Review Article

Mechanical Basis of Lumbar Intervertebral Disk Degeneration

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Abstract

The etiology of degenerative disk disease (DDD) is multifactorial. Among the various factors, mechanical processes contributing to endplate or discal injuries have been discussed as the initiating events in the degenerative cascade. DDD encompasses the multitudinous changes undergone by the different structures of the spinal segment, namely intervertebral disk (IVD), facet joints, vertebral end plate (VEP), adjoining marrow (Modic changes), and vertebral body. It has been etiologically linked to a complex interplay of diverse mechanisms. Mechanically, two different mechanisms have been proposed for intervertebral disk degeneration (IVDD): endplate-driven, especially in upper lumbar levels, and annulus-driven degeneration. VEP is the weakest link of the lumbar spine, and fatigue damage can be inflicted upon them under physiological loads, leading to the initiation of DDD. Disk calcification has been put forth as another initiator of inflammation, stiffening, and abnormal stresses across the IVD. The initial mechanical disruption leads to secondary IVDD through unfavorable loading of the nucleus pulposus and annulus fibrosis. The final degenerative cascade is then propagated through a combination of biological, inflammatory, autoimmune, or metabolic pathways (impaired transport of metabolites or nutrients). Abnormal spinopelvic alignment, especially pelvic incidence, also significantly impacts the degenerative process. Hence, the etiology of DDD is multifactorial. Mechanical pathways, including VEP injuries, increased disk stiffness, and abnormal spinopelvic alignment, play a significant role in the initiation of IVDD.

Keywords: Degenerative disk disease, disk prolapse, intervertebral disk degeneration, spinopelvic alignment, vertebral endplate

Introduction

The intervertebral disk (IVD) constitutes a composite organic ecosystem, which is sustained by a homeostatic milieu.[1,2] Similar to any natural ecosystem, senescence, degeneration, and death occur in the IVD consequent to a combination of multitudinous physiological and biomechanical processes.[3,4] Over the past decades, our growing understanding of the complexity underlying the phenomenon of degenerative disk disease (DDD) has led to an etiology-specific approach to the development of preventive and management strategies. It has also been well-acknowledged that the key to the ideal management of DDD must involve a clear identification of the component problem and a direct intervention aimed at preventing or correcting it.[5-9] Among such preventive strategies, genetic or tissue engineering has been purported as a potentially effective approach to decelerate the degenerative process during the early stages.

IVD is the largest avascular structure in the body and consists of a predominantly anaerobic environment. A combination of ischemic, biochemical, inflammatory, and mechanical factors, including repetitive microtrauma, have been purported as underlying etiological contributors to the pathophysiology of DDD.[10-12] Once the degenerative process is fully established, none of the treatment strategies offer a complete cure. However, interventions at the molecular level before the onset or during the early course of degenerative processes can

Received: 23-Jan-2024, **Revised:** 03-Mar-2024,
Accepted: 17-Mar-2024, **Published:** 25-Jul-2024.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/isoj

DOI: 10.4103/isj.isj_6_24

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How to cite this article: Muthu S, Visawanathan VK, Chellamuthu G. Mechanical basis of lumbar intervertebral disk degeneration. Indian Spine J 2024;7:121-30.

provide a potentially successful primary or secondary preventive approach to this disorder.[13] In this context, stem cells and tissue engineering technologies have been heralded as prospective prophylactic strategies imminent in the management of DDD.[5-12,14]

Multiple studies have acknowledged the fact that the efficacy of the endogenous stem cell/progenitor cell-based treatment does not remain consistent in all individuals. Such an erratic effect of these strategies has been attributed to the bottleneck secondary to compromised tissue microenvironment, such as persistent, unfavorable mechanical loads, hypoxia, local tissue acidosis, lack of nutrition to the disk, inimical tissue equilibrium or metabolism, and endogenous genetic defects or molecular deficiencies.[8,14,15] In the backdrop of this understanding, the mechanical issues leading to DDD have gained progressive importance over the past years. The current review was thus planned to comprehensively discuss the issues regarding mechanical factors associated with DDD.

Materials and Methods

Search for relevant literature

A thorough literature search was performed on 15 December, 2023 using the five databases (Pubmed, Embase, Web of Science, Google Scholar, and Cochrane Library) to identify the studies, which were published during the period 2000–2023. The search was performed using the keywords in combination with Boolean operators, such as (((Degenerative disc disease) OR (DDD) OR (Disc Degeneration) AND ((Etiology) OR (Mechanical factors) OR (Mechanical trauma) OR (Microtrauma) OR (Physical factors) OR (Biomechanical stress))). All the studies reporting on lumbar DDD and the mechanical basis of its etiopathogenesis were considered for this review article. Among these manuscripts, letters to the editor, opinions, reviews (narrative or systematic), and manuscripts published in non-English literature were excluded. The search outputs from the included databases were first downloaded, extracted in EndNote, and then manually selected following deduplication. The titles were initially screened, after which the individual abstracts were carefully shortlisted by two authors. Further, during the second round of screening, full-text versions of the manuscripts were reviewed, and the final selection of the articles was performed. Any discrepancy during the article selection was resolved with discussion until consensus was achieved. The major research objectives were on the epidemiology, etiopathogenesis, molecular basis of DDD, and the mechanical factors leading to DDD.

Results

Literature search

The literature search yielded 1211 manuscripts. Following deduplication and manual selection of manuscripts with EndNote, 669 articles were selected. Following the title screening, 73 articles were included for further screening. Finally, 48 studies were selected for inclusion in this review **[**Figure 1**]**.

Discussion

Disk degeneration is described broadly as a combination of biological (cellular) changes, which are predominant within the nucleus pulposus (NP), and structural alterations, which are more pronounced within the annulus fibrosus (AF) and vertebral endplates (VEP).[16-19] Some of the main structural changes in the IVD morphology include radial fissures or circumferential clefts, rim tears within the annulus, radial annular bulging, inward buckling of the annulus, decreased height of the IVD, endplate transgressions, and vertical bulging of the endplates into adjoining vertebral bodies.[20,21] In addition to these aforementioned degenerative changes, herniation of the NP through the defects in the AF leads to symptomatic presentation due to compression of the neural elements (lumbar disk herniation—LDH). These changes within the IVD are associated with concurrent arthritic changes of the facet joints, as well as osteophyte formation around the margins of vertebral bodies.[17,20] Consequent to these structural modifications, there is a corresponding functional deterioration of the IVD. While a healthy IVD is soft and contains a hydrated central NP acting as a hydraulic cushion capable of even stress distribution across the vertebrae, degenerated IVDs have significantly compromised hydrostatic regions, leading to high-stress concentrations within the AF.[18,22]

Quintessentially, IVD degeneration (IVDD) has been described as a mechanical failure of the structure; however, studies have also revealed substantial molecular changes in the composition of these degenerated IVD tissues.[23] In addition to these mechanical versus biological factors, evidence has also shown crucial genetic influences, such as genetically weak collagen framework of the IVD or genetic influences on the disk's nutrition and vascularity, to influence the degenerative cascade.[24,25] Although there has been considerable focus on the identification of biochemical, metabolic, and molecular abnormalities of the degenerated disk elements over the past years, it has been acknowledged that these abnormalities can be consequences of mechanical disk failure rather than an underlying cause (a "cause-and-effect" conundrum).[26,27] The precise concatenation of biological events following mechanical disruption can help us in devising strategies for the prevention and treatment of disk-related low back pain. The current narrative review focuses on the mechanical events contributing to the degenerative cascade of vertebral segments.

Degenerative cascade

As per the concept of IVD degenerative disease put forth by Kirkaldy–Willis and Farfan[28] in 1982, a majority of the studies have agreed upon the degenerative cascade that is

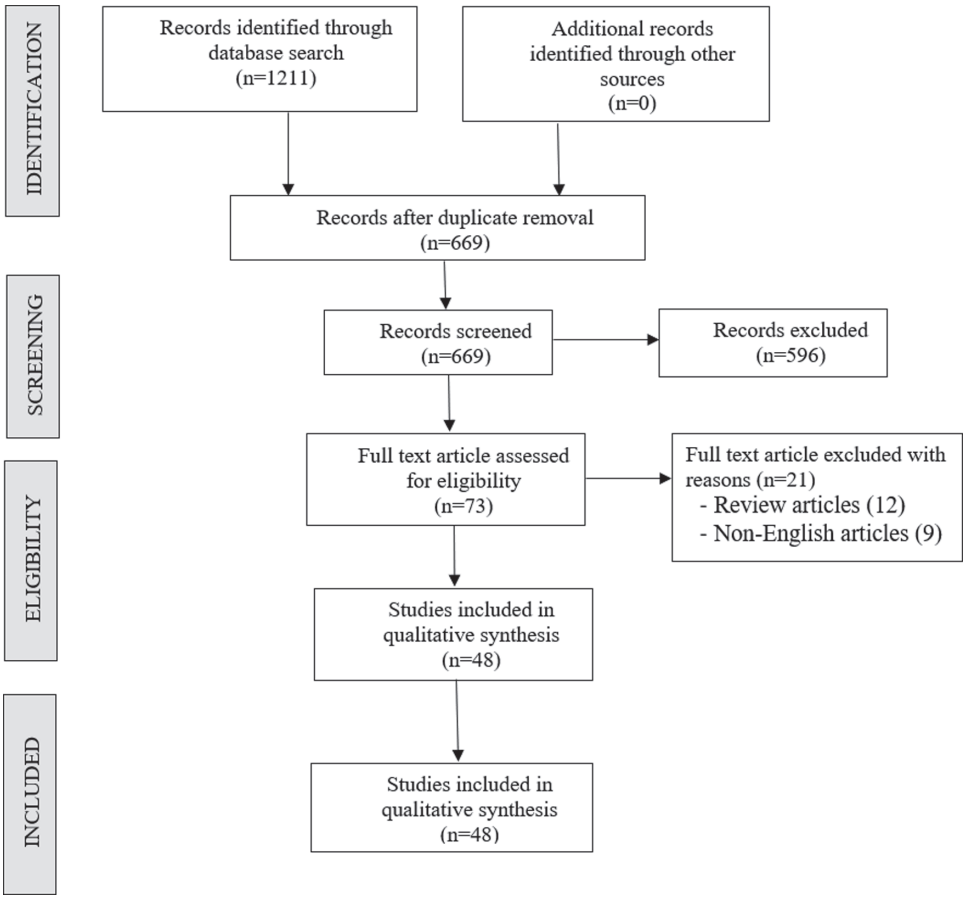

Figure 1: PRISMA flow diagram of inclusion of studies in the review

secondary to the progression of IVD and facet degeneration. Following a period of enhanced motion with segmental instability, the end stage of IVDD is characterized by a stage of restabilization.[29,30] This sequential chain of events involved in the progression of degenerative spinal disorders has been shown in Figure 2 and broadly includes three stages: a. Dysfunction, b. instability, and c. stabilization. A combination of events occurs at the IVD, facet, and vertebral body levels during each stage, which eventually leads to multilevel spondylotic changes in the spine.

Pathophysiology of IVDD

The basic etiological factors contributing to DDD include age-related or genetic factors, imbalanced transport of metabolites, and unfavorable loading patterns.[31] Following excessive mechanical loading, the structure of IVD is disrupted, leading to a cascade of cell-mediated immune response with exposure of the immune system to the IVD material. This, in turn, leads to further disk disruption (lumbar DD) and chronic low back pain (CLBP).[32]

IVD and facet joints play a critical role in biomechanical (both kinetic and kinematic) behavior of the lumbar spine. Both these structures have been associated with a cascade of degenerative events in the lumbar spine.[33] The VEP injuries have been implicated in the pathogenesis, and the marrow adjoining VEP also undergoes sequential changes, which have been described as modic changes (MC).[34,35] The severity grading of degenerative changes in these structures has been shown in Tables 1–3.[36-38] Adams and Dolan[39] proposed two mechanisms for IVDD: endplate-driven and annulus-driven degeneration. The characteristics of endplate-driven degeneration (more common in the upper lumbar levels) include damaged endplates, circumferential tears between annular lamellae, and internal bulging or collapse of the AF into NP. On the other hand, the annulus-driven DD is characterized by pronounced reduction in the disk height and radial fissures in the NP extending posteriorly or posterolaterally. Moreover, the degraded cartilaginous tissues progressively stiffen secondary to nonenzymatic glycation.[40] The resultant NP, which is fibrous and dehydrated, is characterized by focal lamellar thickening and extensive lamellar disorganization. Such physical changes lead to the concentration of the focal compressive stresses within the AF, which, in turn, results in the gradual propagation of annular tears and disk disruption.[41]

The degenerative cascade is typically initiated by an imbalance between the catabolic and anabolic pathways

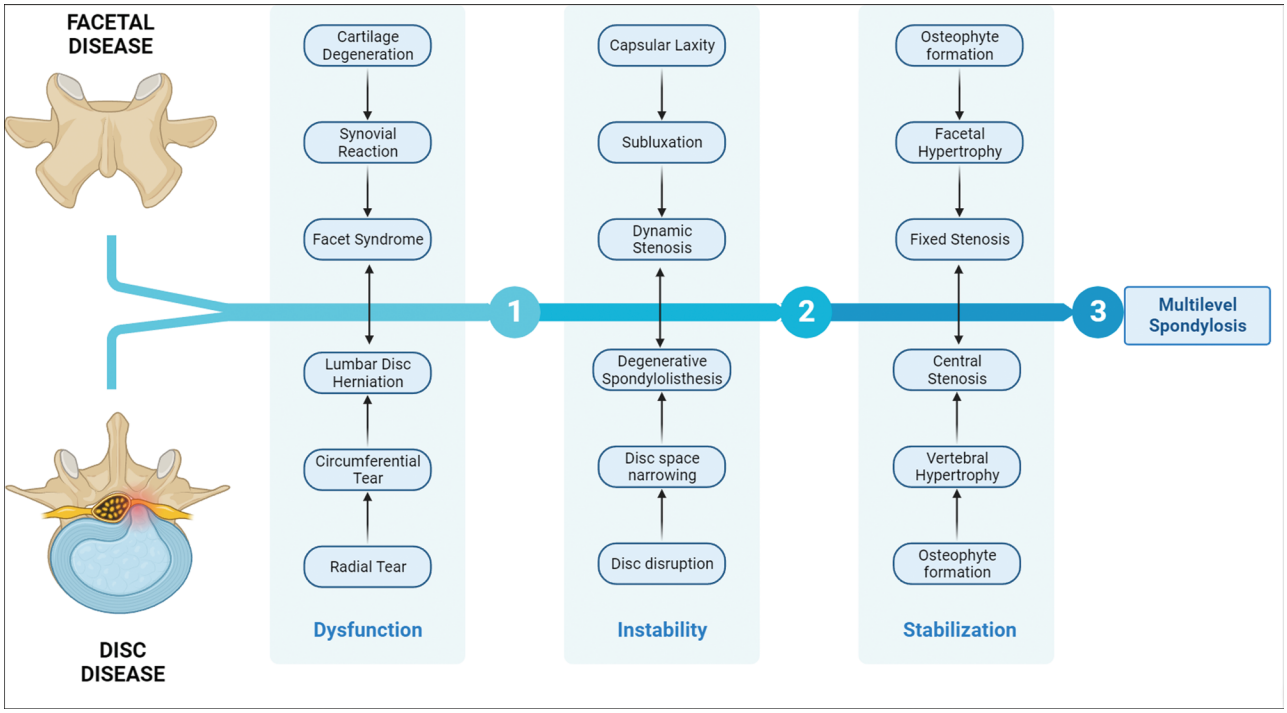

Figure 2: Degenerative cascade of events leading to multilevel degenerative spondylosis

Table 1: Pfirrmann classification of disk degeneration[36]

Grade	Structure	Distinction nucleus/annulus	Signal intensity	Disk height
I	Homogeneous, bright white	Clear	Isointense to cerebrospinal fluid	Normal
II	Inhomogeneous with or without horizontal bands	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
III	Inhomogeneous, gray	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogeneous, gray to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogeneous, black	Lost	Hypointense	Collapse disk space

Table 2: Weishaupt grading of facet osteoarthritis[37]

Grade	Criteria
0	Normal facet joint space (2–4 mm)
1	Narrowed facet joint space (<2 mm) and/or small osteophytes and/or mild hypertrophy of the articular process
2	Narrowed facet joint space (<2 mm) and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions
3	Narrowed facet joint space (<2 mm) and/or large osteophytes and/or severe hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts

Table 3: Classification of Modic changes noted in vertebral body[38]

Type	Features	MRI findings
0	Normal disk, vertebral body	Normal findings
1	Bone marrow edema within vertebral body and hyper-vascularization	Hypointense signal intensity on T1; hyperintense bone marrow lesion on T2 weighted images
2	Fatty replacement of the vertebral body bone marrow	Hyperintense signal intensity on T1 and T2 weighted images
3	Subchondral bone sclerosis	Hypointense signal intensity on T1 and T2 weighted images

within the IVD. Consequent to the extracellular matrix (ECM) degeneration, neo-innervation and neo-vascularization of the discal tissues occur. This further leads to degenerative processes, such as disk bulge, loss of water and proteoglycan, and progressive collapse of disk height. Patients with CLBP have been demonstrated to have significant ingrowth of nociceptive neural fibers into the inner AF and NP, as well as neovascularization, the exact mechanisms of which are still largely unknown.[42]

Mechanical factors

Cadaveric experimental studies have remained the most effective strategy to demonstrate the impact of

repetitive, unfavorable mechanical loading of the IVD in the pathogenesis of pathologies such as LDH, annular bulging, and radial fissures of the annulus.[43,44] The validity of cadaveric experiments to substantiate the short-term mechanical parameters has been reported to be fairly reasonable in view of the extremely low cell density and metabolic rate of IVD, as well as minimal effects of frozen storage on intradiscal pressure or biomechanics of the motion segments.[45,46]

VEP damage and IVDD

Biomechanical studies by Adams *et al.*[18,19,22,23,26,39,43] demonstrated that the VEPs as the weakest link of the lumbar spine, and fatigue damage can be inflicted upon these structures by physiological load ranges. The mechanical vertebral endplate damage, thus inflicted, can negatively impact the stress distributions in the adjacent IVD, thereby the integrity of the disk structure may be significantly disrupted. In their cadaveric study, it was demonstrated that endplate violation, especially disks of patients aged between 50 and 70 years, can potentially reduce the pressure in adjacent NP by 25%–27% and generate peak compressive stresses in the annulus. Such repetitive, compressive loads can potentially inhibit the cellular metabolism throughout the IVD and result in progressive matrix depletion. Thus, they concluded that minor fatigue injuries to the VEP secondary to cyclical, compressive physiological loads are the initiating insult resulting in the progressive structural changes of the adjacent IVD. Such VEP disruption may further lead to secondary IVD degeneration through other biological, such as hindering the transport of metabolites from the vertebral body to the NP, inflammatory, or autoimmune pathways.[47-49] The pathophysiology of internal disk disruption secondary to VEP injury has been depicted in Figure 3. Schmorl's nodes, located adjacent to VEP defects, have been reported to present as harbingers of multilevel disk degeneration.[20]

Pang *et al.*[50] recently described the "ultra-short-time-to-echo (UTE) Disk sign" (UDS) on magnetic resonance images and showed its strong association with lumbar disk displacements, the severity of disk degeneration, MC, and CLBP. It has been suggested that UDS may represent the calcification of the disk, which is characterized by active inflammation and disk stiffening. This calcification can be attributed to an abnormal loading mechanism within the disk and can adversely affect the kinematics of the disk and motion segment. It has been suggested that UDS may have a potential role in the initiation and propagation of lumbar disk disruptions and endplate damage, which, in turn, results in IVDD and MC.[50-52]

Spinopelvic parameters and IVDD

Balanced sagittal alignment of the spine is defined as the upright position in which the spine and pelvis are in sync

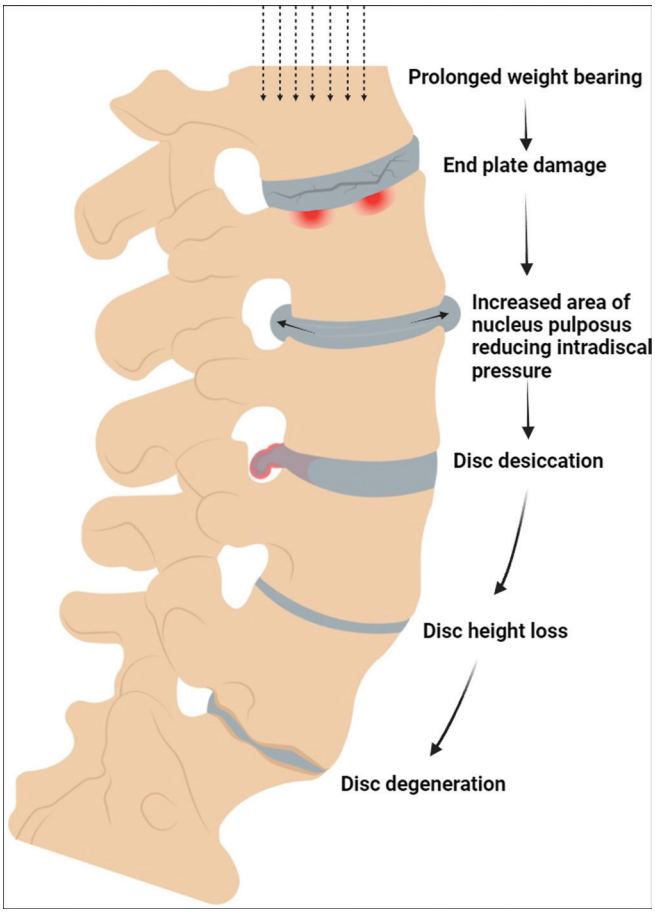

Figure 3: Pathophysiology of internal disk disruption secondary to vertebral endplate injury leading to disk degeneration

with each other.[53,54] The harmonious connection between the pelvis and the spine is defined as "spinopelvic balance," which is primarily defined by three parameters, namely pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS).[55,56] PI was initially described by During *et al*. in the year 1985 and has been shown to remain constant throughout adulthood, irrespective of patients' position or posture.[57,58] The other important parameters of pelvic orientation include SS, PT, and lumbar lordosis (LL).[59] Studies by Keorochana *et al*.[60] and Habibi *et al*.[61] emphasized the significant influence of altered sagittal spinal alignment on the lumbar spine kinematics, which impacted the load bearing of the vertebral segments and incidence of IVDD where patients with degenerative spondylolisthesis are characterized by increased PT and decreased SS compared to the normal control population, suggesting the presence of a pelvic compensation as shown in Figure 4.

In a prospective study[62] comparing the spinopelvic parameters between asymptomatic young and older individuals, the older individuals had significantly greater thoracic or thoracolumbar kyphosis, total and lower LL, greater ratio of lower to total LL, and a longer sagittal axis deviation of T12-S1 plumb line, without any changes

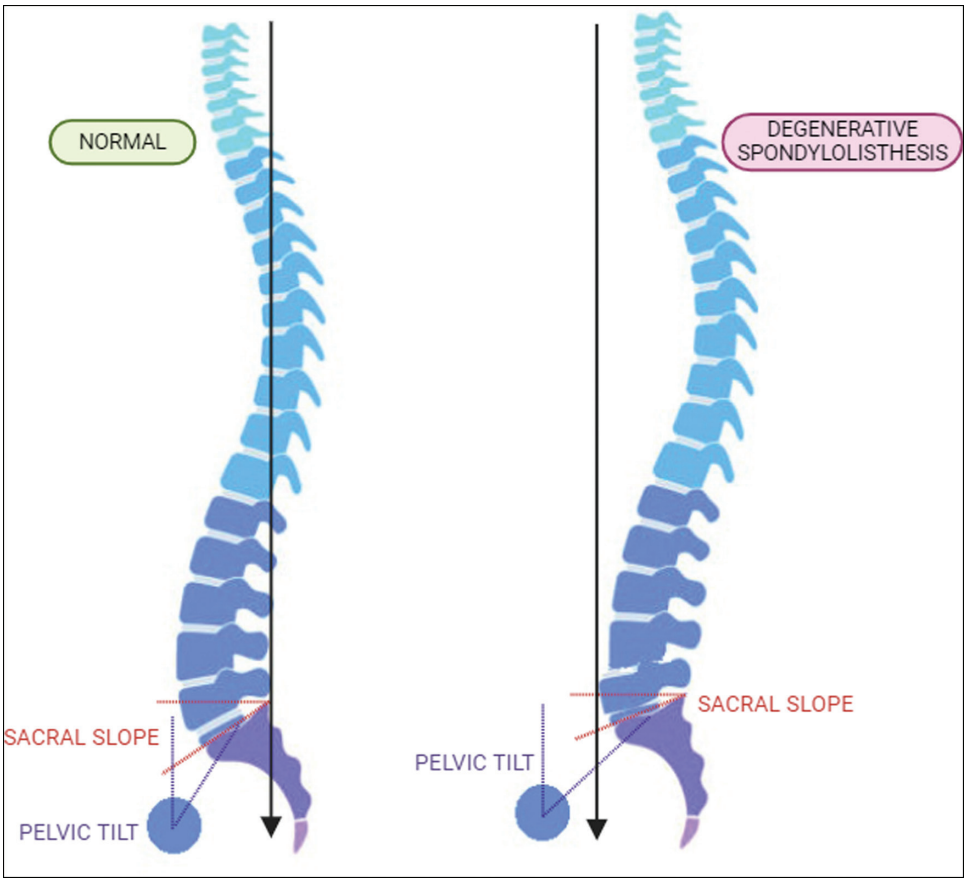

Figure 4: Sagittal and pelvic alignment parameters in normal individuals and in patients with degenerative spondylolisthesis characterized by increased pelvic tilt and decreased sacral slope suggestive of pelvic compensation, thereby shifting the weight-bearing axis anterior to the sacrum.

in SS or global sagittal balance (sagittal vertical axis—SVA). Thus, although sagittal spinal alignment underwent diverse changes with aging, all such alterations did not necessarily lead to progressive symptomatology. In a retrospective study by Vazifehdan *et al.*,[63] the relationship between acquired spondylolysis and spinopelvic parameters was evaluated. Based on their observation, they concluded that patients with high PI, SS, and PI-LL mismatch demonstrated significantly higher incidence of lytic pars interarticularis lesions.

In a prospective study by Ogon *et al.*[64] evaluating quantitative magnetic resonance imaging (MRI) (T2 signal), anterior AF degeneration in patients with CLBP was significantly associated with hypolordosis of the lumbar spine, anterior translation of body trunk (as assessed by SVA), and posterior inclination of the pelvis (as determined by PT). At the lower lumbar disks, anterior AF degeneration was substantially associated with posterior pelvic inclination, while lumbar hypolordosis and anterior truncal translation were significantly correlated with anterior AF degeneration at all lumbar disks. T2 values on MRI in the NP or posterior AF at all lumbar levels did not show any correlation with spinopelvic parameters.

In the recent study by Zehra *et al.*,[51] the complex interactions among factors such as PI, innate adaptability of disks, and VEP, as well as patient-related factors, such as age/ sex, genetics, smoking, nutrition, lifestyle, and occupation, were examined. Based on their analysis, low PI (or a vertical pelvis) was correlated with increased loading stresses across the IVD and VEP, leading to a higher incidence of MC, disk herniations, and UDS. On the other hand, high PI was correlated with raised shear stresses across the spinal segment, resulting in higher facet joint degeneration (FJD) and spondylolisthesis. Biomechanically, previous studies too have shown higher mechanical stress on the lumbar facet joints and greater risk of degenerative spondylolisthesis and mechanical low back pain in patients with high PI.[53,65]

Habibiet *et al*[61] concluded that more straightened lumbosacral profiles predisposed patients to higher IVDD. In a retrospective study by Lv *et al.*,[53] spinopelvic parameters were significantly correlated with FJD. While high PI was associated with FJD at the lower lumbar spine, greater PT magnitude was correlated with severe lumbar FJD. Jentzsch *et al.*[54] also demonstrated a significant relationship between increased PI and FJD of the lower lumbar spine. In the study by Farshad *et al.*,[33]

the impact of degeneration of these two articulations on the overall spinal segmental motion was analyzed. Based on their observation, it was shown that the severity of FJD did not significantly limit spinal motion; however, severe lumbar disk degeneration significantly restricted segmental movement.

Recently, Zehra *et al.*[51] put forth their hypothesis of the "Evolutionary Etiology pathway," wherein they likened the patients with relatively straight alignment (as determined by small spinal curves and small PI) to primates or our earliest upright ancestors. They purported that individuals who are genetically predestined for such altered spinopelvic alignment with suboptimal biomechanics and unfavorable disk-endplate stresses are more predisposed to develop IVDD.

Morphological variations and IVDD

Among the morphological variations in the lumbar spine, the orientation of the facet joints was found to play crucial role in the development of IVDD.[66] Facet tropism refers to the asymmetry in the orientation of the bilateral facets in the sagittal plane. Garg *et al*.[67] in their meta-analysis noted a significant association between facet tropism and the development of LDH and lumbar degenerative spondylolisthesis at mean difference in the facet angles of patients to controls, ranging from 0.31 to 0.54, respectively. Various studies have been conducted to analyze whether facetal tropism is developmental or secondary to degeneration.[68] Investigations on these aspects revealed tropism to be noted in normal levels without IVDD; hence, it was considered a developmental variation that contributes to IVDD and not a secondary phenomenon following DDD.[69] Further, the risk of IVDD increases when the sagittal facet orientation is more than 58 degrees at L4–L5 level without any role of ethical origin of the individual.[70,71]

Apart from the facet tropism, presence of transitional vertebrae not only reduces the range of movement in the transitional segment but also significantly increases the motion at the cranial adjacent segment, thereby increasing the risk of degeneration.[72] Higher grades of transitional vertebrae have been found to be associated with greater functional disability.[73] Further, patients with transitional vertebrae have an increased incidence of pedicle asymmetries, and hence preoperative evaluation is necessary to avoid pedicle screw malposition in these patients.[74]

Muscular causes of IVDD

Paraspinal muscles in the lumbar region undergo age-related degeneration in the form of muscle atrophy and fat infiltration.[75] The degeneration of the paraspinal muscles has been noted in patients with IVDD, where more than 50% fat infiltration has been shown to be associated with root compression and advanced degeneration.[76] Hence, appropriate and timely decompression procedures might mitigate the cycle of denervation followed by atrophy and fat infiltration.[77]

Other factors leading to DDD

Broadly, DDD has been etiologically linked to a complex interplay of diverse mechanisms.[34,78] Apart from the aforementioned mechanical factors, low-grade infective discitis has been purported to initiate degenerative mechanisms within the endplate and the adjoining marrow, especially MC.[79,80] In addition, autoimmune reactions to the NP material after a violation of the endplate have been demonstrated to contribute to the cascade.[81,82] The final common pathways for the inflammatory cascade have been diversely reported and involve a combination of mechanisms such as toll-like receptors (TLR), cytokines (IL-6, IL-8, TNFa/IL-1b, etc.), marrow adipose tissue (MAT)-PPARγ activation, and other osteoclastic factors (RANK-L, M-CSF, etc.).[83-85]

It is well-acknowledged that biochemical aging is manifested by a combination of histomorphological and molecular changes, especially with NP, such as proteoglycan loss, dehydration, alteration in matrix collagen, fragmentation, and brownish pigmentation.[86,87] Such changes are attributed to oxidative stresses within the IVD, secondary to compromise in the disk nutrition. Studies have shown that adverse microenvironment, especially compressive stresses, leads to enhanced cell death and reduced migration of IVD stem/progenitor cells. Such conditions stimulate the degeneration of NP through the processes of autophagy (lysosome-dependent catabolic pathway), apoptosis (genetically controlled programmed cell death), and necroptosis (programmed cell death with necrosis-like picture).[88-90]

Liu *et al.*[10,91] studied the changes in different components of IVD secondary to fatigue loads. They showed that the different layers of the AF responded differently to diverse fatigue loads in specific positions. They also showed that Young's modulus of the IVD significantly increased with a corresponding increase in fatigue time and amplitude. These findings substantiate the role of fatigue loads on discal injuries and provide the basis for strategies aimed at clinical prevention and treatment of IVD disease.

Future directions

In view of the high prevalence of prolonged discogenic pain, regenerative biological therapies such as growth factor or cell-based therapies, gene therapy, and tissue-engineered constructs have attracted significant recognition in the light of their potential ability to directly address, prevent, mitigate, as well as reverse the degenerative processes.[10,11] In this context, the need for understanding the molecular basis underlying the cascade leading to degenerative spinal disease cannot be understated.

Limitations

Our review carries the limitations inherent to all nonsystematic reviews. No specific strategy was utilized to evaluate the methodological quality of the studies. The sample sizes of the included studies were heterogeneous. Nevertheless, the review provides a comprehensive analysis of all the evidence hitherto available on this subject.

Conclusion

The etiology of DDD is multifactorial. Mechanical pathways play a significant role in the initiation of IVDD. Mechanically, two different mechanisms have been proposed for IVDD: endplate-driven, especially in upper lumbar levels and annulus-driven degeneration. VEP is the weakest link of the lumbar spine, and fatigue damage can be inflicted upon them under physiological loads, leading to the initiation of DDD. The initial mechanical disruption leads to secondary IVD degeneration through unfavorable loading of NP and AF. The final degenerative cascade is then propagated through a combination of biological, inflammatory, autoimmune, or metabolic pathways (impaired transport of metabolites or nutrients). Abnormal spinopelvic alignment, especially PI, also significantly impacts the degenerative process.

Ethical policy and institutional review board statement

Not applicable.

Data availability statement

All collected data are available for this study. Data will be provided upon request.

Authors' contributions

All authors contributed substantially to the write-up of the article. All authors reviewed and approved the final draft of the manuscript and all take responsibility of the content of the publication.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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