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REVIEW

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Understanding the etiopathogenesis of lumbar intervertebral disc herniation: From clinical evidence to basic scientific research

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Abstract

Lumbar intervertebral disc herniation, as a leading cause of low back pain, productivity loss, and disability, is a common musculoskeletal disorder that results in significant socioeconomic burdens. Despite extensive clinical and basic scientific research efforts, herniation etiopathogenesis, particularly its initiation and progression, is not well understood. Understanding herniation etiopathogenesis is essential for developing effective preventive measures and therapeutic interventions. Thus, this review seeks to provide a thorough overview of the advances in herniation-oriented research, with a discussion on ongoing challenges and potential future directions for clinical, translational, and basic scientific investigations to facilitate innovative interdisciplinary research aimed at understanding herniation etiopathogenesis. Specifically, risk factors for herniation are identified and summarized, including familial predisposition, obesity, diabetes mellitus, smoking tobacco, selected cardiovascular diseases, disc degeneration, and occupational risks. Basic scientific experimental and computational research that aims to understand the link between excessive mechanical load, catabolic tissue remodeling due to inflammation or insufficient nutrient supply, and herniation, are also reviewed. Potential future directions to address the current challenges in herniation-oriented research are explored by combining known progressive development in existing research techniques with ongoing technological advances. More research on the relationship between occupational risk factors and herniation, as well as the relationship between degeneration and herniation, is needed to develop preventive measures for working-age individuals. Notably, researchers should explore using or modifying existing degeneration animal models to study herniation etiopathogenesis, as such models may allow for a better understanding of how to prevent mild-to-moderately degenerated discs from herniating.

KEYWORDS
biomechanics, injury, structure–function relationships

1 | INTRODUCTION

Lower back pain is a prevalent global health concern affecting nearly 80% of the adult population.[1,2] In the United States, reported annual costs related to low back pain have increased from ~$100 billion in 2006 to $134+ billion in 2016.[3–5] These costs, representing a 12% increase after accounting for inflation, will likely increase further in the upcoming decades due to an aging population and the obesity epidemic.[6–8] Moreover, opioid-based medication for low back pain has been a double-edged sword, partially contributing to the ongoing opioid epidemic.[9–11] Innovative clinical treatment strategies with improved effectiveness are needed to address the significant socioeconomic burdens associated with lower back pain.

Lumbar intervertebral disc herniation is a common cause of lower back pain, affecting up to 10% of the population in some regions.[12,13] Herniation is also the principal diagnosis for working-age individuals to undergo spinal surgery, making it one of the leading causes of productivity loss, disability, and healthcare expenditures.[1,2] Thus, herniation has been the focus of spine clinical research since its emergence at the beginning of the 20th century. Despite significant advancements, there remains a lack of understanding of herniation etiopathogenesis, particularly its initiation and progression mechanisms in the clinical setting. Typically, herniation is evaluated based on cross-sectional patient data and cannot be tracked over time in the clinical setting. This inherent limitation highlights the need for parallel basic scientific research, which has been developing reciprocally and synergistically with clinical studies and has made significant progress over the past 50 years.

The rapid development in herniation-oriented research has facilitated an improved understanding of herniation etiopathogenesis. However, this rapid growth has also resulted in more complicated and interdependent clinical, translational, experimental, and computational research with a wide range of assumptions and approaches. The wide range of frameworks developed and applied over the years has made it difficult for researchers and clinicians to interpret and compare results between studies. Thus, this work aims to facilitate a holistic review of herniation etiopathogenesis by summarizing the development and findings of clinical and basic scientific research and proposing future directions for understanding herniation etiopathogenesis, which can be used to direct more effective preventive measures and therapeutic interventions.

2 | MATERIALS AND METHODS

The current narrative nonsystematic review was conducted using a comprehensive search for peer-reviewed articles from the 1930 to 2022 using the PubMed online database. The MeSH terms primarily centered around terms including “Intervertebral Disc,” “Intervertebral Disc Displacement,” “Low Back Pain,” “Physiopathology,” and “Etiology.” The complete list of MeSH terms is provided in the Supporting Information. The reference lists of the identified articles were searched for relevant publications not identified by the MeSH term search strategy. Additionally, while this review includes both clinical and basic scientific research, it will only discuss studies that present hypotheses that have been evaluated through clinical or experimental studies. For example, cellular biology research suggests that it is highly probable that mechanical overload can lead to herniation by inducing proinflammatory responses. However, as the relationship between mechanical overload, cellular inflammatory responses, and herniation has yet to be directly assessed within a single or a series of related studies, this and similar hypotheses will not be systematically discussed in this review. Additionally, though herniation is considered a degenerative disc disorder, it belongs to its own separate clinical diagnostic category.[14] While the overlap between herniation and degeneration makes it nearly impossible to fully separate the two, evidence has shown that herniation may be due to mechanical overload without the presence of degenerative changes, especially in younger patients.[15,16] Thus, studies that examined degeneration without directly investigating herniation will only be discussed in this article when necessary. The sections below discuss herniation pathophysiology, followed by a review of relevant research and discussions on how these studies advanced knowledge about herniation etiopathogenesis and their limitations.

3 | RESULTS

3.1 | Pathophysiology of lumbar intervertebral disc herniation

3.1.1 | Structure, composition, and function of the healthy disc

The intervertebral disc is a fibrocartilaginous joint located between adjacent vertebrae in the spinal column, playing a critical biomechanical role in daily activities by supporting multiaxial spinal loads and dissipating energy placed on the spine (Figure 1A).[17] The disc is a highly complex, heterogeneous, and hierarchical structure comprising a soft gel-like center (i.e., nucleus pulposus, NP) surrounded by a tough, fiber-reinforced ring (i.e., annulus fibrosus, AF). Both the inner AF (i.e., the portion of the AF lamellae adjacent to the NP) and NP are sandwiched between two cartilage endplates (CEPs), which function as a mechanical barrier and solute transport pathway between the disc and the neighboring vertebral bodies (Figure 1B).[18] The AF is an angle-ply laminate composite with layers of aligned unidirectional collagen fiber bundles embedded in a hydrated proteoglycan-rich matrix, providing tensile strength to the disc joint and maintaining multiaxial joint strength and stability. The outer AF is mainly composed of organized concentric lamellae, primarily containing fibroblast-like cells that produce type I collagen, while the inner AF is more fibrocartilaginous and is composed of both type I and II collagen (Figure 1B). The NP is a highly hydrated proteoglycan-rich structure with randomly oriented collagen fibers (primarily type II) and is populated with rounded nucleus pulposus cells (Figure 1B). Due to its high water content, the NP with the

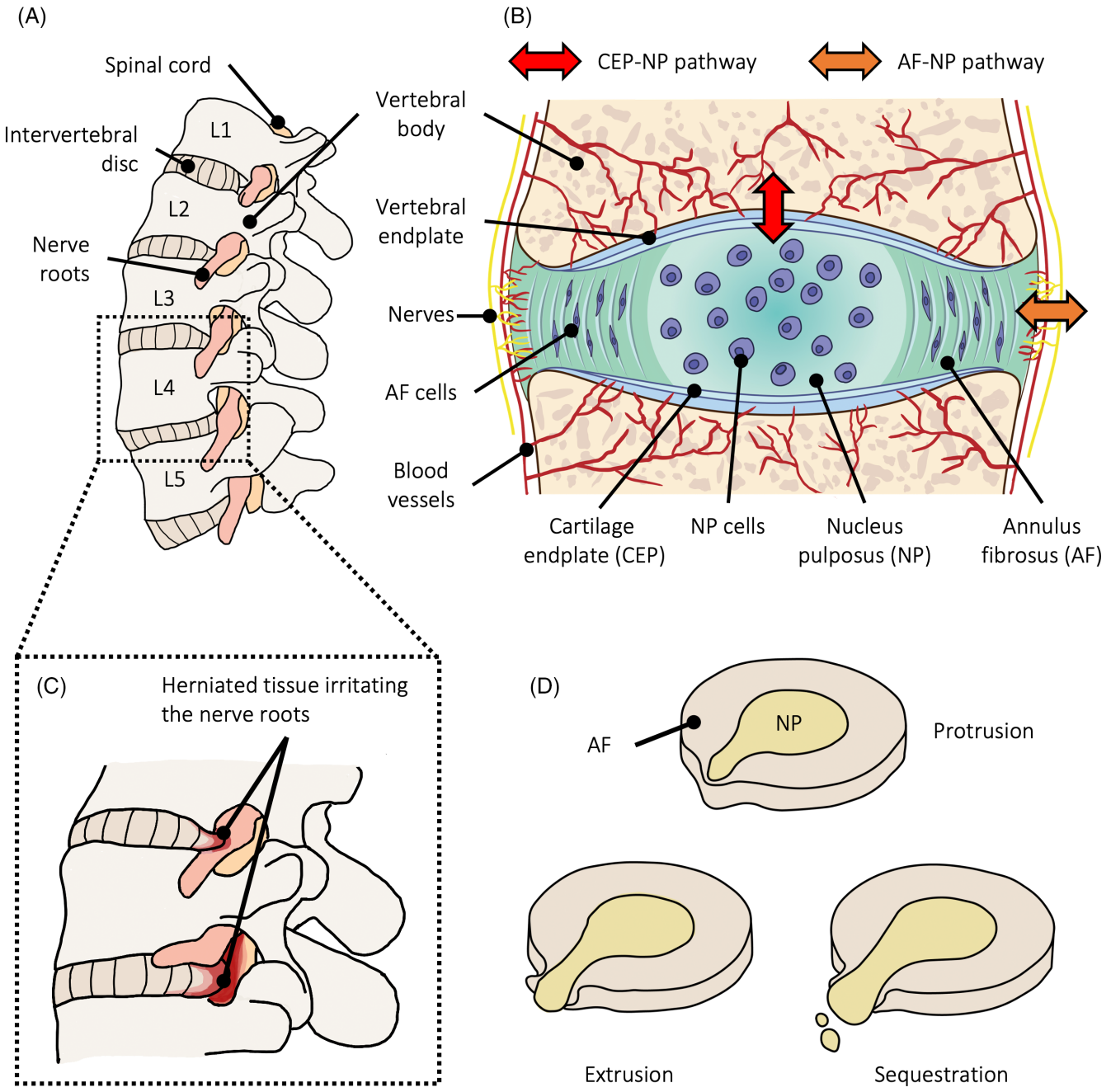

FIGURE 1 Schematic of (A) the lumbar spine and (B) a healthy intervertebral disc with adjacent vertebral bodies and surrounding vascular and neural networks. For clarity, nutrient transport and waste removal pathways are only shown on one side of the disc, and the S1 vertebra in (A) is not shown. Schematics of (C) intervertebral disc herniation with impinged nerve roots and (D) herniation types with increased severity from protrusion to sequestration.

enclosing inner AF functions as a biomechanical shock absorber, allowing the disc to withstand substantial axial compression by distributing the load to the surrounding middle-to-outer AF, primarily in the form of circumferential tensile stresses.[19] The disc is generally considered avascular and aneural except for the limited vascular and nervous networks restricted to the outer AF region (Figure 1B).[18] Thus, nutrient transport and waste removal mainly depend on passive diffusion and convection through the CEP and AF (Figure 1B).[18]

3.1.2 | Pathology of lumbar disc herniation

Intervertebral disc herniation is broadly defined as a localized displacement of disc tissue substance (i.e., NP, AF, CEP, or a combination of them) beyond the limits of the normal disc space (Figure 1C).[14] Clinically, disc herniations are commonly diagnosed in the L4–S1 region of the spine (L: lumbar; S: sacrum; Figure 1A).[20] More particularly, herniations typically occur in the posterior/posterolateral region of the disc and can be categorized into protrusion, extrusion, or sequestration

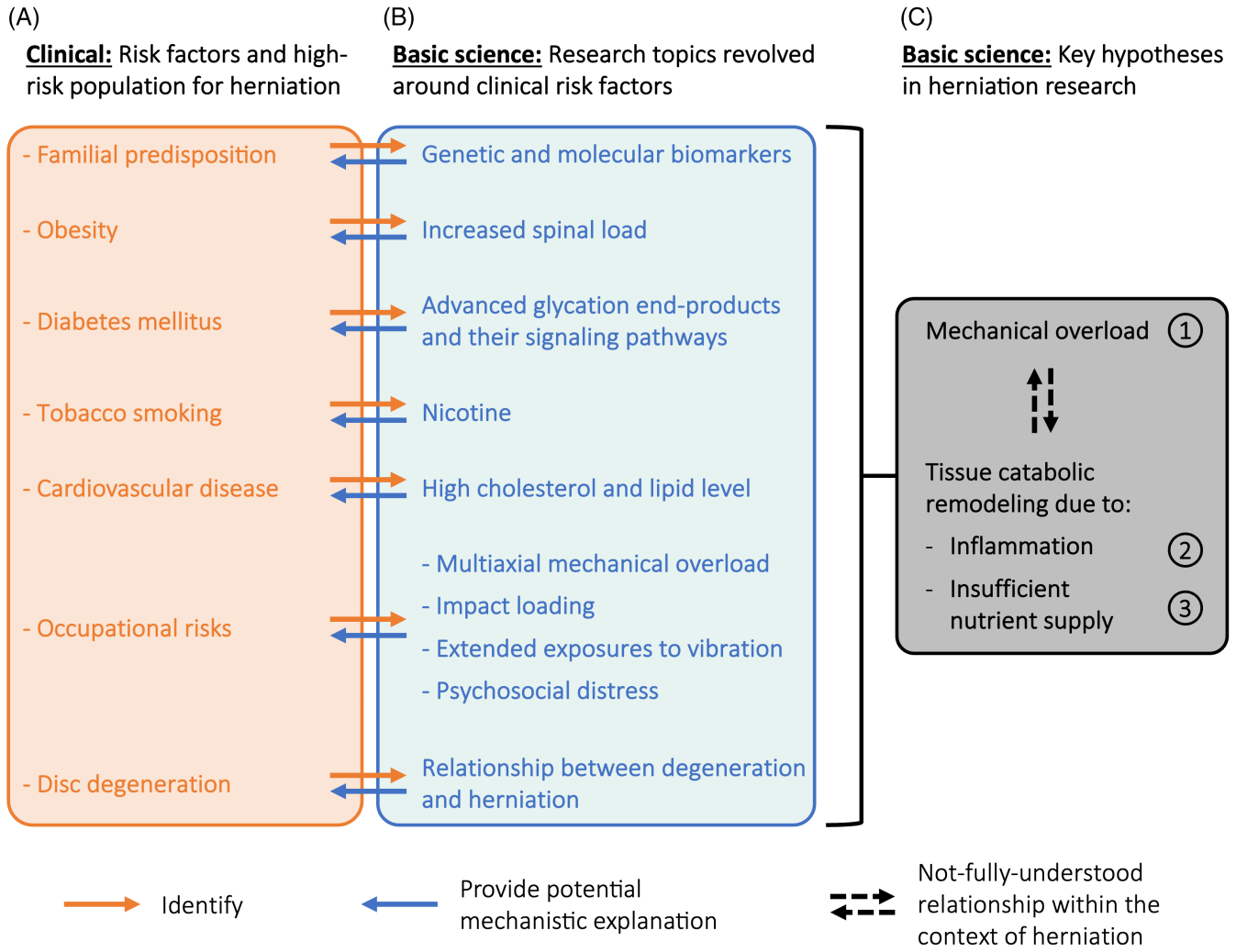

FIGURE 2 Relationship between (A) clinical observational (orange box) and (B) basic scientific herniation-oriented research (blue box). (C) Risk factors established in clinical studies help identify (orange arrows) key research topics (blue box) and hypotheses for basic scientific research (gray box), which, in turn, provide mechanistic explanations (blue arrows) that can potentially inform clinical practice.

based on the level of tissue continuity within the disc space (Figure 1C,D).[1,12,14,20–22] Symptomatic herniations mainly result from the displaced tissue substance mechanically compressing or chemically irritating the lumbosacral nerve roots, causing radicular pain (e.g., sciatica), nerve weakness, and/or lower-extremity sensory abnormalities (Figure 1C,D).[1] Given the significant tissue displacement and degenerative biomarkers observed in herniated discs, mechanical overload, and degeneration have been initially considered the leading causes of herniation.[23,24] However, differential diagnosis over the years has linked herniation to a large variety of mechanical, metabolic, genetic, nutritional, and age-related risk factors, which will be discussed in the following section.

3.2 | Progression of clinical observational research

Clinical data have associated various environmental and personal risk factors with herniation, including familial predisposition, obesity, diabetes, smoking tobacco, cardiovascular disease, and disc degeneration (Figure 2A). Occupations involving heavy physical workloads and mental or emotional distress have also been implicated as risk factors for herniation (Figure 2A). It should be noted that although age and sex are important factors when studying lower back pain, they have not been strong predictors of herniation.[25–28] Specifically, a sex-based bias has not been observed in herniation populations. Additionally, it has been shown that the average age of the herniation population (~40 years) is 15 years younger than that of other degenerative disorders (mean age ~65 years for spinal stenosis and degenerative spondylolisthesis),[25] with herniation incidences reportedly decreasing after the age of 65.[27] However, herniation does tend to occur at slightly higher rates in working-age individuals.[22,25]

3.2.1 | Familial predisposition

There is a significant heritable contribution (i.e., with at least one first-degree relatives diagnosed with herniation or sciatica) to herniation

etiopathogenesis, especially among younger populations. Two earlier case-control studies (103 herniation patients vs. 183 sex- and age-specific controls) showed that a positive family history of herniation increased the risk of herniation in adolescents by approximately five times.[29,30] A retrospective study with 6933 patients showed that almost 70% of herniation patients younger than 25 had at least one first-degree relative diagnosed with sciatica.[16] Similar findings were reported by Zhang et al. (2010 hospitalized low back pain patients vs. 2170 sex-, age-, and weight-specific controls), which found patients under 30 with a family history of herniation were ~14× more likely to experience herniation. While this effect diminished with age, patients between the age of 30 and 55 with a positive family history were still ~5× more likely to suffer from herniation.[31] More recently, a 1254-patient dataset in the Utah Population Database showed that having a first-degree relative with a history of disc degeneration or herniation could triple the risk of herniation.[32]

3.2.2 | Obesity and diabetes mellitus

Clinicians and researchers have long suspected that obesity could elevate the risk of herniation due to the associated increase in spinal load. In an earlier case-control study comparing 332 herniation patients to 1205 sex- and age-specific controls, Heliövarra suggested that a high body mass index was a strong predictor for herniation among men.[33] Two subsequent cross-sectional studies featuring 3000+ patients suggested that being overweight or obese significantly increased the likelihood of herniation, especially the severe herniation cases that required surgery.[34,35] Similarly, a recent case-control study that compared 564 herniation patients to 901 population controls revealed a positive association between weight and the risk of herniation.[36] A meta-analysis of 26 studies indicated that overweight and obesity increased the risk of sciatica and surgery for herniation by ~10%–90%, depending on the severity of herniation symptoms.[37]

Obesity is a strong predictor of Type II diabetes,[38–40] which can also increase the risk of herniation.[41] According to a 16-year prospective study on a 98 407 female-only cohort, diabetes increased the risk of herniation by ~50% after adjusting for age, body mass index, smoking, level of exercise, employment status, medical records, and cardiovascular disease history.[42] Sakellaridis et al. (prospective 200-patient cohort) and Sun et al. (575 herniation patients vs. 219 age-specific controls) also showed that diabetic patients had a greater risk for herniation and were significantly more likely to require surgery due to herniation.[43,44] However, a recent case-control study suggested that diabetes was a risk factor for lumbar spinal stenosis, which is a likely consequence of herniation, instead of herniation itself (220 herniation/stenosis patients vs. 110 sex- and age-specific controls).[45]

3.2.3 | Tobacco smoking

Tobacco smoking has been associated with disc herniation since the 1970s. An early case-control study comparing 223 herniation patients to 494 age-specific controls reported no association between smoking and herniation.[46] However, another case-control study, also led by Kelsey but based on a different 325-patient cohort, suggested that smoking more than 10 cigarettes/day increased the risk of herniation by ~20%.[47] The different results might be due to the latter study accounting for the number of cigarettes consumed daily. The increased risk of herniation with a smoking habit (~50% increase) was confirmed by a subsequent case-control study that compared 163 herniation patients to 205 sex- and age-specific controls.[48] Additionally, Jhawar et al. found a linear relationship between the risk of herniation and the number of cigarettes consumed daily. Particularly, while smoking less than five cigarettes/day increased the risk of herniation by ~20%, consuming 45+ cigarettes/day doubled the risk of herniation.[42] Schumann et al. also reported a 30%–70% increase in herniation risk with smoking, but a dose-dependent response was not found.[36] More recently, multiple meta-analyses showed that smoking increased the risk of herniation by 15%–65%, with greater risks for current smokers.[49,50]

3.2.4 | Cardiovascular disease

Cardiovascular issues, especially atherosclerotic cardiovascular diseases, have been linked to herniation.[51,52] Specifically, Jhawar et al. reported that after adjusting for body mass index, a high cholesterol level increased the risk of herniation by ~25%. The study also reported that hypertension and a history of myocardial infarction increased the risk of herniation by ~13%–25%.[42] More recently, two case-control studies comparing a total of 565 herniation patients to 563 sex-, age-, and body mass index-specific controls reported that patients with symptomatic herniation had statistically significantly higher triglyceride (up to ~20% increase) and total cholesterol concentrations (up to ~9% increase).[53,54]

3.2.5 | Occupational risk factors

Occupational risk factors have been examined extensively due to productivity loss, disability, and healthcare expenditures associated with herniation. The most notable occupational risk identified over the years has been strenuous physical activities that place substantial loads on the spine, including asymmetric heavy lifting (e.g., construction worker) and extended exposures to whole-body vibration (e.g., professional drivers).[16,47,55–65] Psychosocial distress, such as long-term intense deadline pressure and mental/emotional stress, also increases the risk of herniation by up to ~500%.[63,66–68] However, due to significant data heterogeneity between and within these studies (e.g., car model, road condition, and workplace ergonomics), achieving sufficient statistical power has been a great challenge.

Professional athletes (e.g., weightlifters, rowers, and American football players) also experience an increased risk of herniation, likely due to repetitive motions with excessive biomechanical loadings.[69–72] Though strength training might have a protective effect against herniation, this protective effect has yet to be quantified.[36] Additionally, astronauts are more likely to experience herniation immediately after

long-duration space missions (i.e., ~3× higher prevalence in astronauts), likely due to lumbar muscle atrophy and disc overhydration associated with the microgravity environment.[73–80]

3.2.6 | Disc degeneration

Disc herniation is among the most common diagnoses among degenerative abnormalities of the lumbar spine.[12] However, due to the highly complex and interdependent relationship between degeneration and herniation, their association remains unclear. Over the years, researchers have observed that herniation and degeneration induced comparable morphological, histological, and compositional changes in the disc, including a decrease in proteoglycan and water content, neovascularization, and an increase in AF innervation and fissures.[81] Collagen and matrix degradation and upregulation of degenerative remodeling pathways (e.g., cell apoptosis and matrix metalloproteinase expression) have also been identified in herniated disc tissues.[1,19,81–84] Thus, degeneration was considered a risk factor for herniation within the context of this review.

3.2.7 | Summary of clinical observational research

Identifying and validating risk factors of herniation is challenging due to significant heterogeneities in observational research, which can stem from variations in study type (e.g., cross-sectional vs. cohort vs. case-control study), case definitions, inclusion/exclusion criteria, sample sizes, and statistical analyses. Though most of the reviewed risk factors are black boxes that offer little mechanistic explanation for herniation etiopathogenesis, they provide insight into population subgroups at greatest risk for experiencing lower back pain due to herniation. However, more research is needed to clarify the link between occupational risk factors and herniation (e.g., whether consecutive driving or long-term sitting increases the risk of herniation). Such information will help develop preventive measures that can be incorporated into work safety protocols to lower the rate of herniation in working-age individuals.

It should also be noted that the low-socioeconomic status population is predisposed to one or more of the reviewed risk factors, including obesity, diabetes, smoking, and being employed at physically demanding jobs.[38,85,86] People with lower socioeconomic status are also more prone to depression,[38] which can increase pain sensitivity and likelihood of recurring pain episodes, further complicating pain treatment.[85,87,88] Thus, reducing the socioeconomic burden of disc herniation will likely require a multi-disciplinary approach that includes thoughtful public policy, city planning (e.g., fewer food deserts for easier access to healthier food options to reduce the risk of diabetes), and increased access to psychological services.[89–91]

To facilitate a more mechanistic understanding of the discussed risk factors, researchers have used basic scientific research studies that utilized surgically removed human disc tissues or animal disc/tissue analogs to explore several key research topics involving a few essential hypotheses (Figure 2B,C), including the relationship between herniation and mechanical overload (Figure 2C-1), catabolic tissue remodeling due to inflammation (Figure 2C-2), and insufficient nutrient supply (Figure 2C-3). Over the years, these hypotheses have been tested individually with different experimental and computational approaches. The remaining sections summarize the findings and limitations of such studies and propose future work to understand herniation etiopathogenesis.

3.3 | Progression and limitations of herniation-oriented experimental testing research

Modern intervertebral disc experimental testing started in the early 20th century, with an emphasis on characterizing disc anatomical structure and matrix composition.[92,93] In the 1950s, researchers began to characterize biochemical composition (e.g., water, proteoglycan, and collagen content),[94–99] as well as joint- and tissue-level subfailure and failure mechanical properties (e.g., stiffness, strength, range of motion) of healthy and degenerated discs.[100–105] Though these studies did not directly investigate herniation, they laid the theoretical and experimental foundation for subsequent herniation-oriented biomechanics projects.

Following the cornerstone research described above, researchers in the 1980s evaluated the relationship between mechanical overload and herniation etiopathogenesis through multiaxial mechanical testing (Figure 2C-1). Particularly, combined loading conditions (e.g., compression coupled with bending or rotation) were used to simulate physiologically relevant mechanical overload to induce herniation in vitro.[106–115] Meanwhile, a greater emphasis on systematically investigating disc tissue structure and composition led to studies that characterized the microarchitecture and composition of healthy and herniated discs.[83,116–118] Since the 21st century, significant technological advancement brought about a new era of multiscale experimental testing, where many important studies emerged and contributed to improved understanding of herniation etiopathogenesis. Notably, advanced testing setups (e.g., six-degrees-of-freedom tester) helped researchers examine the relationship between complex loading and disc failure behavior.[119–122] Digital image analysis algorithms and advanced morphological and histological characterization helped researchers gain significant insights into tissue-level structure–function relationships during failure.[123–126] Development in relevant studies and their major findings are summarized in Figure 3 and discussed in the following subsections.

3.3.1 | Tissue characterization: understanding temporospatial herniation progression

Histological, morphological, and biochemical composition characterization of herniated discs helped determine the origin and fate of herniated tissues, proposing probable schematics regarding the temporospatial progression of herniation (Figure 3). Based on histological examination of herniated human disc tissues, Yasuma et al. proposed several

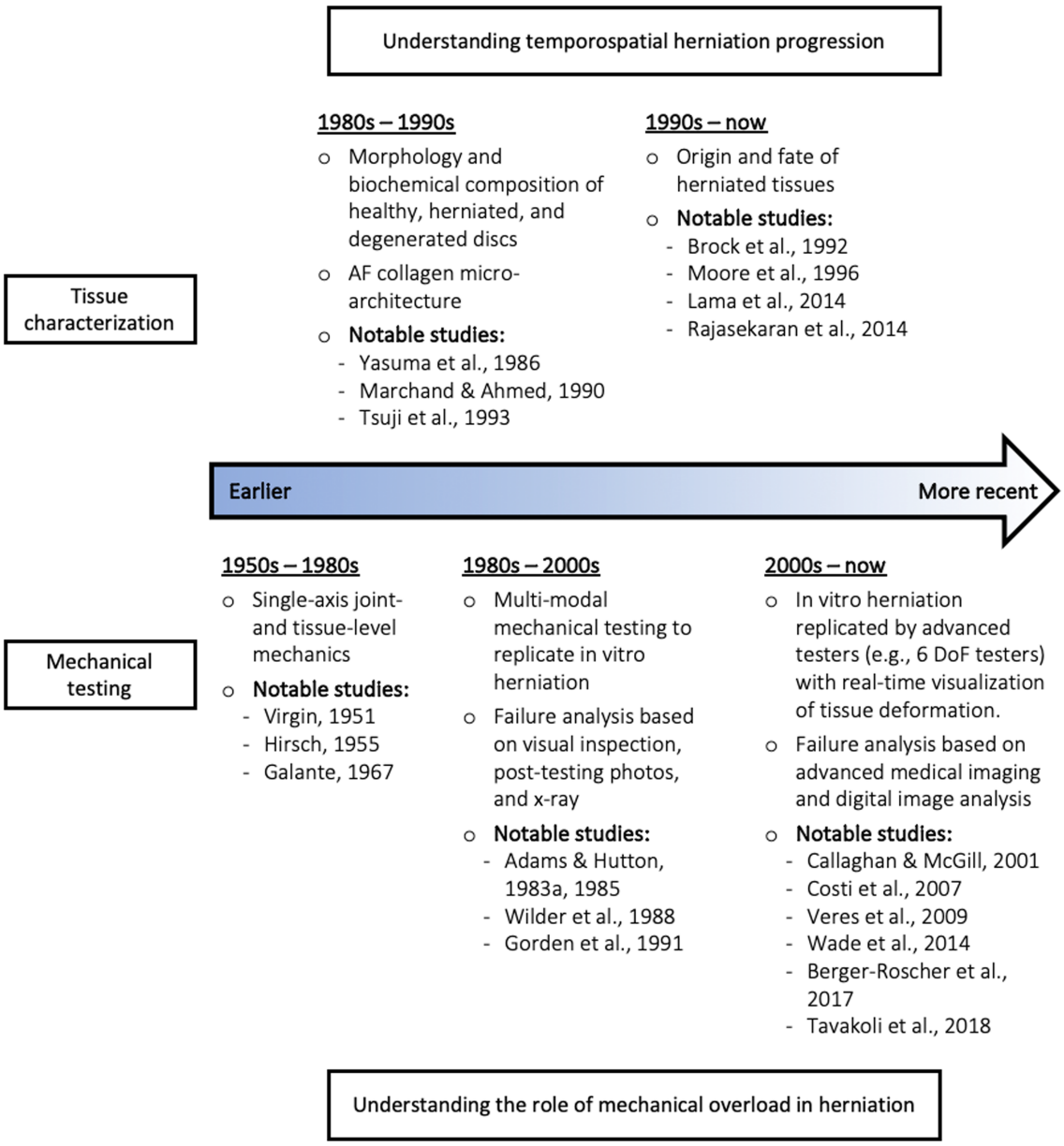

FIGURE 3 Outline of herniation-oriented experimental research.

mechanisms for herniation, including NP protrusion through pre-existed AF fissures, AF protrusion due to AF collapse/buckling, and a mixed herniation failure with both NP and AF protrusions.[118] In the 1990s, subtissue micro-architecture analysis of healthy and degenerated tissue showed that the posterior and posterolateral AF contained 15%–25% thinner and 25%–80% more incomplete lamellae compared to the anterior AF.[127,128] These differences likely contribute to the lower subfailure and failure properties observed in the posterior AF,[129,130] making the posterior and posterolateral AF inherent weak spots for disc failure, while partially explaining why herniations have been predominantly characterized and found in the posterolateral AF by spine specialists, surgeons, radiologists, and basic scientific researchers.[12,131–136]

Herniation mechanisms proposed by Yasuma et al. were partially affirmed by Brock et al., which examined surgically removed human herniated tissue specimens and found NP substance in 55% (55/100) of the samples.[116] The pivotal role of NP in herniation etiopathogenesis was further corroborated by Moore et al., where NP was observed in 98% of the surgically removed herniated tissue specimens (118/120) and was the principal tissue substance in 89% of them (107/120).[83] By contrast, AF was only found in 20% of the surgically removed tissue samples in the two studies combined (42/220).[83,116] In addition, these studies also found CEP fragments in more than half of the examined specimens (125/220). Taken together with a recent experimental study that found cartilage fragments in approximately half (10/21) of the surgically removed human herniated tissue specimens, these findings suggest that the endplate junction could also be involved in herniation development.[83,116,137] The involvement of endplate junction in herniation development was recently demonstrated by a histopathological

study. Particularly, work by Rajasekaran et al. suggested that endplate junction failure (117/185 cases) could be a more common pathway for herniation than AF disruption (21/185 cases), due to the crosstalk between the vertebral bodies and the CEPs.[138] Altogether, these observations help outline a probable schematic for the temporospatial progression of herniation. Specifically, herniation could be a progressive failure process initiated at the NP–AF interface or the endplate junction. The displaced disc substance, consisting primarily of NP and CEP, could traverse through the entire AF or the endplate junction in the posterolateral disc region and forms a complete herniation incidence.

3.3.2 | Mechanical testing: understanding the role of mechanical overload in herniation

Mechanical testing has corroborated mechanisms for herniation as suggested by the previously discussed characterization studies and produced mechanistic explanations for the relationship between mechanical loading and herniation etiopathogenesis (Figures 2C-1 and 3). Specifically, there was a consensus that multi-modal loading (e.g., axial compression combined with flexion) increased the risk of herniation when compared to single-modal loadings (e.g., axial compression or axial rotation alone).[107,109,114,139–146] Among the examined loading conditions with different loading combinations and magnitudes, researchers found that flexion increased the likelihood of NP displacement and AF rupture the most, thus contributing the most to in vitro herniation through the posterior or posterolateral AF,[139,141,142,146–153] while excessive axial compression might contribute more to failure through the endplate junction or the vertebrae.[109,122,140] In comparison, axial rotation, even when combined with other loading directions, was not a significant risk factor, as the posterior structures were more likely to experience failure before the disc.[106,147,149,154]

Mechanical testing has also shown that herniation was more likely to occur under a faster loading rate (up to 40 mm/min or 4 MPa/s). However, even at higher loading rates, the exact loading modalities used can play an important role. For example, high-rate axial compression alone, if applied without flexion, was not able to induce in vitro herniation.[143,144,152] Mechanical testing also showed that extended cyclic loading (5000–120 000 cycles) made the disc more prone to herniation than quasistatic loading of the same magnitude.[114,148,150,155,156] Taken together, mechanical testing findings highlight the pivotal role of multiaxial loading, which is heavily implicated in occupations with demanding asymmetric loading (e.g., construction workers), in herniation progression. These studies also indicate a causal relationship between fatigue loading and increased herniation risk, partially explaining the injurious nature of occupations that expose employees to extended vibrations or repeated motions (e.g., drivers, warehouse line workers).

It should be noted that researchers have also attempted to understand the link between diabetes and the increased risk of herniation through mechanical testing; however, these studies consistently reported an improved disc joint- and tissue-level stability and strength with advanced glycation end-products (AGE) accumulation under monotonic loading conditions,[157–164] contradicting clinical observations.[42–44] The discrepancies may be partially attributed to the lack of fatigue testing for damage accumulation, as a high-AGE environment has been shown to compromise tissue energy dissipation capabilities in tendons.[165,166]

3.3.3 | Ongoing challenges in experimental testing research

Development in experimental testing helped clarify the relationship between mechanical overload and temporospatial herniation progression (Figures 2C-1 and 3). However, these studies were not without limitations, mainly due to challenges in achieving physiologic relevance and utilizing consistent testing protocols between studies. Despite advances in mechanical testing setups, replicating herniation in vitro remains a significant challenge. As a result, many studies inevitably resorted to hyper-physiologic loading conditions (i.e., excessive range of motion or loading magnitude), which could lead to disc herniation failure modes that did not mimic clinical observations,[109,140,167] especially regarding the biochemical composition of the herniated tissues (e.g., no NP leakage vs. heavy NP involvement observed in surgically removed herniated tissues).[150]

Difficulties in replicating physiologically and clinically relevant herniation incidences in vitro might also be in part due to the design of universal testing machines.[167] Specifically, most current mechanical testers confine the instantaneous axis of rotation for torsion and bending to the center of the disc; however, the axis of rotation is likely some distance away from the disc and can shift with the rotation or bending motion in vivo.[17] While several studies attempted to replicate herniation through nuclear pressurization, herniation produced by the setup has had little physiologic relevance.[168–171] Challenges in achieving physiologic relevance also result from difficulties integrating cellular mechanobiology into mechanical testing systems (Figure 2C). Although bioreactors can be used to study cellular mechanobiology, they are currently limited in replicating multiaxial testing conditions and are low throughput testing devices.[172–174]

Similarities between herniated and degenerated discs suggest a link between herniation and degeneration, but inherent variations in human cadaveric disc tissues and challenges in inducing controlled biochemical variations in animal models make it difficult to produce controlled stages of degeneration. Thus, despite great interest in understanding the relationship between degeneration and herniation, such studies are limited, while the few relevant studies reported conflicting results. For example, Adams and Hutton found that degenerated human cadaveric discs with pre-existing ruptures were stable and did not leak NP substance under combined axial compression and flexion.[109] However, Thompson et al. and Wade et al. reported rim lesions and pre-existing degenerative defects in ovine discs reduced the discs' ability to resist motion and made them more prone to in vitro herniation.[153,175] Similarly, the role of hydration on herniation has yet to be systematically investigated, despite the increased awareness of hydration variations with diurnal loading and

TABLE 1 Progression and major findings from mechanics finite element models for disc herniation.

Study	Simulated loadings[a]	Failure criterion	Most "dangerous" loading	Predicted herniation locations
185	Axial compression	Stress-based	N/A	N/A
186	Bending	Strain-based	Flexion	Posterolateral inner AF
187	Axial compression, axial rotation, and bending	Strain-based	Flexion	Posterolateral inner AF
188	Axial compression (varying loading rates) and bending	Stress-based	Lateral bending	Posterior inner AF near the endplate
189	Compressive impact loading (with different durations)	Stress-based	N/A	Endplate region
190	Axial compression and bending (varying loading rates)	Stress-based	Flexion	Posterolateral inner AF
191–193	Axial compression, axial rotation, and bending	Strain-based	Lateral bending and flexion	Posterolateral AF
194	Axial compression, axial rotation, and bending	Stress-based	Lateral bending	Posterior/posterolateral AF or the endplate
195,196	Axial compression and bending (cyclic)	Stress-based	Lateral bending	Posterior AF
197	Axial compression, axial rotation, and bending	Stress-based	Flexion	Posterolateral inner AF
167	Axial compression and bending	Strain-based	Flexion	Posterior inner AF

[a]Bending includes flexion/extension and lateral bending.

microgravity.[73–75,143,144,176] It should be noted that many animal discs (e.g., ovine discs) are excellent human disc analogs due to similar geometric, mechanical, and biochemical properties.[177–180] Thus, it may be advantageous to combine commonly used degeneration animal models (e.g., needle-puncture/stress profilometry animal model) with ex vivo mechanical testing to study disc failure and herniation. Future research directions that might help address these challenges are discussed in Section 4.2.

3.4 | Progression and limitations of finite element modeling herniation research

Challenges in experimental research preclude direct and simultaneous measurements of multiscale stress-sharing mechanisms between tissue- and subtissue-level structures, which are essential for understanding disc failure behavior. This limitation highlights the need for complementary computational models.[181] Accurately modeling disc failure behavior requires robust model predictive power over spatial-, geometry-, and time-dependent properties.[182–184] Since the 1970s, finite element models have been widely used in disc biomechanics research due to their capability to integrate constitutive frameworks with 3D disc geometry, providing a powerful tool for investigating herniation etiopathogenesis and thus will be the focus of this section of the review. Over the years, finite element models that examine herniation etiopathogenesis could be mainly categorized as models that focus on the relationship between loading and disc failure (Figure 2C-1; Table 1), and nutrient transport models (Figures 2C-2 and 3). Since nutrient transport models do not directly examine herniation etiopathogenesis, they are not discussed in this review, but the reader is directed to Volz et al. of such models for disc pathophysiology.[198]

Predictions from computational models agree well with both clinical and experimental observations by predicting the increased risk of herniation due to multiaxial loading and fatigue loading, which was typically in the form of greatly elevated local stresses or strains in the posterolateral AF region.[167,188,191–197] Results from these models suggested that single-loading modalities (e.g., axial compression alone) were not likely to induce herniation,[185,195,199] while flexion and lateral bending, especially when in combination with compression, had the greatest contribution to herniation.[167,186,187,191–194,197] Computational models further complemented the current experimental body of work by demonstrating the increased risk of herniation with impact loading,[189,190] lumbar muscle atrophy/dysfunction,[200] and disc degeneration (i.e., reduced disc height, NP depressurization/dehydration, and osteophyte formation) due to elevated predicted annulus stresses.[192,193,196,201–204] Additionally, multiphasic disc models helped clarify the pivotal role of water in load-bearing capability and behavior, highlighting the detrimental role of degeneration on herniation due to its dehydrating effect.[205,206]

It should be noted that computational models have consistently predicted that herniation occurs in the posterior or the posterolateral disc region, likely caused by greater AF interlamellar shear stresses in that region due to the kidney-shaped disc geometry, agreeing with clinical observations.[167,186,188,191–193,195–197,207] Theoretically, model predictions (predicted stress/strain magnitude and failure location) largely depend on model development decisions (e.g., geometry, loading and boundary conditions, etc.). However, unlike experimental studies that produced a wide range of locations for failure (i.e., herniation) initiation, models of different failure criteria, constitutive material models, and disc geometry consistently predicted that herniation would initiate in the inner AF, or the inner AF near the endplate junction, if the CEP was included.[167,186,188,191–193,195–197] These findings corroborated

clinical observations of herniation locations at individual disc levels and highlighted the robustness of such model predictions.

3.4.1 | Ongoing challenges in finite element modeling herniation research

Over the years, finite element models continue to advance with evolving theoretical frameworks, improving computational power, and progression in imaging and experimental techniques. However, existing models are not without limitations, which mainly stem from limited accessible computational resources and translatability concerns. Accessible computational resources determine the level of model complexity (e.g., disc geometry, material descriptions applied, or spatial information about tissue composition), which are essential for accurately and robustly predicting tissue mechanical responses. However, most current models rely heavily on homogenization theory, which is computationally efficient but cannot accurately represent the heterogeneous native tissue architecture, especially in the AF.[208] Additionally, many models use single-phasic material descriptions that cannot account for the load-bearing contribution of the disc water content. As a result, though these models provide valuable insight into joint-level bulk mechanics, they cannot fully capture tissue failure initiation and propagation behaviors, which are crucial for accurately simulating herniation. To help address these issues, our group has developed a novel multiscale multiphasic structure-based finite element modeling framework for the disc, which has demonstrated excellent model accuracy and robustness (i.e., model predictions were within one standard deviation of the corresponding reported experimental mean values across different specimen geometries, applied boundary and loading conditions, and length scales). However, this framework is more computationally expensive than most existing models, making it difficult to incorporate damage or growth/remodeling descriptions into the system.[209,210]

Model translatability concerns refer to the challenges in translating model predictions to general experimental or clinical observations, which mainly arise from the wide range of assumptions used for model development, the large variations in constitutive descriptions used to simulate tissue behavior, and the lack of a standardized process for model validation.[181,211,212] Specifically, mathematics-based constitutive relationships can lead to model parameters without physical meanings or interpretations. Nonphysical model parameters are difficult to systematically calibrate to represent variations in tissue structure and function associated with different pathophysiologic processes (e.g., reduced swelling capabilities with degeneration). Variations in material models selected by different research groups further complicate this issue by making it difficult to compare model parameters and, thus, model predictions between studies. Additionally, the lack of standardization in model validation can compromise the model predictive power over alternate deformation states not included in the initial validation process, further weakening model's translatability and clinical relevance.[181,213] In recent years, issues centered around model translatability has become a growing concern, as a greater number of implant companies use data from finite element models for regulatory clearance purposes.[211]

4 | DISCUSSION: FUTURE DIRECTIONS

Decades of herniation-oriented research resulted in many important and insightful studies that identified risk factors for herniation, characterized the structure–composition–function relationship in healthy, degenerated, and herniated disc tissues, and examined mechanisms of disc failure. This substantial body of work improved our understanding of herniation etiopathogenesis. However, herniation is a complex pathophysiologic process involving a convoluted interplay between various mechanical, biochemical, and metabolic elements. One current major challenge is establishing a direct relationship between mechanical loading, a necessary factor for herniation, and catabolic remodeling within the context of herniation (Table 2). Experimental testing can replicate herniation in vitro but lacks the capability to incorporate simultaneous cellular investigations into the testing system. Animal models and cellular biology approaches can integrate different factors of interest, such as abnormal mechanical load,[172–174,214–217] diabetes,[218–223] smoking,[224–226] obesity,[227,228] or insufficient nutrient supply,[229,230] into one system. However, these systems rely heavily on inducing in vivo or in vitro degeneration to make inferences about herniation and do not directly report or discuss herniation, even though herniation evidence might be present. Computational models complement experimental research but require improved translatability to robustly replicate and predict clinical and experimental observations. Future directions proposed in the following subsections combine known developments in existing research techniques with ongoing technological advances to provide feasible pathways for addressing the abovementioned challenges.

4.1 | Experimental research: filling the gap of experimental testing studies

Comprehensive literature research highlights many ways that in vitro experimental testing has been used to advance knowledge about disc failure; however, there still exists many unknowns that warrant further research. Specifically, assessing disc mechanics using mechanical testers that create an instantaneous axis of rotation at some distance away from the disc during torsion- and bending-driven testing may help create disc failure that better mimics clinical observations.[231,232] Previous work from our group also showed that the location of the instantaneous axis of rotation had a considerable impact on disc herniation location under combined axial compression and flexion (i.e., herniation through the posterior/posterolateral inner AF with the axis located anterior to the disc versus herniation through the endplate junction with the axis located on the disc).[167] It should be noted that computational models have highlighted lateral bending, a common loading condition in physically demanding jobs, as an important

TABLE 2 Summary of basic scientific research methods to study herniation etiopathogenesis.

	Mechanical testing	Animal models	Cellular biology	Finite element models
Capability to create herniation to directly investigate herniation etiopathogenesis?	Yes, by mechanical overload in vitro	No	No	Yes, by mechanical overload in silico
Capability to simultaneously examine mechanical overload and catabolic remodeling/cellular response in relation to herniation?	No, mechanical overload only	Yes	Yes	No, mechanical overload only

factor for inducing herniation.[188,191–195,197] However, lateral bending has yet to be widely featured in experiments and should be assessed more by mechanical testing.

Additionally, clinical evidence presented by Rajasekaran et al. suggests that the research community could gain valuable insight into herniation etiopathogenesis by examining in vitro herniation at or near the endplate junction,[138] which might offer a more comprehensive understanding of risk factors specific to endplate-based herniation with respective preventive measures. Therefore, it may be important to direct more attention to endplate-driven herniation, as well as the crosstalk between vertebral bodies and CEPs, to gather additional clinical evidence and experimental data. Moreover, further research is needed to understand the relationship between degeneration and herniation, particularly factors that lead early-degeneration-stage discs to herniation. Such understanding may assist clinicians in deciding between conservative and operative treatment strategies.

4.2 | Animal models for disc herniation

Animal models have been used extensively to study disc degeneration etiology and treatment[233–237]; however, few of these models explicitly replicate or examine disc herniation. While animal models designed to study degeneration may present evidence of herniation, studies typically do not describe such observations due to their specific scope. For the few herniation-oriented animal models, in vivo herniation is primarily induced through anterior or anterolateral AF incision or NP removal, which has little clinical relevance, as disc failure is commonly observed in the posterior/posterolateral AF with a NP extrusion.[238,239]

Research is needed to develop and validate animal models for studying herniation etiopathogenesis. For example, existing degeneration animal models may already present herniation evidence and can provide researchers with in vitro or in vivo data to investigate herniation etiopathogenesis. In vivo herniation might also be induced by applying abnormal mechanical loads to the discs from genetically modified animal models.[236,240,241] Such models allow researchers to connect known mechanical loads or biochemical biomarkers to variations in disc structure–function relationships and cellular mechanobiological responses at different stages of herniation development, which can provide invaluable insight into herniation etiopathogenesis. For example, Halanski et al. developed a kyphotic porcine model using a vitamin D-deficient maternal diet,[242] suggesting that spontaneous disc herniation models, even in large animals, may be possible. Such models might provide a pathway for researchers and clinicians to track herniation initiation and progression with time, which is extremely difficult to conduct in the current clinical setting.

4.3 | Combined experimental and computational study designs

The interplay between experimental and computational techniques has significantly advanced spine biomechanics. Mainly, computational models look to experimental measurements to define model inputs, while experimental work resorts to model predictions for insights about difficult-to-measure tissue properties, which, in turn, inspires novel experimental investigations, completing this virtuous cycle. For example, combining experimental and computational frameworks has furthered the understanding of herniation etiopathogenesis by clarifying nutrient transport kinetics under dynamic loading, which is essential for predicting tissue catabolic remodeling.[243–247]

Recent technological advancements have provided researchers with greater access to experimental testing and computational modeling platforms, which will encourage further synergetic development between experimental and computational frameworks within or between research groups.[248,249] Moreover, improved computational resources have facilitated structural finite element models capable of simultaneously investigating multiscale disc mechanics and cellular regulation mechanisms.[250] Integrating mechanics and cellular biological experimental data, such models hold the potential to establish direct relationships between mechanical, biochemical, and metabolic factors within the context of herniation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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