

**THE GUT–SPINE–DISC AXIS IN INTERVERTEBRAL DISC DEGENERATION:
INTEGRATING MICROBIOME, IMMUNE-METABOLIC MECHANISMS, CLINICAL
EVIDENCE, AND THERAPEUTIC PERSPECTIVES — A NARRATIVE REVIEW****Dr. Yogendra Singh***

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ABSTRACT

Intervertebral disc degeneration (IDD) is a significant contributor to chronic low back pain and involves complex, interacting mechanisms that involve mechanical, inflammatory, metabolic, and cellular mechanisms. The growing evidence indicates that disturbances of the intestinal flora can be a modification of these processes via the gut–disc axis. This structured narrative review collates human microbiome, metabolomic, Mendelian-randomization and experimental data since 2014, and up to September 2026. The search of literature was done primarily via PubMed/MEDLINE, and cross checked in PubMed Central and publisher records, using combinations of terms such as 'gut microbiome', 'gut microbiota', 'dysbiosis', 'gut-disc axis', 'intervertebral disc degeneration', 'Modic changes', 'metabolomics', 'short-chain fatty acids', 'lipopolysaccharide', 'Mendelian randomization', and 'fecal microbiota transplantation'. There are several biologically plausible pathways suggested by the 22-study core evidence set: intestinal-barrier impairment and systemic exposure to lipopolysaccharide; activation of toll-like-receptor 4/NF-κB signaling pathways; Th17/Treg and macrophage-polarization shifts; altered short-chain-fatty-acid, tryptophan–indole/AhR and bile-acid/FXR–TGR5 signaling; oxidative stress and mitochondrial dysfunction; and potential microbial signaling at the disc–endplate interface. Microbiome disease-associated profile in human studies and genetic causal-inference and animal studies are complementary and show that specific microbial phenotypes or microbiome manipulation could affect phenotypes associated with degeneration. But existing clinical data has limitations in that small, cross-sectional cohorts, geographic and dietary factors, medication and body-composition confounding, sequencing differences and risk of contamination in low-biomass disc samples of the sample were present. IDD is an area that is currently under investigation with the use of microbiome-directed interventions such as dietary changes, probiotics, postbiotics, and fecal microbiota transplantation. However, before the microbiome can be recommended as a diagnostic or disease-modifying therapeutic target, future studies should include integrated metagenomic, metatranscriptomic, metabolomic, immune, and quantitative-MRI profiling of prospective multicenter cohorts.

KEYWORDS: Gut microbiome; dysbiosis; intervertebral disc degeneration; gut–disc axis; Modic changes; short-chain fatty acids; tryptophan; bile acids; inflammation; metabolomics.**INTRODUCTION**

Low back pain is one of the most important causes of disability worldwide. In 2020, it was estimated that about 619 million people suffered from low back pain and that this figure would increase to about 843 million by 2050, largely due to population ageing and population growth.^[1] A similar study, the Global Burden of Disease 2021, also ranked low back pain as the primary cause of

years lived with disability (YLD) for all ages.^[2] Low back pain is clinically heterogeneous and often referred to as "non-specific" but intervertebral disc degeneration is a major structural substrate in a significant number of chronic axial and radicular pain syndromes.

The intervertebral disc is a special type of largely avascular organ made up of the gelatinous nucleus

pulposus, the collagen-rich annulus fibrosus and the cartilaginous endplates. It is dependent on an extracellular matrix, which is highly hydrated and abundant in aggrecan and type II collagen, to carry out its mechanical function. The degenerated disc is characterized by a vicious cycle of altered biomechanics and biology that involves loss of matrix, loss of hydration and load carrying, mechanical stress, the onset of a catabolic and inflammatory phenotype of disc cells, and progressive disc structural failure.^[3] Additionally, inflammatory cytokines like interleukin (IL)-1 β , tumor necrosis factor α (TNF- α), IL-6 and others drive matrix metalloproteinase and aggrecanase activity, senescence, nociceptive signaling, neovascularization and further breakdown of extracellular-matrix.^[4,5]

There are known factors which contribute to IDD, such as ageing, heredity, smoking, obesity, metabolic disease, physical loading, endplate dysfunction, and local inflammatory events. All of these factors cannot be isolated. Thus, systemics targeting the microenvironment of the disc have become the focus of interest. A notable one of these modifiers is the intestinal microbiome or "gut flora," the community of bacteria, archaea, fungi, viruses, genes, and metabolites, which live in the gastrointestinal tract. The gut microbiome influences epithelial barrier integrity, nutrient metabolism, immune maturation, endocrine signaling and production of circulating metabolites. Dysbiosis, or an imbalance in the composition or activity of the microbial community, has already been linked to inflammatory, metabolic, autoimmune, and musculoskeletal diseases.

The idea of a "gut-disc axis" was raised to account for the possible contributions of intestinal dysbiosis on disc degeneration via three general mechanisms: microbial or bacterial product translocation, modulation of mucosal and systemic immunity, and changes in the production or uptake of microbial metabolites.^[6] This has been further extended to a broader "gut-spine axis" concept, which highlights the fact that the vertebral bone, cartilage, muscle, ligaments, neural tissue and disc cannot be separated from each other, but are linked together by immune and metabolic pathways.^[7] The association between gut microbiome and IDD has been increasingly supported by recent human case-control studies, animal models, metabolomic investigations and Mendelian-randomization analyses that have increasingly provided direct evidence for this association, but the directionality and strength of this relationship is still under debate.^[8-13]

This paper summarizes evidence linking intestinal dysbiosis with IDD, outlines most likely mechanisms, assesses the quality and the gaps of existing human and experimental evidence, and discusses the translational potential of microbiome-directed prevention and treatment strategies. However, the central theme is not that dysbiosis supersedes mechanical or genetic causes of disc degeneration, but rather that it can serve as a systemic amplifier which can alter the inflammatory

and/or metabolic environment in which disc degeneration occurs.

MATERIALS AND METHODS

This article is a structured narrative review to form a pattern of the research in the area and does not represent a systematic review or a meta-analysis. The updated reporting format was clarified by incorporating reporting principles from the PRISMA study-selection reporting guidelines^[23] and reporting considerations specific to microbiomes as outlined in the STORMS checklist.^[24] Identification of literature was done mainly using PubMed/MEDLINE and complemented by PubMed Central and Primary journal-publisher records. The principal publication window was from January 2014 to September 2026; earlier mechanistic studies, of a foundational nature, were kept if required to explain existing inflammatory or disc-biological pathways.

Search Strategy

The search logic used in PubMed/MEDLINE was standardized with the following Boolean strings for reproducibility:

OR

- ("gut microbiome" OR "gut microbiota" OR dysbiosis OR "gut-disc axis" OR "gut-spine axis") AND ("intervertebral disc degeneration" OR "disc degeneration" OR "lumbar disc herniation" OR "Modic changes") (intervertebral disc degeneration OR disc degeneration) AND (short-chain fatty acids OR butyrate OR lipopolysaccharide OR LPS OR tryptophan OR indole OR "bile acid" OR "bile acids" OR metabolomics)
- (intervertebral disc degeneration) or (lumbar disc herniation) or (Modic changes) AND (Mendelian randomization) or (metagenomics) or (fecal microbiota transplantation) or (FMT) or (microbiome).

Backward citation checking of relevant reviews and primary studies was also conducted for searches, and the publishers or PubMed records were checked for bibliographic accuracy. Since this is an updated narrative review, and the original search log was no longer in existence, counts of exact deduplications were not reconstructed. The final core synthesis consists of 22 studies, with additional reporting, low-biomass methodology and pathway references cited separately and not included in the 22 studies that make up the gut-disc evidence corpus.

Eligibility Criteria

Inclusion criteria were

- Peer-reviewed human observational, case-control, cohort, genetic causal-inference, animal, ex vivo, or cell-based studies that have a direct connection to IDD, lumbar disc herniation, Modic changes, or the gut-disc/gut-spine axis.
- Studies that assess gut microbiome composition, microbiome metagenomics, metabolomics, microbiome metabolites, systemic immune

activation, or microbiome manipulation, with outcomes relevant to disc degeneration.

- However, recent reviews that were peer-reviewed incorporated mechanisms when they were directly synthesizing evidence from the gut–disc, or the low-biomass microbiome methodology.
- Records in English that provide adequate methodological detail to appraise the study design, population/model, main exposure, and disc-related outcome.

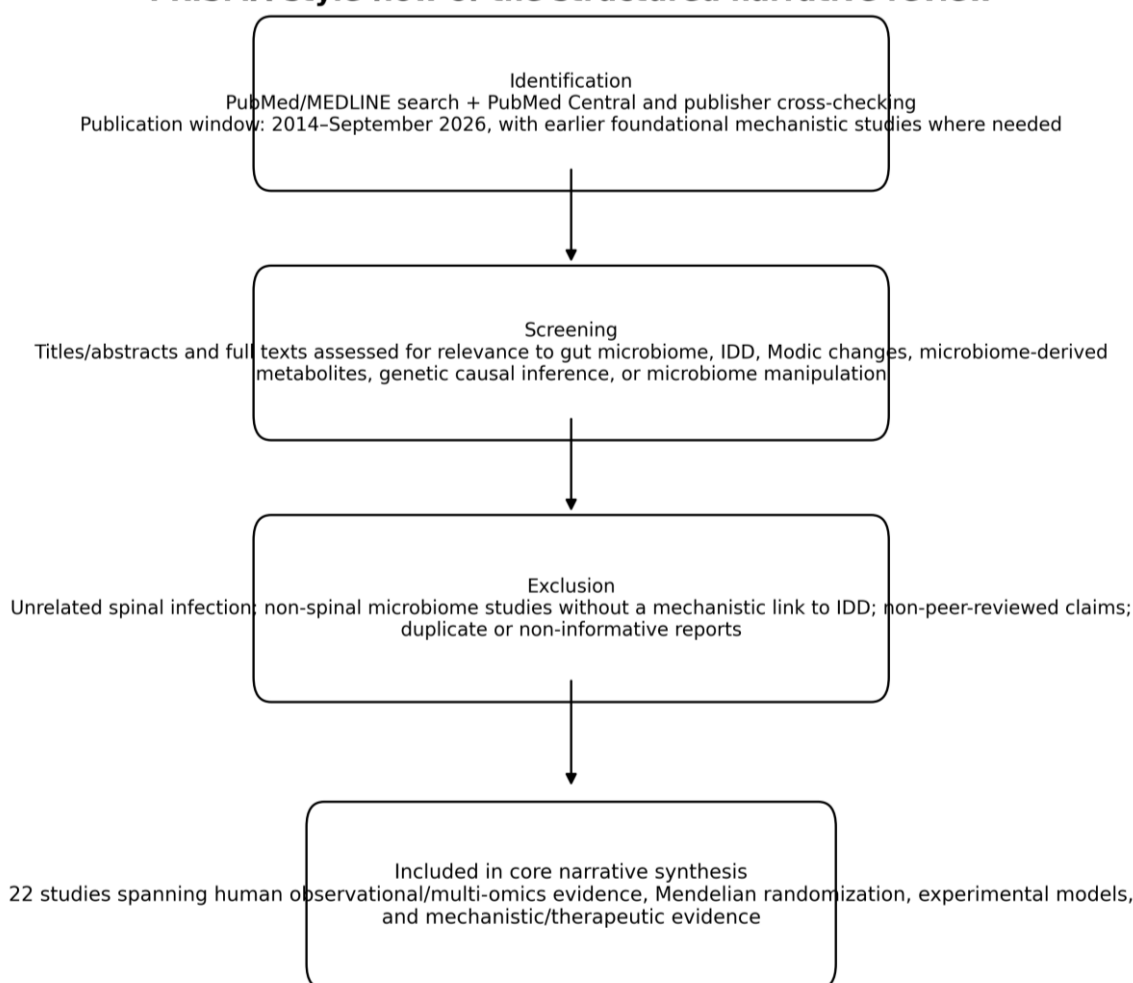
Exclusion criteria were

- Primary spinal infection studies that have no connection to deg. disc.
- Microbiome research in organs other than spine without a plausible link to IDD.

- Claims with no primary or review evidence that are used in editorial or commercial publications or that are unsupported or lack peer-reviewed evidence.
- Duplicate reports or records that did not add independent evidence to the narrative synthesis.

Due to the diversity in the literature included, a quantitative meta-analysis was not attempted; the included literature ranged from 16S rRNA profiling, to shotgun metagenomics, metabolomics, Mendelian randomization, animal models, disc-cell experiments, to heterogeneous imaging phenotypes. Results were combined in four areas: human microbiome and metabolomic evidence, genetic/causal-inference evidence, experimental/mechanistic evidence, and therapeutic implications. It was not necessary to gather new patient or animal data and therefore institutional ethical approval was not required for this review.

PRISMA-style flow of the structured narrative review



Transparency note: exact retrospective record and deduplication counts were not retained in the original search log and are therefore not reconstructed or fabricated.

Figure 1: PRISMA-style study-selection flow for the structured narrative review. Exact retrospective identification and deduplication counts were not available from the original search log and are therefore not fabricated.

RESULTS

Human Evidence for Dysbiosis in Disc Disease

The evolution of human evidence, from conceptual association to direct human microbiome profiling. In a pilot case control study carried out in 2024, Rajasekaran et al. compared 40 patients who were undergoing surgery for disc degeneration with 20 healthy volunteers. A significant difference was found in the gut dysbiosis of healthy participants versus patients with degenerative disc disease and in patients with versus without Modic changes. The Modic group had a depletion of commensals *Bifidobacterium* and *Ruminococcus* and enrichment of organisms such as *Streptococcus*, *Prevotella*. Beneficial short-chain-fatty-acid-producing bacteria decreased and markers of systemic and local inflammation, such as serum C-reactive protein and fatty-acid-binding protein 5, increased, suggesting that the microbial changes were associated with inflammatory markers.^[8]

The fMRI study by Liu, Li, and Jiang was an untargeted multi-omics, 16S rDNA sequencing and liquid-chromatography mass spectrometry of faecal samples from patients across Pfirrmann grades (IDD and healthy controls) in 2025. The microbial and metabolite profiles were distinct between patients with IDD and healthy controls with higher abundances of Proteobacteria and Fusobacteriota and changes in lipid-like metabolites. Nucleotide metabolism, taurine and hypotaurine metabolism, arginine and proline metabolism, carbohydrate digestion and absorption, and FoxO signaling were all found to be involved in the pathway analysis.^[9] The study was important as it was small, but it was linked to the functional metabolic output instead of based on taxonomy.

A case-control study of Modic changes using metagenomic analysis in 2025 corroborates this additional support. In their study, Lan and colleagues used shotgun metagenomics to compare 31 patients with Modic changes and 25 healthy controls (matched by age and sex) to discover the disease-associated microbial and functional signatures.^[10] All of these data further support the hypothesis that vertebral endplate pathology, disc degeneration and gut dysbiosis might have a common inflammatory-metabolic basis. These are however cross-sectional studies, and cannot determine whether the structural degeneration comes before the dysbiosis, or if the dysbiosis is due to pain-related behaviour or exposure to pain medications, or to both.

A scoping review in 2026 found 26 relevant preclinical and clinical studies of the microbiome of the gut and local disc in relation to lumbar disc herniation. Biomechanical links were identified in the review to inflammation, immune activation and sensitization of pain and although significant heterogeneity was identified, no definitive mechanistic evidence was identified in humans.^[14] This assessment is consistent with the rest of the literature: there is now repeated

evidence of association, but the strength of the association; the possibility that the association is not reproducible; and whether the association is present at a later time rather than earlier, are not yet known.

Genetic evidence and causal-inference evidence

One approach to control for some types of confounding and reverse causation that has been developed to date is 'Mendelian randomization' (MR), which is achieved by using instrumental variables, namely genetic variants linked to a microbial trait. Zheng and colleagues published genetic data that resulted in the association of a number of microbial characteristics with IDD, uncovering a number of taxa that might have causal relationships.^[11] Fang et al then subjected gut microbial taxa and metabolic pathways to analyses in relation to IDD, low back pain and sciatica. They found several candidate taxa and pathways but they were able to get to an even more stringent correction and still had the *Eubacterium coprostanoligenes* group as the most robust association with IDD.^[12]

In 2025, Ge and colleagues used MR analysis in multiple types of intervertebral-disc disease and again identified evidence that supports a gut-disc relationship, noting that causal estimates differ both across taxa and outcomes.^[13] Yan et al carried out a two-sample MR study in 2026 to examine the gut microbial taxa, inflammatory cytokines and IDD. The study revealed that there was a suggestive association between microbiome and IDD, but the recruited circulating inflammatory cytokines didn't clearly explain the genetic association, indicating that the mechanisms of action involved in the microbiome effects may be via multiple metabolic, barrier, immune-cell, or tissue-specific pathways rather than through one common cytokine pathway.^[15]

MR helps support the argument that a person's microbiome may have a role in disc disease, but it doesn't prove that altering a person's microbiome will lead to the prevention or reversal of disc disease. The taxonomic resolution of genome wide association studies of the microbiome can be low, the validity of the instrument might be influenced by population stratification and the abundance of microbes is environmentally sensitive. Therefore, a genetic finding should only be considered as supportive evidence, toward biological pathways, but not as a prescription to manipulate the microbiome.

Table 1: Representative evidence supporting the gut–disc axis.

Study	Design	Key finding	Interpretation
Rajasekaran et al., 2024 ^[8]	Human case-control; 40 disc-degeneration patients, 20 healthy controls	Dysbiosis in disc disease; depletion of SCFA-producing commensals; inflammatory markers increased	Direct human association between gut ecology and disc disease phenotype
Liu et al., 2025 ^[9]	Human 16S sequencing + fecal metabolomics	Distinct taxa and metabolite profiles across IDD patients and controls	Supports a functional microbiome–metabolome component of IDD
Lan et al., 2025 ^[10]	Shotgun metagenomic case-control; Modic changes	Disease-associated microbial and functional signatures	Links dysbiosis with vertebral endplate/disc inflammatory phenotype
Zheng et al., 2024 ^[11] ; Fang et al., 2024 ^[12]	Two-sample Mendelian randomization	Selected microbial taxa showed potential causal associations with IDD	Reduces some confounding but remains dependent on genetic-instrument validity
Yao et al., 2023 ^[16]	Rat IDD model with fecal microbiota transplantation	FMT reduced inflammatory and matrix-degradation markers and improved histology	Experimental evidence that microbiome manipulation can alter degeneration
Ni et al., 2024 ^[17]	Rat + cell model; METTL3/TLR2 pathway and FMT	Microbiome changes interacted with nucleus pulposus cell senescence pathways	Connects microbiome state with molecular regulation of cellular senescence
Cui & Du, 2026 ^[18]	Contemporary mechanistic review	Integrates barrier failure, LPS/TLR4/NF- κ B, SCFAs, tryptophan/bile acids, lipid/iron metabolism	Provides current immune-metabolic framework for gut–disc signaling

Mechanistic Pathways Linking the Gut to the Disc

The intervertebral disc is vascularly underdeveloped, has an atypical nutrient supply, low oxygen tension and a metabolically restricted cell population. Hence, it can be especially sensitive to changes in the systemic environment. There are currently several pathways that are all interrelated, not one originating in the gut.

Barrier Failure and LPS & Innate Immune Signaling

First, dysbiosis may affect the integrity of the intestinal-barrier. Increased permeability allows more systemically available microbial molecules, like lipopolysaccharide (LPS). Pattern-recognition receptors such as toll-like receptor can trigger NF- κ B activation, the activation of inflammasome signaling and downstream inflammatory mediators. In the disc, these pathways intersect with known IDD biology, such as through increased expression of MMPs and ADAMTS enzymes, decreased expressions of anabolic matrix proteins, cell death and senescence, and sensitization of nociceptive pathways.^[4,5,18] The gut–disc model therefore links a systemic source of inflammatory stimulation with a tissue known to be sensitive to negative effects of chronic inflammatory signaling.

Short-Chain Fatty Acids

Second, the metabolites that microbes produce can be beneficial or detrimental, depending on the chemical nature, quantity, and context. Fermentation of dietary fibers by commensal bacteria results in the production of short-chain fatty acids (SCFAs) which are linked to intestinal-barrier function and immune regulation. The inhibitory activity of butyrate was demonstrated in

degenerated human disc tissue on IL-1 β -induced production of inflammatory mediators and inhibition of the activation of NF- κ B.^[19] In contrast, there are reports of patients with degenerative disc disease having a reduction in SCFA-producing bacteria.^[8] Supporting these findings, there was a plausible linkage between diet, microbial ecology, systemic inflammation, and behavior of disc cells.

Tryptophan–Indole–AhR Signaling

In addition to SCFA, a second layer of metabolites is created through the metabolism of tryptophan. Tryptophan can undergo host kynurenine metabolism and bacterial metabolism to form indole derivatives that serve as ligands for the aryl hydrocarbon receptor (AhR). AhR signaling is involved in the regulation of epithelial barrier integrity, mucosal immune tolerance, antimicrobial programs and T-cell differentiation. Increased or decreased availability of tryptophan, as well as an imbalance of AhR-active microbial indoles, can therefore occur as a result of dysbiosis. An altered Tryptophan–AhR axis may polarize the production of cytokines and the regulatory immune tone in inflammatory environments.^[28] Direct disc specific human evidence is relatively limited in IDD and the relevance is mechanistic since the systemic inflammation and oxidative status of the body influence the process of disc degeneration. The idea is that loss of protective indole/AhR signaling might have a negative effect on barrier function and promote pro-inflammatory immune programming and therefore enhance catabolic signaling at the disc–endplate unit, not as an endplate-specific pathway.

The signaling of bile acids through FXR and TGR5

The gut microbiota also alters the pool of circulating bile-acids by deconjugating and converting primary bile-acids to secondary bile-acids. These metabolites act through the nuclear farnesoid X receptor (FXR) and the membrane G-protein coupled bile-acid receptor TGR5, which regulate metabolic homeostasis, innate immune activation, epithelial integrity and inflammatory signaling. Skeletal literature of recent vintage also reveals that FXR regulates osteoblast and osteoclast pathways, chondrocytes and cartilage-degrading pathways, as well as interactions with the Wnt/ β -catenin and NF- κ B pathways.^[30] A changed primary/secondary bile-acid ratio may thus have an indirect impact on the nutrition of vertebral endplate and discs through systemic metabolic and inflammatory mechanisms in the context of IDD. It has not been adequately validated in longitudinal IDD cohorts yet, however, this pathway remains a possible pathway to investigate and test.

The interaction between cells of the immune system: Th17/Treg balance and macrophage polarization.

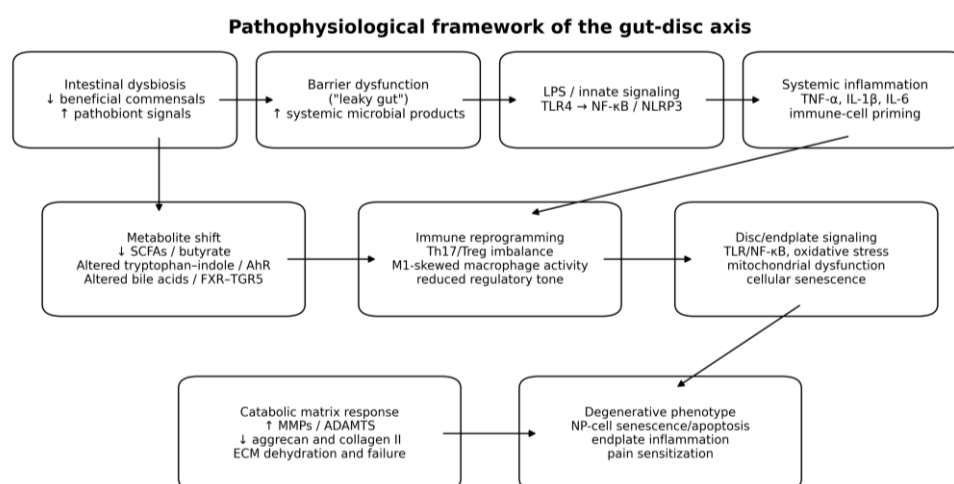
Metabolites from the gut and microbial molecules can reprogram systemically resident T-cells and monocytes/macrophages. The relevance of a pro-inflammatory shift to Th17 activity lies in the fact that IL-17 has been found to be elevated in degenerated disc tissue and may stimulate NF- κ B and MAPK signaling, induce degradation of extracellular matrix and strengthen the production of cytokines.^[29] In contrast, the activity of regulatory T-cells has the capacity to regulate inappropriate inflammation, and a dysbiosis-induced imbalance between T-helper cells (Th17) and regulatory T-cells (Treg) offers a plausible link between immune perturbation in the intestine and an already predisposed disc microenvironment for catabolism. Macrophages are also found in large numbers in degenerative and herniated discs and have a context-dependent

inflammatory or reparative phenotype. IDD literature is dominated by the concept of a shift toward pro-inflammatory M1-like signaling and inadequate resolution by M2-like signaling, which leads to matrix breakdown, matrix senescence, angiogenesis and nociceptive sensitization.^[31] The M1/M2 concept is a convenient shorthand for a continuous activation spectrum, but it is not an exhaustive one.

Pathways involved in Oxidative, Mitochondrial and Cell-Senescence.

Third, dysbiosis can impact tryptophan, bile-acid, lipid, amino-acid and redox metabolism. A 2026 review of the field identified altered SCFA, tryptophan, and bile-acid signaling, endotoxin load, immune-cell shifts, and lipid/iron metabolism as potential mechanisms by which the gut microbiome can alter the endplate-disc microenvironment.^[18] A human metabolomic study in 2025 also reported disruptions of lipid-like molecules and of a number of metabolic pathways.^[9] The relevance of metabolic changes is due to the fact that nucleus pulposus cells already operate in a hypoxic and acidic environment, and further oxidative or mitochondrial stress can lead to senescence, apoptosis, ferroptosis and loss of extracellular-matrix.

These pathways are connected to each other in a mechanistic way. Failure of barriers can lead to a greater exposure to LPS; exposure to LPS can lead to an increase in ROS production and mitochondrial dysfunction; cytokine amplification can lead to a development of a SASP; and senescence of nucleus pulposus cells can increase production of MMP and ADAMTS. This loop would allow relatively small changes in the general microbiologic balance to accentuate a local degenerative process resulting from mechanical or endplate injury, providing a biologically logical pathway.



Conceptual synthesis: systemic immune-metabolic signaling is better supported than routine direct intradiscal colonization.

Figure 2: Integrated pathophysiological model of the gut–disc axis, linking intestinal dysbiosis and barrier dysfunction to LPS/TLR4/NF- κ B signaling, immune-cell reprogramming, altered microbial metabolites, extracellular-matrix catabolism, and disc-cell senescence.

Table 2: Proposed gut–disc mechanisms and their disc-level consequences.

Gut-derived change	Intermediate pathway	Potential disc consequence
Loss of intestinal barrier integrity	Endotoxin/LPS exposure; TLR signaling; NF- κ B/NLRP3 activation	Inflammatory cytokines, matrix catabolism, cell stress
Reduced SCFA-producing commensals	Lower butyrate and altered immune regulation	Weaker barrier function; increased inflammatory signaling
Altered tryptophan and bile-acid metabolism	AhR and metabolic/immune signaling changes	Changes in immune tone, oxidative stress and cell homeostasis
Dysregulated lipid/redox metabolism	Mitochondrial dysfunction, ROS, iron/lipid peroxidation pathways	Senescence, apoptosis/ferroptosis, impaired matrix synthesis
Immune-cell reprogramming	Macrophage polarization; T-cell/Th17–Treg imbalance	Persistent disc/endplate inflammation and pain sensitization
Possible microbial translocation/local microbial signal	Direct innate immune stimulation	Potential focal inflammation; remains methodologically uncertain

Low-Biomass Disc Microbiome and Contamination Control

While stool-microbiome associations can be established with relatively low levels of evidence, claims of intradiscal microbial colonization must be supported by much stronger evidence as the disc tissue specimen is surgically removed and has a very low biomass sample. Small amounts of reagent, skin, operating room, instrument or lab DNA can comprise a significant portion of the observed microbial signal in low biomass sequencing. In sequence based microbiome studies, there has been well documented contamination of the reagents and it is particularly impactful where microbial biomass is low.^[25] Hence, the presence of a bacterial sequence in the disc tissue does not necessarily mean the tissue is colonized by viable bacteria, and must be verified by orthogonal methods and appropriate control testing.

The study of the disc-microbiome in the future will require minimum controls.

- Extraction blanks treated with the same kit lot and the same processing as tissue samples, but no template PCR/sequencing controls.
- The peri-operative skin, instrument and environmental controls (where possible) were identified to detect any contamination brought in during the surgical procedure or sample handling.
- Bioinformatic analysis that is contamination-aware, such as prevalence- and frequency-based bioinformatic tools like decontam that can detect sequences that are present at high levels in negative controls but not highly associated with the DNA concentration.^[26]
- Orthogonal tissue validation prior to asserting the presence of microbes in the disc: RNA-FISH, DNA-FISH with spatial localization, immunohistochemistry (if appropriate), targeted quantitative PCR with independent primers, and culture in appropriate conditions.
- Reporting of DNA yield, batch, extraction-kit lot, sequencing depth, thresholding rules, etc., and all negative controls; current consensus guidance suggests contamination controls through collection, processing, analysis, and reporting.^[27]

Based on this, the available evidence favors systemic immune-metabolic communication over a more general direct bacterial colonization of degenerated discs. Future reports need to distinguish between “microbial DNA detected” and “viable organism demonstrated”, and causal infection terminology should only be used when viability, spatial localization and contamination exclusion are positively proven.

Experimental evidence and manipulation of the microbiome

Animal studies can be used as an experimental test of the possibility of influencing IDD by manipulating the microbiome, not only accompanying it. Yao et al. applied a rat puncture model of IDD and gave fecal microbiota transplantation (FMT). IDD rats had elevated levels of collagen II, aggrecan, TNF- α , NLRP3, caspase-1, IL-1 β , and IL-6, while the levels of MMP-3 and MMP-13 were decreased. These changes were partially reversed, with the gut microflora composition and abundance being changed and disc histology being improved by FMT.^[16] The experiment suggests a functional association between gut ecology and disc degeneration and although the results from animal FMT can not be directly applied to clinical practice, the results do indicate a functional association.

Fecal microbiota and metabolome changes were also found during experimental disc degeneration in rabbits, further supporting the idea that structural disc injury is associated with systemic microbial-metabolic changes.^[20] Importantly, the direction can be both ways: injury to the discs, pain, reduced activity, stress, altered feeding and exposure to medication can all alter the gut microbiome. The gut–disc axis should therefore be considered as a feedback loop instead of a one way causal arrow.

Recent molecular research has correlated changes in the microbial population with certain pathways of a disc-cell. In an IDD rat model, Ni and colleagues found that the regulation of m6A modification in TLR2 expression was correlated with the senescence of nucleus pulposus cells and the changes of gut microbiota, with which fecal

microbiota transfer was involved in the observed phenotype.^[17] Other experimental research with the combined microbiome and metabolomic analysis has found that the interventions that are able to alter the intestinal flora can decrease inflammatory markers and extracellular-matrix degradation in animal IDD models. While these findings are of a hypothesis-generating nature and highlight potential intervention points, they also show how hard it is to tease out the microbiome effect from direct pharmacological effects in multi-component treatments.

DISCUSSION

The collected data presented in this review suggest that the gut-disc axis is a plausible extension of the existing pathophysiological framework of IDD. Convergence is the strongest one. There are different microbiome profiles in disc disease in human case-control studies, functional differences in gut-derived chemistry in metabolomic studies, evidence consistent with a causal gut microbiome contribution to disc disease in MR studies, microbiome-altering effects in animal experiments on inflammatory and degenerative disc outcomes, and direct effects of gut microbes on inflammatory signaling in disc-cell studies. The findings of the individual studies converge to an immune metabolic framework, but no one study is conclusive.

The framework doesn't mean that dysbiosis is the root cause of all the degenerating discs. Mechanical loading, local cell biology, genetics, ageing, endplate transport, obesity, smoking, injury, and local cell biology are still central to IDD, despite this condition being multifactorial. It seems more likely that the microbiome is a modifier for susceptibility and progression. Due to differences in metabolic health, intestinal barrier integrity, microbial metabolite production and immune regulation, two equally mechanically loaded individuals can have different inflammatory responses. In this model, the biological "gain" of the degenerative process is influenced by dysbiosis that increases matrix catabolism, senescence, endplate inflammation, and pain sensitization, once degeneration has started.

However, caution should be taken when interpreting the human evidence. Geography, age, diet, BMI, diabetes, physical activity, smoking, socioeconomic status, antibiotic use, PPIs, metformin, analgesics and more drugs all very strongly influence the makeup of the microbiome. A number of them are also linked with low back pain or IDD. It is difficult for small case control studies to completely adjust for this confounding. Also, the taxonomic results are not necessarily going to be the same from one population to another, due to the fact that different organisms can carry out similar metabolic activities. Functional metagenomics/metabolomics may therefore be more informative than simply a "good" or "bad" bacteria list.

The other is a reverse causation issue. Restricted physical activity, disturbed sleep, altered dietary habits, heightened psychological stress and repeated medication may all occur as a result of chronic back pain. All these can impact the gut microbiome. Therefore, candidates for surgery with severe disc disease are not necessarily representative of early IDD. Longitudinal studies that start prior to onset of severe symptoms will be needed to assess if dysbiosis is a predictor of future imaging progression or persistent pain.

Critical Appraisal of Human Evidence

The present human literature should be understood as hypothesis supporting, not as practice-changing. The majority of cohorts are cross-sectional, with a tendency to include surgical patients with advanced disease, and are relatively small. This type of design opens the door to selection bias, reverse causation, and confounding. Other factors such as habitual diet, geography and ethnicity, physical activity, body mass index and metabolic disease, smoking, sleep, socioeconomic factors, antibiotic exposure, proton-pump inhibitors, NSAIDs and other analgesics, and metformin are inconsistently measured and/or adjusted for. Other factors such as habitual diet, geography and ethnicity, physical activity, body mass index and metabolic disease, smoking, sleep, socioeconomic factors, antibiotic exposure, proton-pump inhibitors, NSAIDs and other analgesics, and metformin are inconsistently measured and/or adjusted for. Many of these exposures are associated with both microbiome composition and low-back-pain pheno- and/or genotypes independently, which can easily lead to apparent disease-associated microbiomes due to residual confounding.

There is more to it than that due to sequencing heterogeneity. Various studies have applied 16S rRNA amplicon sequencing, shotgun metagenomics, different extraction methods, various taxonomic databases and statistical pipelines. So, changes in taxonomy do not necessarily reflect direct comparisons between studies. For replication, the results of functional convergence may be more reproducible than organism-level results, which makes shotgun metagenomics, metatranscriptomics, and targeted metabolomics particularly valuable. Laboratory and analytical techniques should also be reported in full, following STORMS guidelines^[24], in microbiome studies.

Table 3: Critical appraisal of representative human studies. This is an evidence-oriented appraisal of major bias domains, not a formal ROBINS-I or GRADE score.

Study	Design / sample	Major strengths	Principal limitations / bias concerns	Interpretive weight
Rajasekaran et al., 2024 ^[8]	Case-control; 40 disc-degeneration patients, 20 controls	Direct human profiling; Modic subgroup; inflammatory markers	Small surgical cohort; cross-sectional; diet/medication/geography confounding; limited temporal inference	Association-supporting; causality unresolved
Liu et al., 2025 ^[9]	16S + fecal metabolomics across IDD grades	Links taxonomy with functional metabolite output	Small sample; platform-dependent 16S resolution; cross-sectional; multiple-testing and confounding concerns	Mechanistically informative but exploratory
Lan et al., 2025 ^[10]	Shotgun metagenomic case-control; 31 Modic cases, 25 controls	Higher taxonomic/functional resolution; matched controls	Modest sample; single-region recruitment; residual lifestyle/medication confounding	Supports Modic-associated dysbiosis; needs external replication
Zheng et al., 2024 ^[11]	Two-sample Mendelian randomization	Reduces conventional confounding and reverse causation	Instrument strength, taxonomic resolution, pleiotropy, ancestry/population structure	Causal-inference support, not intervention evidence
Fang et al., 2024 ^[12]	Two-sample Mendelian randomization	Multiple microbial taxa and pathways tested; sensitivity analyses	Multiple testing; database-dependent microbial traits; weak-instrument risk for some taxa	Suggestive causal signals; strongest only after correction
Ge et al., 2025 ^[13] / Yan et al., 2026 ^[15]	MR across disc-disease phenotypes / inflammatory mediators	Triangulates microbial traits, disc outcomes, and mediation hypotheses	Genetic proxies do not equal modifiable exposure; cytokine mediation may be underpowered or incomplete	Supports pathway causality with substantial mechanistic uncertainty

Therapeutic Perspectives

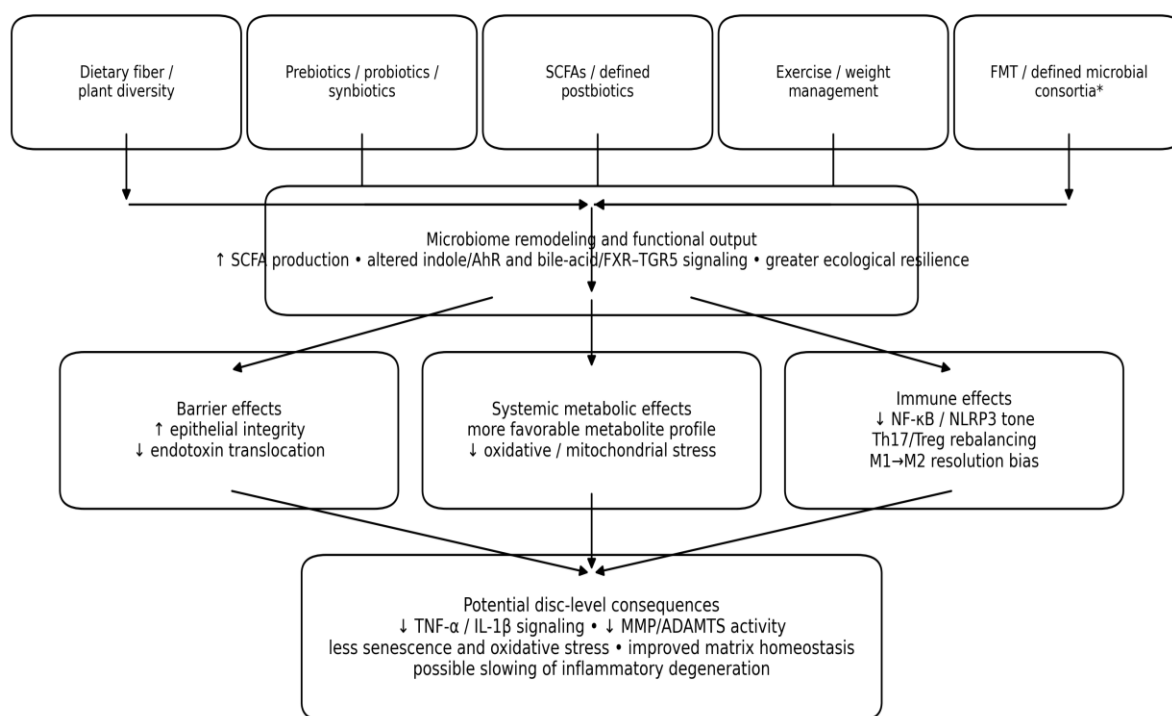
From a therapeutic perspective, the microbiome is attractive because it is modifiable. Diets rich in diverse plant fiber can increase microbial substrate availability for SCFA production, while regular physical activity and weight management support metabolic health. These measures already have broader health benefits and are consistent with general low-back-pain care, but their ability to specifically slow radiographic IDD through microbiome mechanisms has not yet been proven. Probiotics, prebiotics, synbiotics, postbiotics, and targeted microbial metabolites may eventually offer more specific approaches. However, a generic probiotic is unlikely to be effective for all patients because baseline microbiomes, diet, genetics, medications, and disease phenotypes differ substantially.

FMT deserves particular caution. Although the rat study by Yao et al. provides proof of concept^[16], FMT is a medical procedure with infectious and ecological risks and is currently established primarily for selected gastrointestinal indications, not for IDD. The animal data

should motivate controlled mechanistic studies rather than clinical self-treatment. A safer translational route may be to identify the specific microbial functions or metabolites associated with protection and develop defined consortia, dietary strategies, or postbiotic molecules that can be standardized and tested.

Precision stratification may become important. Patients with IDD are heterogeneous: some have inflammatory Modic changes, some have predominantly mechanical degeneration, some have obesity or insulin resistance, and some have neuropathic pain or herniation. A future microbiome-guided approach might combine MRI phenotype, stool metagenomics, circulating and fecal metabolomics, inflammatory markers, dietary data, and clinical features to identify subgroups more likely to benefit from a specific intervention. The 2026 immune-metabolic framework similarly proposes patient classification based on gut, immune, and metabolic features rather than treating all disc disease as biologically identical.^[18]

Microbiome-targeted therapeutic concepts and expected biological effects



*FMT evidence for IDD is preclinical. None of these microbiome-directed strategies is established as disease-modifying standard care for IDD.

Figure 3. Conceptual workflow linking microbiome-targeted interventions to barrier, metabolic, immune, and potential intradiscal outcomes. Current IDD evidence is predominantly mechanistic or preclinical; these approaches should not be interpreted as established clinical treatments.

Future Perspectives

Prospective Multicenter Longitudinal Cohorts

The most important clinical need is the prospective sampling prior to any advanced radiographic change or surgical interventions. Participants in multicenter cohorts should be recruited at multiple stages of disease, and data collected on stool, blood, diet and medication, body-composition, physical activity, sleep, pain, and imaging should be collected at multiple time points. This design would enable investigators to determine if baseline microbial functions or metabolites can predict new Pfirrmann-grade progression, Modic change development, endplate abnormality, and/or persistent pain, as well as simply reflect established disease behavior. It is important to account for the following pre-specified factors: Antibiotics, PPIs, NSAIDs, Metabolic disease, BMI, Smoking, Geography, Dietary patterns.

Integrated Multi-Omics and Quantitative Imaging

Moving beyond 16S taxonomic comparisons needs to be done in future studies. Future clinically useful gut-disc model will likely need to include integrated shotgun metagenomics (gene-level microbial capacity), metatranscriptomics (active microbial pathways), targeted metabolomics (stool) and untargeted metabolomics (serum), serum cytokine, phenotyping of immune cells and advanced quantitative MRI.

Standardized Pfirrmann grading and Modic classification, and – if possible – quantitative T2/T1ρ mapping, diffusion measures, endplate evaluation, and disc hydration measures by compositional images should be included. The integration of these layers can reveal transferable functional signatures that can be more useful than individual taxonomy within and across populations.

Improved medicine response testing and therapeutic targeting

Bioavailability (and tissue exposure) should be studied for candidate metabolites – it is not enough to demonstrate that a molecule is altered in the stool if there is no biological concentration in circulation or disc/endplate. Microbiome manipulation should thus be coupled with a serum pharmacometabolomic approach, a disc-cell or endplate model approach and a mechanistic approach including the measurement of NF-κB activity, oxidative stress, senescence markers, MMP/ADAMTS expression and matrix synthesis. Clinical endpoints (pain, function, and structural imaging progression) should be clinically relevant as should microbiome/metabolite outcomes be controlled intervention trials pre-defined. Triangulation between longitudinal epidemiology, MR, animal models, ex vivo human tissues, and intervention studies will yield the best foundation for causal confidence.

CONCLUSION

The gut microbiome has been suggested to be a potential systemic modulator of IVD health. To date, there is some evidence that intestinal dysbiosis can play a role in IDD through dysregulated barrier function, endotoxin, innate immune signaling, immune-cell dysfunction, disrupted pathways of microbial metabolites (such as short-chain fatty acids), oxidative and metabolic stress and, in some contexts, microbial translocation. While there is growing evidence for a gut–disc relationship from human microbiome and metabolomic studies, animal experiments, and genetic causal-inference analyses, it is insufficient to define a diagnostic microbiome signature or recommend microbiome-targeted therapy as standard treatment for IDD. The best defensible explanation is that the microbiome is one modifiable, but not the only, factor within a larger mechanical, genetic, metabolic and inflammatory pathway. Future longitudinal and interventional studies will confirm causality, and if this is the case, maintaining or restoring a healthy gut microbial ecosystem could prove to be a part of a disease modifying approach to spine health, rather than just being used for symptom management.

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Ethics Approval and Consent to Participate

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Consent for Publication

Not applicable. The manuscript contains no identifiable individual participant data, images, or case material requiring publication consent.

Competing Interests / Conflict of Interest

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