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ASSOCIATION BETWEEN CONNECTIVE TISSUE DISORDERS AND LUMBAR DISC HERNIATION: A SYSTEMATIC REVIEW

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ABSTRACT

Lumbar disc herniation (LDH) is one of the most common structural causes of low back pain worldwide. While mechanical overload and age-related degeneration are widely recognized as key factors, recent research suggests that connective tissue disorders (CTDs) and related genetic abnormalities may also play a significant role in disc pathology. This systematic review aimed to evaluate the current evidence on the relationship between CTDs and LDH from clinical, genetic, and mechanistic perspectives. A comprehensive literature search was performed in PubMed and Google Scholar up to April 2025, according to PRISMA guidelines. Thirteen studies were included, encompassing genome-wide association studies, cohort and case-control studies, experimental animal models, and proteomic analyses. Several genetic variants related to extracellular matrix components and sulfate transport, including CHST3, ADAMTS17, and COL11A2, were found to be associated with lumbar disc degeneration. Clinical studies showed a potential link between joint hypermobility or rheumatoid arthritis and higher LDH prevalence or postoperative complications, although findings were inconsistent. Mechanistic models highlighted local molecular changes, such as altered TGF-β signaling and overexpression of CILP or AEBP1, which may impair disc integrity. Despite growing molecular insights, the clinical correlation between CTDs and LDH remains insufficiently explored. More longitudinal studies with standardized definitions of CTDs and better genetic profiling are necessary to clarify these associations and improve patient stratification.

KEYWORDS

Lumbar Disc Herniation, Connective Tissue Disorders, Joint Hypermobility, Ehlers-Danlos Syndrome, Genetic Polymorphism, Extracellular Matrix, Disc Degeneration

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1. Introduction

Low back pain is the leading global cause of disability, with lumbar disc herniation (LDH) representing one of its most common structural origins [1, 2, 31]. LDH occurs when nucleus pulposus material protrudes through the annulus fibrosus, often compressing neural structures [3]. Although mechanical stress and age-related changes are primary contributors to intervertebral disc degeneration [4], emerging evidence points to the involvement of systemic factors, including genetic predispositions and connective tissue disorders. Moreover, experimental data suggest that even short-term opioid exposure may accelerate disc structural deterioration, further exacerbating degenerative spinal conditions [32]. Connective tissue disorders (CTDs), such as Marfan or Larsen syndrome, affect extra-cellular matter (ECM) components including collagen and glycosaminoglycans, potentially predisposing to disc degeneration [5-7]. Genes involved in ECM maintenance- like CHST3, ADAMTS17, or RSPO2- have been implicated in both syndromic CTDs and disc pathology [6, 8- 10]. Despite these molecular links, the clinical association between CTDs and LDH remains under-explored [29, 30].

This review aims to systematically assess current evidence regarding the relationship between connective tissue disorders and lumbar disc herniation, incorporating genetic, clinical, and mechanistic perspectives.

2. Materials and Methods

This review was conducted according to PRISMA guidelines. The protocol was not registered. We searched the databases PubMed and Google Scholar from inception to April 2025. Search terms included combinations of:'lumbar disc herniation', 'connective tissue disorders', 'joint hypermobility', 'Ehlers-Danlos syndrome', 'Marfan syndrome', 'genetics', 'GWAS', 'risk factors', 'reoperation'. Searches were limited to English-language. Observational studies (cross-sectional, cohort, case-control); genetic association studies (GWAS, candidate gene studies); studies reporting on incidence, risk, severity, or outcomes of LDH in patients

with connective tissue disorders; studies published after 2010. Case reports, narrative reviews, systematic reviews; studies focused exclusively on cervical/thoracic discs; studies lacking primary data. Two independent reviewers screened titles and abstracts, followed by full-text review. Disagreements were resolved by consensus. For each included study, we extracted: author, year, study type, sample size, definition of LDH and CTD, follow-up duration, key findings, and bias assessment. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), with a maximum of 9 points. Genetic studies and reviews were included based on relevance but not formally scored. Due to heterogeneity in study design and outcomes, no meta-analysis was conducted. Findings were synthesized narratively and categorized thematically.

3. Results

We included 13 studies encompassing data from 2, 665, 625 patients. The analyzed articles consisted of: four genome-wide association studies (GWAS), three cohort studies (two retrospective, one prospective), one experimental study (animal model), one proteomic analysis, one cross-sectional study, two case-control studies, and one retrospective clinical analysis. The results are presented in the table below:

Table 1. Summary of Included Studies on Connective Tissue Disorders and Lumbar Disc Herniation

Title	Author (Year)	Author (Year)	Population (N)	Connective Tissue Disorder	Follow-up Duration	Key Findings	Bias Assessment
Rare SLC13A1 variants associate with intervertebral disc disorder highlighting role of sulfate in disc pathology	Björnsdóttir et al. (2022)	GWAS	457, 514	Not applicable	Not applicable	GWAS identified 41 variants incl. rs1871452-T (CHST3) and LoF in SLC13A1 (OR = 1.44).	Not applicable
Genome-wide analysis identifies significant contribution of brain-expressed genes in chronic, but not acute, back pain	Bortsov et al. (2022)	GWAS	375, 158	Not applicable	Not applicable	Chronic back pain linked to brain-expressed genes; acute pain pathway included RSPO2, TNFRSF11.	Not applicable
A common variant rs2054564 in ADAMTS17 is associated with susceptibility to lumbar spondylosis	Taniguchi et al. (2023)	GWAS	265	Not applicable	Not applicable	rs2054564 in ADAMTS17 (OR = 1.27); associated with CTD phenotype.	Not applicable
Genome-wide meta-analysis of 158, 000 individuals of European ancestry identifies three loci associated with chronic back pain	Suri et al. (2018)	Meta-analysis GWAS	158, 000	Not applicable	Not applicable	SOX5 (OR = 1.07), CCDC26/GSDMC (OR = 1.05) linked to chronic back pain and disc degeneratio.	Not applicable
The impact of generalized joint laxity on the occurrence and disease course of primary lumbar disc herniation	Kim et al. (2015)	Cohort	125	GJL	2 years	GJL increased LDH risk (OR = 2.3; p = 0.03) and worsened clinical outcomes.	NOS: 6/9

Risk factors for reoperation after surgical treatment for degenerative spinal disease in Poland	Sobstyl et al. (2023)	Retrospective cohort	38, 953	Not applicable	12 months	CTDs not linked to reoperation; depression and obesity were significant risk factors.	NOS: 6/9
Cartilage intermediate layer protein promotes lumbar disc degeneration	Seki et al. (2014)	Experimental (animal)	Not applicable	Not applicable	Not applicable	CILP overexpression inhibited TGF-β, reduced collagen II and aggrecan, promoting degeneratio.	Not applicable
Rheumatoid arthritis patients are at increased risk for adverse events following lumbar discectomy	Kumar et al. (2023)	Retrospective cohort	10, 634 (2, 149 RA)	RA	90 days	RA increased risk of postoperative complications (OR = 3.30; $p < 0.0001$).	NOS: 7/9
Proteomic profiling reveals matrisomal, not plasma, biomarkers of disc degeneration	Dube et al. (2023)	Proteomic	47 (25 DDD, 22 control)	Not applicable	Not applicable	AEBP1 expression elevated in DDD ($log_2FC = 1.56$; $p = 0.004$); no markers in plasma.	Not applicable
Is There a Relationship Between Joint Hypermobility and Lumbar Disc Degeneration	Yildiz et al. (2020)	Cross-sectional	98	BJHS	Not applicable	No significant association between BJHS and disc degeneration ($p = 0.65$).	NOS: 5/9
Genetic variants in COL11A2 of lumbar disk degeneration among Chinese Han population	Yang et al. (2019)	Case-control	768	Not applicable	Not applicable	rs2071025 in COL11A2 significantly associated with LDH (OR = 1.34; $p = 0.001$).	NOS: 7/9
Relationship Between Lumbar Disc Herniation and Benign Joint Hypermobility Syndrome	Aktas et al. (2017)	Case-control	200	BJHS	Not applicable	BJHS more frequent in LDH patients (18% vs 8%; $p = 0.03$).	NOS: 6/9
Study of Symptoms and Surgical Management of Lumbar Disc Herniation in Damascus Hospital	Al-Khaled et al. (2022)	Retrospective	180	Not applicable	2021–2022	Diabetes (12.3%) linked to LDH (OR = 2.14; $p = 0.05$).	NOS: 6/9

Genetic studies

Björnsdóttir et al. conducted a large GWAS study on over 170, 000 cases of dorsalgia and intervertebral disc disorder (IDD), identifying 41 significant gene variants across 33 loci. The strongest association was observed for the rs1871452-T variant in CHST3 (OR = 0.92; $p = 1.6\times10^{-39}$), and for rare loss-of-function (LoF) variants in SLC13A1 (OR = 1.44; $p = 3.1\times10^{-11}$), which were also associated with decreased serum sulfate [11]. Both genes are involved in sulfate metabolism and extracellular matrix synthesis.

Suri et al. identified three loci associated with chronic back pain in a GWAS meta-analysis of 158, 025 individuals. The most robust finding was rs12310519 variant in SOX5 (OR = 1.07; $p = 4.5\times10^{-19}$), a gene regulating chondrogenesis and collagen type II expression. Additional loci (CCDC26/GSDMC and DCC) were linked to disc degeneration, skeletal phenotypes, and pain processing pathways [14, 25].

Borysov et al. analyzed 375, 158 individuals and found that brain-expressed genes significantly contribute to chronic back pain, whereas acute pain was more strongly associated with RSPO2 and TNFRSF11B, genes implicated in connective tissue and bone remodeling [12, 26, 27].

Taniguchi et al. identified rs2054564 variant in ADAMTS17 (OR = 1.27; $p = 8.6\times10^{-5}$) as a risk variant for lumbar spondylosis in a GWAS of 265 patients. ADAMTS17 is involved in extracellular matrix organization and is allelic to Marfan-like syndromes, suggesting a connective tissue link [13, 24].

Yang et al. (case-control study, N = 768) found a significant association between COL11A2 - collagen type II encoding gene variants and lumbar disc degeneration. The strongest association was with rs2071025 (OR = 1.34; 95% CI: 1.12–1.60; p = 0.001), supporting the role of collagen gene polymorphisms in disc pathology [21].

Clinical observational studies

Kim et al. (prospective cohort study, N = 125) showed that generalized joint laxity (GJL) increased the risk of lumbar disc herniation (LDH) (OR = 2.3; 95% CI: 1.1–4.8; p = 0.03) and was associated with poorer outcomes after conservative treatment [15].

Sobstyl et al. (retrospective cohort study, N = 38, 953) evaluated reoperation risk after surgical interventions in degenerative spinal disorders. Although patients with connective tissue disorders (CTDs) were included, no statistically significant association with reoperation was found. The most relevant factors contributing to increased reoperation risk were depression (OR = 1.45) and obesity (OR = 1.25) [16].

Kumar et al. (retrospective cohort, N = 10, 634; 2, 149 with rheumatoid arthritis) reported a higher risk of postoperative complications in RA patients after lumbar discectomy (OR for any complication = 3.30; $p < 0.0001$), particularly in those receiving biologics. Reoperation risk at 5 years was not significantly different [18]. Al-Khaled et al. (retrospective clinical study, N = 180) identified diabetes mellitus (12.3%) as a frequent comorbidity in patients with LDH. Statistical analysis suggested a borderline significant association between diabetes and LDH (OR = 2.14; 95% CI: 1.00–4.55), indicating a potential metabolic contribution to disc pathology [23, 28].

Experimental and molecular studies

Seki et al. (mouse model) demonstrated that overexpression of CILP gene in the nucleus pulposus suppressed TGF-β signaling, reducing collagen II and aggrecan synthesis. This led to degeneration of the intervertebral disc, revealing a mechanistic pathway linked to connective tissue remodeling [17].

Dube et al. (proteomic analysis, N = 47) compared disc tissue and plasma from patients with degenerative disc disease (DDD) and controls. AEBP1 was significantly overexpressed in DDD discs ($\log_2FC = 1.56$; p = 0.004), while no disease-specific biomarkers were detected in plasma, emphasizing localized extracellular matrix remodeling [19].

Yildiz et al. (cross-sectional, N = 98) found no significant association between benign joint hypermobility syndrome (BJHS) and radiographic signs of disc degeneration (p = 0.65), suggesting BJHS may not independently predispose to LDH [20].

Aktas et al. (case-control, N = 200) observed a higher prevalence of BJHS in patients with LDH (18% vs 8%; p = 0.03), supporting a possible link between joint hypermobility and disc herniation [22].

4. Discussion

This systematic review highlights a growing evidence supporting the involvement of connective tissue abnormalities in lumbar disc herniation (LDH). Genetic studies consistently demonstrate associations between LDH or chronic back pain and variants in genes responsible for extracellular matrix (ECM) integrity- including CHST3, COL11A2, SOX5, and ADAMTS17- as well as sulfate transport pathways such as SLC13A1. These genes are functionally linked to cartilage and ligament structure and are often implicated in connective tissue disorders (CTDs). Clinical studies offer complementary insights, particularly regarding generalized joint laxity (GJL) and benign joint hypermobility syndrome (BJHS). While some findings suggest a higher incidence of LDH and worse treatment outcomes in individuals with these phenotypes, the data are somewhat heterogeneous, indicating that joint hypermobility alone may not be sufficient to initiate disc pathology without other contributing factors. Mechanistic studies further support this link. For example, CILP over-expression was shown to inhibit TGF-β signaling, a key regulator of ECM remodeling, while AEBP1 over-expression was observed in patients with degenerated disc tissue. Both alterations suggest a pathophysiological mechanism where disrupted ECM signaling promotes localized disc damage. Interestingly, these changes were not reflected in systemic plasma biomarkers, emphasizing the local nature of disc degeneration. Additionally, comorbid conditions such as rheumatoid arthritis and diabetes have been associated with increased postoperative complication rates, likely due to systemic inflammation and impaired tissue repair, further reinforcing the role of connective tissue and immune homeostasis in spinal health.

5. Conclusions

Connective tissue status- both genetically determined and clinically expressed- appears to play a contributory role in the development and progression of lumbar disc herniation. While the evidence is strongest for select genetic variants and extreme phenotypes, it suggests that structural connective tissue vulnerability may influence disc integrity, symptom severity, and treatment outcomes. Further well-designed longitudinal studies with standardized CTD diagnostics and genetic profiling are warranted to clarify these associations and to identify patients at elevated risk for LDH. Ultimately, this may enable personalized approaches to prevention, diagnosis, and management of lumbar disc disorders in individuals with underlying connective tissue pathology.

Author contributions

Conceptualization, M.B. and K.B.; methodology, M.B. and K.B.; software, M.B.; validation, M.B., K.B., and C.L.; formal analysis, M.B. and J.K.; investigation, J.K., A.O., and C.L.; resources, P.F., K.S., and P.Ś.; data curation, M.Z. and A.K.; writing – original draft preparation, M.B. and K.B.; writing – review and editing, A.O., C.L., and M.Z.; visualization, K.B. and M.B.; supervision, M.B.; project administration, K.B.; All authors have read and agreed to the published version of the manuscript.

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