147/JPR.S516571
198. Azeem N, Myers TJ, Tate JL, Gilmore CA, Harper AS, Block JE. Supplemental nucleus pulposus allograft in patients with lumbar discogenic pain: evaluation of clinical outcomes and quality of life in medicare beneficiaries. *Clin Interv Aging*. 2025;20:717–726. doi:10.2147/CIA.S523457
199. Nguyen C, Lefevre-Colau MM, Kennedy DJ, Schneider BJ, Rannou F. Low back pain. *Lancet*. 2018;392(10164):2547. doi:10.1016/S0140-6736(18)32187-1
200. Nicol V, Verdaguer C, Daste C, et al. Chronic low back pain: a narrative review of recent international guidelines for diagnosis and conservative treatment. *J Clin Med*. 2023;12(4):1685. doi:10.3390/jcm12041685
201. Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2019;364:1689.
202. Buttermann GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. A prospective, randomized study. *J Bone Joint Surg Am*. 2004;86(4):670–679. doi:10.2106/00004623-200404000-00002
203. Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. *JAMA*. 2006;296(20):2451–2459. doi:10.1001/jama.296.20.2451
204. Fisher C, Noonan V, Bishop P, et al. Outcome evaluation of the operative management of lumbar disc herniation causing sciatica. *J Neurosurg*. 2004;100(4 Suppl Spine):317–324. doi:10.3171/spi.2004.100.4.0317
205. Ng LC, Sell P. Predictive value of the duration of sciatica for lumbar discectomy. A prospective cohort study. *J Bone Joint Surg Br*. 2004;86(4):546–549. doi:10.1302/0301-620X.86B4.14419
206. Bailey JF, Fields AJ, Ballatori A, et al. The relationship between endplate pathology and patient-reported symptoms for chronic low back pain depends on lumbar paraspinal muscle quality. *Spine*. 2019;44(14):1010–1017. doi:10.1097/BRS.0000000000003035
207. Kjaer P, Korsholm L, Bendix T, Sorensen JS, Leboeuf-Yde C. Modic changes and their associations with clinical findings. *Eur Spine J*. 2006;15(9):1312–1319. doi:10.1007/s00586-006-0185-x
208. Yang D, Hoehl BU, Schonnagel L, et al. Modic changes are associated with increased pain intensity, greater disability, and reduced quality of life in low back pain: a cross-sectional study. *Clin Orthop Relat Res*. 2025. doi:10.1097/CORR.0000000000003565
209. Farshad-Amacker NA, Hughes A, Herzog RJ, Seifert B, Farshad M. The intervertebral disc, the endplates and the vertebral bone marrow as a unit in the process of degeneration. *Eur Radiol*. 2017;27(6):2507–2520. doi:10.1007/s00330-016-4584-z
210. Kerttula L, Luoma K, Vehmas T, Gronblad M, Kaapa E. Modic type I change may predict rapid progressive, deforming disc degeneration: a prospective 1-year follow-up study. *Eur Spine J*. 2012;21(6):1135–1142. doi:10.1007/s00586-012-2147-9
211. Luoma K, Vehmas T, Kerttula L, Gronblad M, Rinne E. Chronic low back pain in relation to Modic changes, bony endplate lesions, and disc degeneration in a prospective MRI study. *Eur Spine J*. 2016;25(9):2873–2881.
212. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91(1):4–15.
213. Blair P, Flaumenhaft R. Platelet alpha-granules: basic biology and clinical correlates. *Blood Rev*. 2009;23(4):177–189. doi:10.1016/j.blre.2009.04.001
214. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. *Arthroscopy*. 2012;28(3):429–439. doi:10.1016/j.arthro.2011.10.018
215. Davis VL, Abukabda AB, Radio NM, et al. Platelet-rich preparations to improve healing. Part I: workable options for every size practice. *J Oral Implantol*. 2014;40(4):500–510. doi:10.1563/AAID-JOI-D-12-00104
216. Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair. *Arthritis Res Ther*. 2014;16(1):204. doi:10.1186/ar4493
217. Manchikanti L, Knezevic E, Knezevic NN, et al. Effectiveness of intradiscal regenerative medicine therapies for long-term relief of chronic low back pain: a systematic review and meta-analysis. *Pain Physician*. 2024;27(10):E995–E1032.
218. Muthu S, Jeyaraman M, Chellamuthu G, Jeyaraman N, Jain R, Khanna M. Does the intradiscal injection of platelet rich plasma have any beneficial role in the management of lumbar disc disease? *Global Spine J*. 2022;12(3):503–514. doi:10.1177/2192568221998367
219. Schepers MO, Groot D, Kleinjan EM, Pol MM, Mylenbusch H, Klopper-Kes AHJ. Effectiveness of intradiscal platelet rich plasma for discogenic low back pain without Modic changes: a randomized controlled trial. *Interv Pain Med*. 2022;1(1):100011. doi:10.1016/j.inpm.2022.100011
220. Lin W, Xie L, Zhou L, Zheng J, Zhai W, Lin D. Effects of platelet-rich plasma on subchondral bone marrow edema and biomarkers in synovial fluid of knee osteoarthritis. *Knee*. 2023;42:161–169. doi:10.1016/j.knee.2023.03.002
221. Buttermann GR. The effect of spinal steroid injections for degenerative disc disease. *Spine J*. 2004;4(5):495–505. doi:10.1016/j.spinee.2004.03.024
222. Cao P, Jiang L, Zhuang C, et al. Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. *Spine J*. 2011;11(2):100–106. doi:10.1016/j.spinee.2010.07.001
223. Khot A, Bowditch M, Powell J, Sharp D. The use of intradiscal steroid therapy for lumbar spinal discogenic pain: a randomized controlled trial. *Spine*. 2004;29(8):833–836. doi:10.1097/00007632-200404150-00002
224. Nguyen C, Boutron I, Baron G, et al. Intradiscal glucocorticoid injection for patients with chronic low back pain associated with active discopathy: a randomized trial. *Ann Intern Med*. 2017;166(8):547–556. doi:10.7326/M16-1700
225. Simmons JW, McMillin JN, Emery SF, Kimmich SJ. Intradiscal steroids. A prospective double-blind clinical trial. *Spine*. 1992;17(6 Suppl):S172–175. doi:10.1097/00007632-199206001-00019
226. Tavares I, Thomas E, Cyteval C, et al. Intradiscal glucocorticoids injection in chronic low back pain with active discopathy: a randomized controlled study. *Ann Phys Rehabil Med*. 2021;64(2):101396. doi:10.1016/j.rehab.2020.05.003
227. Yu Y, Liu W, Song D, Guo Q, Jia L. Diagnosis of discogenic low back pain in patients with probable symptoms but negative discography. *Arch Orthop Trauma Surg*. 2012;132(5):627–632. doi:10.1007/s00402-011-1448-5
228. Navani A, Manchikanti L, Albers SL, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2019;22(1S):S1–S74. doi:10.36076/ppj/2019.22.s1

229. McCormick ZL, Lehman VT, Plastaras CT, et al. Low-pressure lumbar provocation discography according to spine intervention society/international association for the study of pain standards does not cause acceleration of disc degeneration in patients with symptomatic low back pain: a 7-year matched cohort study. *Spine*. 2019;44(19):E1161–E1168. doi:10.1097/BRS.0000000000003085
230. Conger A, Burnham T, Salazar F, et al. The effectiveness of radiofrequency ablation of medial branch nerves for chronic lumbar facet joint syndrome in patients selected by guideline-concordant dual comparative medial branch blocks. *Pain Med*. 2020;21(5):902–909. doi:10.1093/pm/pnz248
231. Conger A, Burnham TR, Clark T, Teramoto M, McCormick ZL. The effectiveness of intraosseous basivertebral nerve radiofrequency ablation for the treatment of vertebrogenic low back pain: an updated systematic review with single-arm meta-analysis. *Pain Med*. 2022;23(Suppl 2):S50–S62. doi:10.1093/pm/pnac070
232. Conger A, Smuck M, Truumees E, Lotz JC, DePalma MJ, McCormick ZL. Vertebrogenic pain: a paradigm shift in diagnosis and treatment of axial low back pain. *Pain Med*. 2022;23(Suppl 2):S63–S71. doi:10.1093/pm/pnac081
233. Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J*. 2018;27(5):1146–1156. doi:10.1007/s00586-018-5496-1
234. Khalil JG, Smuck M, Koreckij T, et al. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain. *Spine J*. 2019;19(10):1620–1632. doi:10.1016/j.spinee.2019.05.598
235. Truumees E, Macadaeg K, Pena E, et al. A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain. *Eur Spine J*. 2019;28(7):1594–1602. doi:10.1007/s00586-019-05995-2
236. Fogel G, Musie J, Phillips TR, et al. Assessment and management of patients developing low energy vertebral compression fractures following basivertebral nerve ablation. *Pain Med*. 2024;25(3):249–251. doi:10.1093/pm/pnad132
237. Smuck M, Khalil J, Barrette K, et al. Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results. *Reg Anesth Pain Med*. 2021;46(8):683–693. doi:10.1136/rapm-2020-102259
238. Dower A, Davies MA, Ghahreman A. Pathologic basis of lumbar radicular pain. *World Neurosurg*. 2019;128:114–121. doi:10.1016/j.wneu.2019.04.147
239. Allegri M, Montella S, Salici F, et al. Mechanisms of low back pain: a guide for diagnosis and therapy. *F1000Res*. 2016;5:1530. doi:10.12688/f1000research.8105.2
240. Jinkins JR, Whittemore AR, Bradley WG. The anatomic basis of vertebrogenic pain and the autonomic syndrome associated with lumbar disk extrusion. *AJR Am J Roentgenol*. 1989;152(6):1277–1289. doi:10.2214/ajr.152.6.1277
241. Jarvik JG, Deyo RA. Diagnostic evaluation of low back pain with emphasis on imaging. *Ann Intern Med*. 2002;137(7):586–597. doi:10.7326/0003-4819-137-7-200210010-00010
242. Sizer PS Jr, Brismee JM, Cook C. Medical screening for red flags in the diagnosis and management of musculoskeletal spine pain. *Pain Pract*. 2007;7(1):53–71. doi:10.1111/j.1533-2500.2007.00112.x
243. Choudhri TF, Mummaneni PV, Dhall SS, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 4: radiographic assessment of fusion status. *J Neurosurg Spine*. 2014;21(1):23–30. doi:10.3171/2014.4.SPINE14267
244. Resnick DK, Choudhri TF, Dailey AT, et al. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 6: magnetic resonance imaging and discography for patient selection for lumbar fusion. *J Neurosurg Spine*. 2005;2(6):662–669. doi:10.3171/spi.2005.2.6.0662
245. Vora AJ, Doerr KD, Wolfer LR. Functional anatomy and pathophysiology of axial low back pain: disc, posterior elements, sacroiliac joint, and associated pain generators. *Phys Med Rehabil Clin N Am*. 2010;21(4):679–709. doi:10.1016/j.pmr.2010.07.005
246. Eck JC, Sharan A, Ghogawala Z, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 7: lumbar fusion for intractable low-back pain without stenosis or spondylolisthesis. *J Neurosurg Spine*. 2014;21(1):42–47. doi:10.3171/2014.4.SPINE14270
247. Bono CM, Ghiselli G, Gilbert TJ, et al. An evidence-based clinical guideline for the diagnosis and treatment of cervical radiculopathy from degenerative disorders. *Spine J*. 2011;11(1):64–72. doi:10.1016/j.spinee.2010.10.023
248. Mummaneni PV, Dhall SS, Eck JC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion. *J Neurosurg Spine*. 2014;21(1):67–74. doi:10.3171/2014.4.SPINE14276
249. Resnick DK, Choudhri TF, Dailey AT, et al. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 10: fusion following decompression in patients with stenosis without spondylolisthesis. *J Neurosurg Spine*. 2005;2(6):686–691. doi:10.3171/spi.2005.2.6.0686
250. Weber KT, Jacobsen TD, Maidhof R, et al. Developments in intervertebral disc disease research: pathophysiology, mechanobiology, and therapeutics. *Curr Rev Musculoskelet Med*. 2015;8(1):18–31. doi:10.1007/s12178-014-9253-8
251. Carragee EJ, Lincoln T, Parmar VS, Alamin T. A gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. *Spine*. 2006;31(18):2115–2123. doi:10.1097/01.brs.0000231436.30262.dd
252. Willems PC. Provocative diskography: safety and predictive value in the outcome of spinal fusion or pain intervention for chronic low-back pain. *J Pain Res*. 2014;7:699–705. doi:10.2147/JPR.S45615
253. Lorio MP, Beall DP, Calodney AK, Lewandrowski K-U, Block JE, Mekhail N. Defining the Patient with lumbar discogenic pain: real-world implications for diagnosis and effective clinical management. *J Pers Med*. 2023;13(5):821. doi:10.3390/jpm13050821
254. Noriega DC, Ardura F, Hernandez-Ramajo R, et al. Treatment of degenerative disc disease with allogeneic mesenchymal stem cells: long-term follow-up results. *Transplantation*. 2021;105(2):e25–e27. doi:10.1097/TP.0000000000003471
255. Lee DW, Pritzlaff S, Jung MJ, et al. Latest Evidence-Based Application for Radiofrequency Neurotomy (LEARN): best practice guidelines from the American Society of Pain and Neuroscience (ASPN). *J Pain Res*. 2021;14:2807–2831. doi:10.2147/JPR.S325665
256. Faur C, Patrascu JM, Haragus H, Anglitoiu B. Correlation between multifidus fatty atrophy and lumbar disc degeneration in low back pain. *BMC Musculoskelet Disord*. 2019;20(1):414. doi:10.1186/s12891-019-2786-7
257. Crawford RJ, Elliott JM, Volken T. Change in fatty infiltration of lumbar multifidus, erector spinae, and psoas muscles in asymptomatic adults of Asian or Caucasian ethnicities. *Eur Spine J*. 2017;26(12):3059–3067. doi:10.1007/s00586-017-5212-6
258. Hebert JJ, Koppenhaver SL, Teyhen DS, Walker BF, Fritz JM. The evaluation of lumbar multifidus muscle function via palpation: reliability and validity of a new clinical test. *Spine J*. 2015;15(6):1196–1202. doi:10.1016/j.spinee.2013.08.056

259. Gilligan C, Volschenk W, Russo M, et al. Three-year durability of restorative neurostimulation effectiveness in patients with chronic low back pain and multifidus muscle dysfunction. *Neuromodulation*. 2023;26(1):98–108. doi:10.1016/j.neurom.2022.08.457
260. Schwab F, Mekhail N, Patel KV, et al. Restorative neurostimulation therapy compared to optimal medical management: a Randomized Evaluation (RESTORE) for the treatment of chronic mechanical low back pain due to multifidus dysfunction. *Pain Ther*. 2025;14 (1):401–423. doi:10.1007/s40122-024-00689-0
261. Xia XP, Chen HL, Cheng HB. Prevalence of adjacent segment degeneration after spine surgery: a systematic review and meta-analysis. *Spine*. 2013;38(7):597–608. doi:10.1097/BRS.0b013e318273a2ea
262. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization task-force for osteoporosis. *Osteoporos Int*. 1999;10(4):259–264. doi:10.1007/s001980050224
263. Greendale GA, DeAmicis TA, Bucur A, et al. A prospective study of the effect of fracture on measured physical performance: results from the MacArthur Study--MAC. *J Am Geriatr Soc*. 2000;48(5):546–549. doi:10.1111/j.1532-5415.2000.tb05001.x
264. Papaioannou A, Watts NB, Kendler DL, Yuen CK, Adachi JD, Ferko N. Diagnosis and management of vertebral fractures in elderly adults. *Am J Med*. 2002;113(3):220–228. doi:10.1016/S0002-9343(02)01190-7
265. Huang C, Ross PD, Wasnich RD. Vertebral fracture and other predictors of physical impairment and health care utilization. *Arch Intern Med*. 1996;156(21):2469–2475. doi:10.1001/archinte.1996.00440200087011
266. Rapado A. General management of vertebral fractures. *Bone*. 1996;18(3 Suppl):191S–196S. doi:10.1016/8756-3282(95)00501-3
267. Siminoski K, Warshawski RS, Jen H, Lee K. The accuracy of historical height loss for the detection of vertebral fractures in postmenopausal women. *Osteoporos Int*. 2006;17(2):290–296. doi:10.1007/s00198-005-2017-y
268. Green AD, Colon-Emeric CS, Bastian L, Drake MT, Lyles KW. Does this woman have osteoporosis? *JAMA*. 2004;292(23):2890–2900. doi:10.1001/jama.292.23.2890
269. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA*. 2001;285(3):320–323. doi:10.1001/jama.285.3.320
270. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721–739. doi:10.1359/jbmr.2000.15.4.721
271. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1999;14(5):821–828. doi:10.1359/jbmr.1999.14.5.821
272. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8 (9):1137–1148. doi:10.1002/jbmr.5650080915
273. Theodorou DJ, Theodorou SJ, Duncan TD, Garfin SR, Wong WH. Percutaneous balloon kyphoplasty for the correction of spinal deformity in painful vertebral body compression fractures. *Clin Imaging*. 2002;26(1):1–5. doi:10.1016/S0899-7071(01)00350-3
274. Ledlie JT, Renfro MB. Kyphoplasty treatment of vertebral fractures: 2-year outcomes show sustained benefits. *Spine*. 2006;31(1):57–64. doi:10.1097/01.brs.0000192687.07392.f1
275. Buchbinder R, Johnston RV, Rischin KJ, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev*. 2018;11(11):CD006349. doi:10.1002/14651858.CD006349.pub4
276. Lou S, Shi X, Zhang X, Lyu H, Li Z, Wang Y. Percutaneous vertebroplasty versus non-operative treatment for osteoporotic vertebral compression fractures: a meta-analysis of randomized controlled trials. *Osteoporos Int*. 2019;30(12):2369–2380. doi:10.1007/s00198-019-05101-8
277. Goz V, Errico TJ, Weinreb JH, et al. Vertebroplasty and kyphoplasty: national outcomes and trends in utilization from 2005 through 2010. *Spine J*. 2015;15(5):959–965. doi:10.1016/j.spinee.2013.06.032
278. Evans AJ, Kip KE, Brinjikji W, et al. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. *J Neurointerv Surg*. 2016;8(7):756–763. doi:10.1136/neurintsurg-2015-011811
279. Rodriguez AJ, Fink HA, Mirigian L, et al. Pain, quality of life, and safety outcomes of kyphoplasty for vertebral compression fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2017;32(9):1935–1944. doi:10.1002/jbmr.3170
280. Anderson PA, Froyshteter AB, Tontz WL Jr. Meta-analysis of vertebral augmentation compared with conservative treatment for osteoporotic spinal fractures. *J Bone Miner Res*. 2013;28(2):372–382. doi:10.1002/jbmr.1762
281. Carli D, Venmans A, Lodder P, et al. Vertebroplasty versus active control intervention for chronic osteoporotic vertebral compression fractures: the VERTOS V randomized controlled trial. *Radiology*. 2023;308(1):e222535. doi:10.1148/radiol.222535
282. Sanli I, van Kuijk SMJ, de Bie RA, van Rhijn LW, Willems PC. Percutaneous cement augmentation in the treatment of osteoporotic vertebral fractures (OVFs) in the elderly: a systematic review. *Eur Spine J*. 2020;29(7):1553–1572. doi:10.1007/s00586-020-06391-x
283. Hinde K, Maingard J, Hirsch JA, Phan K, Asadi H, Chandra RV. Mortality outcomes of vertebral augmentation (vertebroplasty and/or balloon kyphoplasty) for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. *Radiology*. 2020;295(1):96–103. doi:10.1148/radiol.2020191294
284. Cawley DT. Motion attenuation surgery in the degenerative lumbar spine: is cement discoplasty a safe and effective option? *Brain Spine*. 2025;5:104220. doi:10.1016/j.bas.2025.104220
285. Fusini F, Girardo M, Aprato A, et al. Percutaneous cement discoplasty in degenerative spinal disease: systematic review of indications, clinical outcomes, and complications. *World Neurosurg*. 2022;168:219–226. doi:10.1016/j.wneu.2022.10.008
286. Zhang H, Gao J, Tang X. Percutaneous cement discoplasty for the treatment of lumbar degenerative diseases: a system review and meta-analysis. *Medicine*. 2024;103(34):e39345. doi:10.1097/MD.0000000000039345
287. Manchikanti L, Soin A, Boswell MV, Kaye AD, Sanapati M, Hirsch JA. Effectiveness of percutaneous adhesiolysis in post lumbar surgery syndrome: a systematic analysis of findings of systematic reviews. *Pain Physician*. 2019;22(4):307–322. doi:10.36076/ppj/2019.22.307
288. Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery*. 2016;79 (5):667–677. doi:10.1227/NEU.0000000000001418