Host–Gut Microbial Environmental Axis in Musculoskeletal Disorders

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Abstract

The gut-musculoskeletal axis has become an important interdisciplinary paradigm between the ecology of the intestinal microbial environment of host and the pathophysiology of musculoskeletal disorders. Disruptions in the composition and function of the gut microbiota, i.e. dysbiosis, have a profound effect on systemic immunity, tolerance, metabolism and inflammatory cascades associated with the pathogenesis of osteoarthritis, rheumatoid arthritis, osteoporosis, sarcopenia and related disorders. The gut microbiome influences osteoimmune signaling through metabolites like short-chain fatty acids, bile acids and indole derivatives which influence the signaling of the RANKL-OPG pathway, bone turnover, chondrocyte catabolism and muscle protein synthesis. Concurrently, the inflammatory reactions mediated by TLR/TLRs resulting from impaired intestinal wall permeability and endotoxemia contribute to the Th17/Treg imbalance, accelerate the destruction of the joint cartilage, bone resorption, and skeletal muscle atrophy. Emerging evidence from germ-free models, studies of fecal microbiota transplantation and from large-scale metagenomic analyses has underlined unique microbial signatures of disease onset and severity and disease progression. Therapeutic approaches that target the microbiome, includes probiotics, prebiotics, dietary manipulation, postbiotics, next-generation microbial therapeutics, show great potential in re-establishing musculoskeletal homeostasis, although there are particularly large gaps in terms of cause and effect, mechanism, and inter-individuality. In the context of the evolving health environment, advances in multi-omics technologies, systems biology, and AI-driven predictive modelling are expected to play an increasingly important role in the development of precision microbiome-based therapies for musculoskeletal disorders.

Keywords: Gut–musculoskeletal axis; Gut-microbiome; Osteoimmunology; Dysbiosis; Musculoskeletal disorders

1. Introduction

The conceptualization of the gut-musculoskeletal axis has undergone a dramatic change in the last decade, moving the scientific paradigm from an investigation of tissue pathology to the integrated systems biology perspective. Earlier theories were based mainly on biomechanical overload, hormonal decline, autoimmunity and senescence-related tissue degeneration (Z. Li, Wang, et al., 2024; Sun, Zhang, et al., 2025). With the emergence of microbiome science, researchers realised that the gastrointestinal tract, traditionally thought to be a digestive organ, actually acts as a central immune-metabolic hub with distal effects in bone, cartilage and skeletal muscle (G et al., 2025; Roberts et al., 2025). This paradigm shift took the theory of musculoskeletal disease from a purely host-centric model towards a model which incorporates the contribution of microbes. This development in conceptual understanding occurred at the same time as advances in technology in 16S rRNA sequencing, shotgun metagenomics, metabolomics, and in gnotobiotic animal models, paving the way to deeper mechanistic exploration. (Bastiaanssen et al., 2023; Y. Li et al., 2024) These new tools showed that dysbiosis often preceded inflammatory bone loss, joint degeneration and sarcopenia, suggesting a causal, rather than simply associative, role.(Vella et al, 2021c; Zhang et al., 2021) Strengthened by the accumulation of evidence, the gut-musculoskeletal axis became a legitimate interdisciplinary discipline with connections in several other areas including rheumatology, orthopaedics, immunology, The evolution of this concept is therefore a huge step in the direction of precision therapeutics using microbial pathways towards maintaining musculoskeletal health. The realization that the gut flora can modulate systemic inflammation, osteoclast - osteoblast balance, chondrocyte metabolism and muscle anabolism was a significant conceptual breakthrough (Gilat et al., 2025; Y. Wang et al., 2025). Discovery of microbe-derived metabolites such as the short chain fatty acids (SCFAs), secondary bile acids, and tryptophan derivatives offered biochemical connections between the activities of the gut biota and the regulation of musculoskeletal tissue homeostasis. (A et al., 2024; Hong et al., 2024) Studies showed that gut-derived signals are capable of modulating the RANKL - OPG axis, modulating monocyte activation, changing the cytokine patterns in the joint, and modifying the bioenergetics of muscle mitochondria, thereby firmly establishing (Reynders et al., 2024; Simorgh et al., 2024). Under physiological conditions, the gut microbiome has a key role in maintaining immune homeostasis, regulating metabolic flow, and maintaining the integrity of the epithelial barrier, keeping up a state of optimal functioning of musculoskeletal systems. (Collins et al., 2021; S. Huang et al, 2021c) In this synergistic interaction, balanced microbial communities produce SCFAs that inhibit NF-kB signaling and suppress pro-inflammatory cytokines as well as improve calcium absorption and transformation of osteoblast cells into osteoblasts. (Y. Li et al, 2021b; X. Xu et al, 2021a). Commensal microbes are also instrumental in maintaining a continuous Th17/Treg equilibrium to prevent excessive inflammation with potentially harmful results in bone and cartilage. (Chu et al, 2021c) The effect of commensal microbes represents a Pathology occurs when this balance is disturbed via dysbiosis, which is characterized by a decrease in the microbial biome's richness and the absence of beneficial taxa.(Zhang et al, 2021a)Dysbiosis leads to dysfunction of tight junction proteins that result in gut barrier dysfunction ("leaky gut") and the translocation of lipopolysaccharides (LPS) into circulation. (S. Wang et al, 2021a) LPS activates TLR2 and TLR4 receptors, leading to IL-1-beta, IL-6, and TNF-alpha production, systematic low-grade inflammation, a key component of osteoarthritis pathogenesis, rheumatoid arthritis exacerbations, bone resorption and muscle wasting. (Chang et al, 2021a; Z. Li et al, 2022). Concurrently, gut microbial dysbiosis impairs nutrient digestion, hinder nutrient availability and metabolic signaling, further contributing to promotion of musculoskeletal dysfunction.

Emerging evidence shows the involvement of specific microbes, whether bacterias (*Prevotella copri*, Clostridium XIVa, *Bacteroides fragilis*) triggering autoimmunity, altering BMD, or modulating muscle metabolism in fact, germ free animal models show consistent dysfunction of bone architecture, decreased muscle mass, and increased susceptibility to inflammation suggesting both causal and exciting relationship of host and microbiome is occurring (Berenbaum et al, 2022d; S. K. Kim et al, 2022a). Germ free animal models consistently exhibit dysfunctional bone architecture and decreased muscle mass and increased susceptibility to inflammation reinforcing the experienced causal relationship of microbiome-host interactions and help transform localized musculoskeletal dysfunction into systemic inflammatory state mediated by microbial (Britton et al, 2014; Z. Huang et al, 2020).

Despite how quickly microbiome research is progressing and despite all the unique challenges of investigating the microbiome, the interweaving and integration of microbiome-mediated mechanisms in the biology of bone, cartilage and muscle is still patchwork. Previous data has often consisted of isolated disease models such as rheumatoid arthritis or osteoporosis and these data have not been integrated in to a gathered narrative of mind-boggling common ground (the media traveling in the same direction in collecting, processing, and expressing data) in microbial and immunometabolic pathways already converging in the combined pathway polytetra-logical significance in the full biological spectrum of the AEC (the gut-musculoskeletal axis) (Ohlsson et al, 2020b; Schett et al, 2016). The rationale of this review is to collect and plan these scatter-gathered data to altruistic their and individual into an unified mechanistic composed story that captures the totality of biological range

Another driving motivation is the increased translational interest in microbiome-targeted interventions consisting of probiotics, prebiotics, synbiotics, postbiotics, dietary modulation and fecal microbiota transplantation (FMT) (Britton et al, 2014; J. Li et al, 2019)While these approaches display considerable promise, the clinical relevance of these approaches depends on a mechanistic basis for the target of association between different microbe taxa, metabolites, and outcomes to the human musculoskeletal system. Therefore, such an approach documents important therapeutic targets in this review to fill the gap between basic mechanistic science and clinical evidence and identify gaps to be addressed before microbiome-based approaches can be made mainstream in musculoskeletal medicine.

Therefore, to trace the conceptual evolution of the gut–musculoskeletal axis; for critical evaluation of the complex microbiome–host interactions that influence musculoskeletal health and disease; have been undertaken to explore emerging therapeutic opportunities and future research directions, particularly in the context of multi-omics approaches, systems biology, and precision microbiome engineering (Picca et al,2018; Kang et al,2020). By integrating biological, clinical, and translational perspectives, this article aims to provide a comprehensive foundation that can support the development of innovative strategies and interventions in this rapidly advancing field.

2. Methodology

A comprehensive and systematic literature pursuit strategy to identify germane findings on the correlation between gut microbiome and musculoskeletal diseases. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for articles published between 2000 and 2025. Keywords used in the methodology of the article included “gut microbiome,” “gut-musculoskeletal axis,” “osteoarthritis,” “rheumatoid arthritis,” “osteoporosis,” “sarcopenia,” “dysbiosis,” and “microbial metabolites.” Boolean operators (AND, OR) were applied to refine the search. Inclusion criteria comprised peer-reviewed original research articles, review papers, and clinical studies published in English that investigated the relationship between gut microbiota and musculoskeletal health or disease mechanisms. Exclusion criteria included non-English publications, conference abstracts, duplicate records, and studies lacking clear relevance to the topic. Articles were screened based on title and abstract, followed by full-text evaluation for eligibility.

Data were extracted and synthesized qualitatively, focusing on microbial composition, mechanisms such as immune modulation, inflammation, and metabolite signaling, and their association with musculoskeletal disorders. Priority was given to high-quality, recent studies (2022–2025) to ensure updated scientific evidence. The collected information was organized into thematic sections, and relevant findings were summarized in tables and figures to enhance clarity and understanding (Farmakiotis et Kontoyiannis, 2017; Sellam et Berenbaum, 2010).

3. The Human Gut Microbiome: Composition, Dynamics And Apparent Architecture Of Function

3.1 Taxonomy of gut microbial communities

The human gut microbiome constitutes a very diverse ecological community that is dominated by four main bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria (S. Huang et al, 2021b; Qin et al, 2010a). These phyla harbour hundreds of species with unique metabolic and immunomodulatory potential that influence the physiology of the host at several systemic levels. Firmicutes including *Faecalibacterium prausnitzii*, Clostridium XIVa and Roseburia spp. are major producers of butyrate and Bacteroidetes including Bacteroides and Prevotella play an important role in carbohydrate fermentation and in the transformation of bile acids(Louis et Flint, 2017). Actinobacteria, especially Bifidobacterium spp. influences in early immune development, while Proteobacteria contains the pathobionts that are expanded in dysbiosis (Narulla et Diwan, 2025a).

Microbial ecosystem composition is strongly influenced by diet, age, host genetics, geography and medication exposure (Hong et Zhao, 2024; Z. Li et Wang, 2024). High-fiber diets are associated with an enrichment of beneficial saccharolytic taxa from Firmicutes and Bacteroidetes whereas high-fat Western diets promote the expansion of Proteobacteria and the development of low-grade inflammation (Reynders et al, 2024c; Simorgh et al, 2024b). Early-passing modulating factors (breastfeeding, antibiotic exposure, delivery mode) impress long term microbial trajectories with repercussions on immune maturation in adulthood (Berenbaum et al, 2022b; Y. Li et Zhang, 2022). With age the microbial diversity is reduced which contributes to systemic inflammation and susceptibility to loss of musculoskeletal integrity.

Importantly, the gut is a functioning interconnected network of microbes as opposed to a static composition. Cross feeding interaction, metabolic co-dependency and niche competition maintains ecological stability (S. K. Kim et al, 2022d). Perturbations, such as antibiotics, infections, diet changes, cause destabilization, and there is expansion of the opportunistic species and loss of beneficial taxa (Chu et al, 2021d). These taxonomic changes have an impact in bone remodelling, cartilage turnover and metabolism in muscles showing the importance of microbial composition in musculoskeletal diseases (Collins et al, 2021c; X. Xu et al, 2021c).

3.2 Microbial Metabolites: SCFAs & BCAAs, Indoles, Bile Acids.

Microbial metabolites represent the most important biochemical dialogue of the gut microbes to host tissues distant from the gut. SCFsAs and propionate and butyrate are produced as a result of fermentation of dietary fibers and have multiple beneficial effects on the host, including epithelial reinforcement, suppression of NF-kB, and stimulation of osteoblast differentiation.(S. Huang et al, 2021a)SCFAs modulate the activity of the RANKL - OPG axis, reducing osteoclasticity and preserving against bone loss (Zhang et al, 2021e). They are also known to support chondrocyte metabolism and extracellular matrix synthesis, which is thought to be one way that microbial metabolism is linked to cartilage physiology (Vella et al, 2021d).

Aside from possible SCFAs, the gut microbial metabolism of proteins is a source of branched-chain amino acids (BCAAs), which are involved in skeletal muscle protein synthesis and regulation of energy use in mitochondria (Agus et al, 2021; J. Y. Li et al, 2020). Dysregulated BCAA synthesis has been linked to metabolic inflammation and impaired insulin signaling secondary to impact on the musculoskeletal homeostasis(Peterson et Artis, 2014). Tryptophan-derived indoles regulate mucosal immunity through the AhR pathway, affect the integrity of the mucosal barriers and control systemic inflammatory tone and influence joint and bone health (Johansson et al, 2011).

Microbial Bile Acid Alteration Is another important metabolic axis. Gut microbe metabolites modify lipid homeostasis, mitochondrial function and inflammatory pathways by converting primary bile acids to secondary forms through interactions with the FXR and TGR5 receptors (Camilleri, 2019). These interactions affect osteoblast activity as well as the bone turnover and metabolic efficiency of muscle (Ghosh et al, 2014; Guo et al, 2015). Dysbiosis leads to a disruption of metabolite production, impairing these signaling pathways along with the inflammation and progressive muscle and skeletal decline (Rogier et al, 2017).

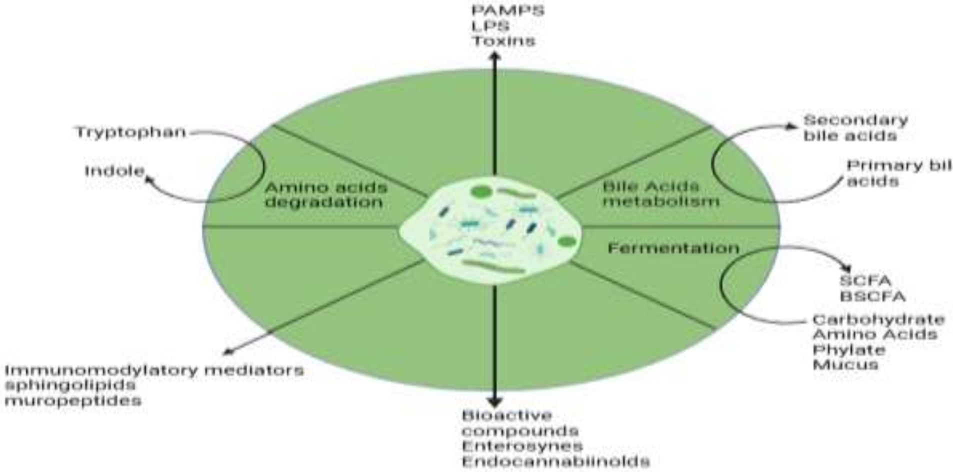

Fig 1: Microbial Metabolite Signaling Pathways Linking the Gut Microbiome to Musculoskeletal Health

The figure 1 outlines the pivotal position of the gut microbiota as an active and signifying compartment that interacts with dietary components and host-derived substances to produce a rich repertoire of biologically active substances. The microorganisms in the gut break down amino acids like tryptophan into the compounds like indole, which regulate the gut barrier functionality and immune control. They also convert primary bile acids to secondary bile acids hence controlling lipid metabolism and cellular signalling pathways. The microbiota produces short-chain fatty acids (SCFA) and branched-chain fatty acids (BSCFA) through the fermentation of carbohydrates, amino acids, mucus as well as phytates and these are energy sources with anti-inflammatory effects. Also, microbial activity results in the release of the immune-modulatory molecules of sphingolipids and muropeptides, bioactive compounds of enterosynes and endocannabinoids that mediate systemic signalling, such as the gut-brain axis. At the same time, microbial elements like pathogen-associated molecular patterns (PAMPs), lipopolysaccharides (LPS) and toxins may also stimulate immune activities and inflammation, especially in dysbiosis. On the whole, this figure shows that the gut microbiome presents a combination of metabolic, immune and signalling pathways, which play a central role in systemic health, such as the control of musculoskeletal functionality and disease.

3.3 Gut Barrier Physiology and the “Leaky Gut” Paradigm

Intestinal barrier is a comprised of mucus layers, antimicrobial peptides, immune cells, and tight-junctional proteins, claudins and occludins. In physiological circumstances, the given structure hampers the translocation of microbial products and allows absorbing nutrients. Microbiota of the gut and its maintenance of the epithelial integrity is mediated by the butyrate metabolite which promotes colonocyte metabolism and assembling tight-junction(Manickam et al, 2018). Gut barrier is preserved by high epithelial turnover, secretion of mucin, and due to immune tolerance (Belkaid et Harrison, 2017; J. Chen et al, 2019).

Dysbiosis impairs tight junctions and impairs epithelial cohesion, thereby leading to greater intestinal permeability, which is leaky gut(Honda et Littman, 2016). This allows entry of lipopolysaccharides, peptidoglycans and other microbial fragments into the system (Dalile et al, 2019a). These MAMPs stimulate TLR2/TLR4 signaling inducing inflammation that facilitates synovial activation, osteoclasto-genesis, cartilage damage, and skeletal muscle catabolism (Roberts et al, 2025b). The chronic permeability forms low-grade systemic inflammation that has harmful implications on the musculoskeletal tissues.

It has been demonstrated that gut permeability is closely related to such disorders as RA, OA, and osteoporosis (Sun et al, 2025b; Y. Wang et al, 2025b). Repeated LPS stimulation shortens the differentiation stage of the osteoclasts and stimulates bone resorption (G et al, 2025b; Gilat et al, 2025a). LPS-induced inflammation in muscle disrupts the functionality of mitochondria and anabolic resistance, which leads to sarcopenia (Y. Xu et He, 2025a). Therefore, the leaky-gut paradigm is one of the major mechanism connectors between the disturbance of the microbiome and the systemic musculoskeletal inflammation.

3.4 MICR Immunomodulatory activity of microbiota in Systemic Inflammation.

The intestinal microbiota has a powerful impact on the systemic immunity. Commensals are known to control the maturation of dendritic-cells and promotes Treg differentiation and prevents the excessive proliferation of Th17 cells (Z. Li et al, 2024a). Microbial communities with equal balance of both maintain immune tolerance and stop any overproduction of cytokines that might be harmful and may damage bone, cartilage, and muscle(A et al, 2024b; Hong et al, 2024b). SCFAs and indole suicide interfere with cytokine expression, stimulates IL-10, and inhibits TNF-a, IL-1b, and IL-6 signaling (Reynders et al, 2024a).

Dysbiosis changes this balance of immune response to pro-inflammatory phenotype. Displacement of advantageous taxa and increase in the presence of pathobionts heightens the osteoimmune imbalance by boosting the RANKL expression which lead to osteoclastogenesis, synovial inflammation, and bone erosion (Bastiaanssen et al, 2023a). Immune activation due to dysbiosis also interferes with bone remodelling, cartilages and muscle protein degradation (S. K. Kim et al, 2022c). These immunological changes are capable to cause permanent degeneration of the skeletal muscles.

Immune signals mediated by microbiota are spread to extraintestinal tissues such as bone marrow, synovium, and skeletal muscle (Berenbaum et al, 2022a; Y. Li et al, 2021c). Microbial antigens are able to sensitize the monocytes/macrophages which increases the inflammatory process in the bone tissue and joints (X. Xu et al, 2021b). Satellite-cell activation is also inhibited by gut-derived cytokines which inhibit muscle regeneration (Collins et al, 2021b). Collectively, these results validate the fact that gut microbes are major controllers of systemic inflammation whose direct effects may be seen on musculoskeletal pathology.

4. INVISIBLE LANDSCAPE OF THE GUT-MUSCULOSKELETAL AXIS

4.1 Immune Reprogramming and its antagonism mediated by microbiota (Th17/Treg Imbalance and Cytokine Networks)

The gut microbiota also has the most critical influence on the development of systemic immunity by maintaining the balance between Th17 and Treg, which is a key cause of musculoskeletal inflammation. In healthy settings, the commensal microbes favor differentiation of regulatory T cells (Tregs), which cover immune tolerance and restraining over-production of IL-6, IL-17, and TNF-a. The Firmicutes that produce butyrate are especially crucial in Treg induction, as well as, peripheral immune homeostasis (Vella et al, 2021a; Zhang et al, 2021c). Dysbiosis, in turn, derail the process of Treg development and results in the growth of Th17 cells, which increase the production of IL-17 and GM-CSF, two cytokines that have an important role in the destruction of joints, inflammation of the synovium and bone erosion (S. Huang et al, 2021d).

Microbial ecosystem perturbations also re organize cytokine networks by adjusting the dendritic-cell presentation of antigens as well as the macrophage polarization. The depletion of advantageous commensals lowers the release of IL-10 and TGF-b and at the same time enhances the production of M1-style macrophages that stimulate the release of high quantities of IL-1b, TNF-a, and IL-6(L. Chen et al, 2020). These cytokines target osteoblasts, osteoclast precursors, and chondrocytes, which stimulate osteoclastogenesis, degradation of cartilage matrix and proliferation of synovia (Chu et al, 2021a). This gut re-shaping of immune systems is a mechanistic linkage between gut dysbiosis and whole organism musculoskeletal inflammatory disease.

New evidence reveals that particular taxa, including *Prevotella copri*, *Klebsiella pneumoniae* and some others of the

Proteobacteria actively induce the Th17 differentiation and RA-like phenotypes of germ-free mice. Tregs inducing microorganisms on the other hand, which include Clostridium XIVa and *Bacteroides fragilis*, reverse autoimmune inflammation. Such results demonstrates that the composition of microbes of the gut is not merely associated with musculoskeletal disease but has a mechanobiological role in reprogramming the immune system in the systemic context (Zhang et al, 2020).

4.2 Endotoxemia (LPS/TLR Pathways) and Low-Grade Chronic Inflammation.

Endotoxemia is another of the most powerful mechanistic connections between Musculo-skeletal pathology and gut dysbiosis. Over-permeabilization of the intestinal mucosa permits translocation of lipopolysaccharides (LPS) into the bloodstream leading to interaction of LPS with TLR4/CD14 on monocytes and macrophages, initiation of NF-kB and triggering of pro-inflammatory cytokines (K. A. Kim et al, 2019). Low doses of the circulating LPS can cause chronic low-grade inflammation, which is one of the key causes of osteoarthritis, rheumatoid arthritis, osteoporosis, and sarcopenia (Bolduc et al, 2019).

TLR signaling is not only associated with the release of inflammatory cytokines, but also the acceleration of osteoclast precursor (OP) differentiation by increased levels of RANKL and M-CSF(Johnson et al, 2015). Excessive levels of LPS in the systemic compartment disrupt the action of osteoblasts, amplify oxidative stress, and activate matrix metalloproteinases (MMPs) in joint tissues (Liguori et al, 2018). This generates a sustainability of inflammatory microenvironment which hastens cartilage degradation, bone resorption, and breakdown of muscles protein.

According to recent clinical evidence, higher levels of LPS-binding protein (LBP) and soluble CD14 are observed in patients with osteoarthritis, rheumatoid arthritis and severe osteoporosis, which in a direct cause-and-effect relationship directly relates endotoxemia with the severity of musculoskeletal diseases(Ulici et al, 2018). In this way, this pathway of the LPS-TLR is a pathological compartment that links gut dysbiosis with both chronic systemic and musculoskeletal inflammation. Inhibition Bone remodeling, a widely used technique, entails adjusting the microbial population within bone marrow cavities.

4.3 Microbial Metabolite Signaling in Bone Remodeling (RANKL-OPG Axis)

Inhibition Bone remodeling is a common method in which the cellular population of bone marrow cavities is altered. Microbial metabolites are extremely regulatory on bone remodeling as they orchestrate the actions of osteoblast and osteoclast, using the RANKL-OPG axis. Fatty acids that are short-chain, especially the butyrate and propionate, repress the differentiation of osteoclasts by suppressing the expression of the RANKL and inducing the expression of OPG in osteoblasts (Y. Li et al, 2021a; Pacifici, 2017). The SCFAs also suppress the histone deacetylases (HDACs) and change the gene-expression profiles which suppress osteoclast precursor proliferation (Ticinesi et al, 2019a).

In contrast, the depletion of SCFA-producing bacteria by dysbiosis interferes with this homeostasis, favored in the osteoclastogenesis via RANKL, and led to the rapid bone loss. According to metabolomic studies, dysbiotic microbiota reduce the access of major metabolites, including the derivatives of indoles and secondary bile acids that are the activators of FXR/TGR5 pathways linked to osteoblast differentiation and antiinflam-matory bone signaling (Boer et al, 2019; Yamada et al, 2019a).

Further evidence to test this is experimental studies on the use of the microbiome in the examination of bone homeostasis via use of germ-free mice. Butyrate-producing bacteria colonization positively influences the increase in bone mass, and the colonization with pro-inflammatory taxa stimulates the expression of RANKL and bone fragility. These results emphasize the idea that microbiome is one of the key regulators of bone remodeling through the metabolite-mediated control of the RANKL-OPG axis.

4.4 Gut Microbiota and Oxidative Stress in the Degeneration of Musculoskeletal.

Oxidative stress is one of the major pathogenic processes in OA, RA, osteoporosis and muscle atrophy. Gut microbiota have intense effects on the maintenance of oxidative homeostasis affecting the generation of reactive oxygen species (ROS), the functioning of mitochondria, and antioxidant mechanisms. Positive commensals contribute to the immunoprotective processes of Nrf2-regulated antioxidants to alleviate the effects of ROS on musculoskeletal muscles. Conversely, dysbiosis augments intestinal and systemic ROS, and plays a role in the impaired functioning of the mitochondrion in muscle and bone (Collins et al, 2021a; Z. Huang et al, 2016).

The metabolites and toxins secreted by inflammatory pathobionts stimulate NADPH oxidase and cause dysfunctions of electron transport chains in the mitochondria, increasing the quantity of ROS. High levels of ROS cause the destruction of chondrocytes, faster degradation of type II collagen, and osteoblast stress and injury coupled with increased differentiation in osteoclasts (Berenbaum et al, 2022c; Dunn et al, 2020). Excessive oxidative stress in skeletal muscle results in a decrease in mitochondrial ATP production and protein synthesis and activation of muscle-wasting signaling including FOXO and ubiquitin-proteasome systems(Maeda et al, 2016).

The above clinical studies demonstrate elevated oxidative biomarkers MDA, 8-OHdG, protein carbonyls in dysbiosis-related musculoskeletal diseases patients(Scher et al, 2013). This shows that oxidative stress is not a combination effect but a mechanistic continuation of juncture of microbiome of the gut to bone, cartilage, and muscle integrity.

4.5 Intestinal Dysbiosis Intestinal Dysbiosis: Systemic Effects of Cartilage, Bone and Muscle Microenvironment.

The systemic effects of intestinal dysbiosis cause a cascade effect on musculoskeletal tissues by changing the microenvironment of the structure and cellular composition. Inflammatory cytokines caused by dysbiosis infiltrate joint tissues and stimulate synoviocytes, chondrocytes, and resident macrophages, thus, leading to an increase of MMPs and faster cartilage destruction (Vella et al, 2021b; Zhang et al, 2021d). Production of anti-inflammatory metabolites which are crucial in chondrocyte homeostasis is also lost through loss of beneficial taxa (Ohlsson et al, 2020a).

In bone, dysbiosis improves osteoclast precursor recruitment and activation which results in trabecular thinning and cortical bone fragility. At the same time, there is a decrease in Osteoblast activity by inhibiting the Wnt and OPG systems by the systemic inflammatory mediators(Tyagi et al, 2018; Weaver et al, 2019). The combination of these changes is what causes the osteoporosis-like phenotypes in classical risk factor-deficient conditions.

Dysbiosis in skeletal muscle decreases the SCFAs and BCAAs availability, disrupting mitochondrial biogenesis and causing inflammatory myotoxic pathways(Jones et al, 2020; Zaiss et al, 2019). Gut-derived cytokines and LPS also disrupt the activation of the satellite-cell and muscle regeneration rates(Ticinesi et al, 2019b). Collectively, these mechanisms prove that dysbiosis has a multiorgan musculoskeletal effect, which is the key to its importance in the overall tissue degeneration.

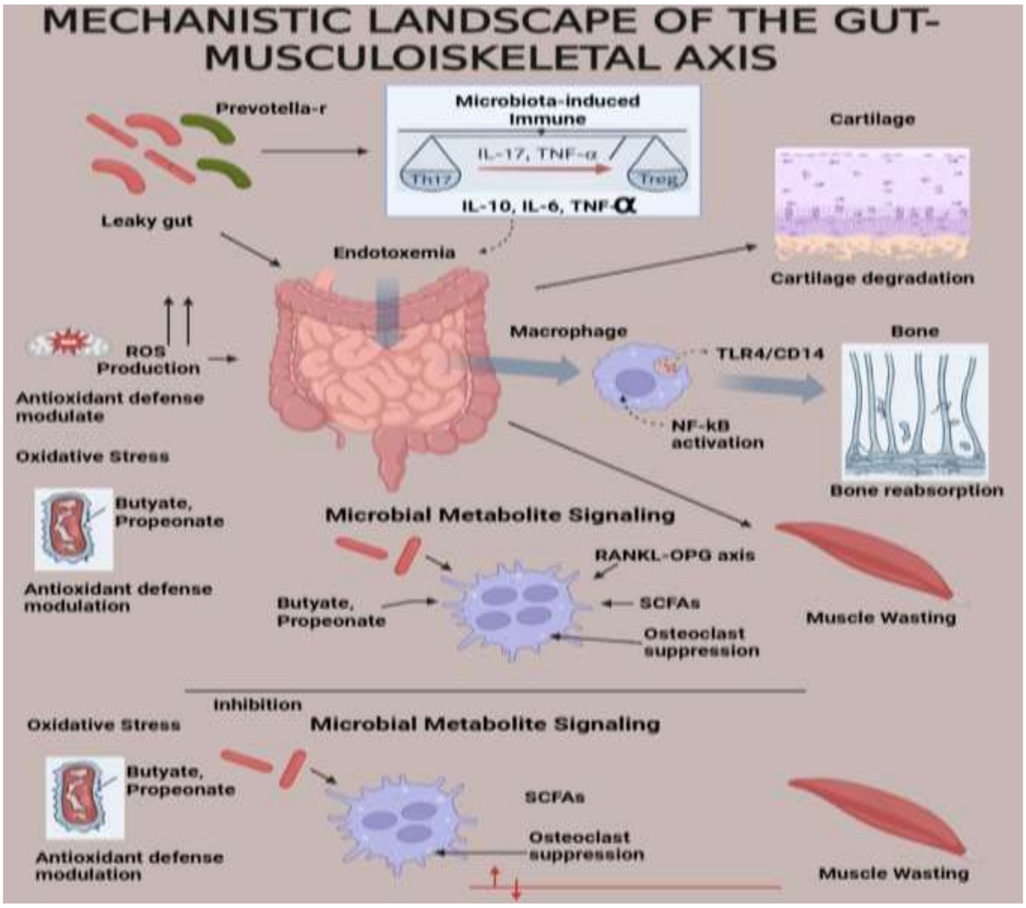

Fig 2: Integrated Mechanisms Linking Gut Dysbiosis to Musculoskeletal Degeneration

The figure 2 shows the mechanistic environment of the gut–musculoskeletal axis, which illustrates that manipulations in the gut microbiota alter the immunological reactions, the metabolic crosstalk, and ultimately influences musculoskeletal well-being.

An overrepresentation of certain taxa (e.g. an overabundance of Prevotella) is termed dysbiosis, associated with increased intestinal permeability, commonly termed as leaky gut, and allows microbial derivatives (most notably lipopolysaccharides, or LPS) to enter systemic circulation, a condition known as endo-toxemia. This translocation leads to innate immune signaling cascades, especially activation of macrophages by TLR4/CD14, which results in the translocation of NF- 2 -and release of pro-inflammatory cytokines, such as IL-17, TNF- 2 -receptor, and IL-6, in conjunction with an imbalance in the Th17/Treg balance. The produced cytokine environment promotes cartilage breakdown and osteoclastic bone erosion. Meanwhile, an increased oxidative load is also noted, and it can be ascribed to an increase in the generation of reactive oxygen species (ROS) and loss of antioxidant defense systems. On the other hand, short-chain fatty acids (SCFAs) including butyrate and propionate are beneficial microbial metabolites that have protective functionality by regulating immune responses, fortifying antioxidant defenses, and inhibiting osteoclastogenesis via the RANKL- OPG signaling pathway. These metabolites also alleviate inflammations and reduce muscle wasting. The combination of the two numbers highlights the dualistic role of the gut microbiome: in the dysbiotic conditions, the microbiota promotes inflammatory activity, oxidative stress, and the consequent musculoskeletal damage, in healthy microbiota, the microbiota serves as the protective signal of metabolic support of a healthy bone/cartilage/muscle tissue.

5. GUT MICROBIOME IN MAJOR MUSCULO-SKELETAL DISORDERS

5.1 Osteoarthritis (OA)

Dysbiosis plays a significant role in the pathogenesis of osteoarthritis, including inflammatory mechanisms, a change in the metabolite, and the activation of cartilages-degrading mechanisms. The heightened prevalence of inflammatory pathobionts including Escherichia/Shigella, Prevotella and phylum Proteobacteria, catalysts of IL-6, IL-1b and TNF-a, is common in osteoarthritis patients(Lahiri et al, 2019). The cytokines trigger chondrocytes, increase the NF -kB signaling, and amplify cartilage destruction led by matrix metalloproteinase (MMP). It has been shown using experimental models that low-grade endotoxemia caused by dysbiosis has a direct adverse effect on the severity of osteoarthritis (Yamada et al, 2019b). Microbial products also enhance cartilage catabolism. The decrease in the group of taxa producing short-chain fatty acids reduces the provision of butyrate, which is an anti-inflammatory metabolite that is necessary to provide chondrocyte viability and the down-regulation of MMP expression (Rosenbaum et al, 2019). On the other hand, harmful metabolites like secondary bile acids and aromatic amass in dysbiosis, rupture extraluminal matrix substances, and hasten cartilage decomposition (Chu et al, 2021b).

More recent studies propose the possibility that osteoarthritis can be not completely sterile; the joint microbiome hypothesis postulates that the bacteria DNA or the fragments of microbes can get to the synovial cavity through circulation, initiating the local immune response (Dalile et al, 2019b; Minerbi et al, 2019b). The results highlight the fact that osteoarthritis is not only a mechanical disease; inflammation caused by microbiomes is also a major etiological factor.

Table 1. Microbiome-Driven Mechanisms in Osteoarthritis (OA)

Mechanism	**Microbial Contribution**	**Pathological Effect**	**References**
Dysbiosis-driven inflammation	Increased abundance of pro-inflammatory taxa such as *Prevotella* and *Proteobacteria*; reduction in beneficial commensals like *Lactobacillus* and *Bifidobacterium*; disruption of gut barrier integrity leading to enhanced immune activation	Elevated pro-inflammatory cytokines (↑ IL-1β, IL-6, TNF-α); activation of Th17 immune responses; chronic low-grade systemic inflammation; increased cartilage-degrading enzymes; progression of cartilage degeneration and joint damage	(C et al, 2021; Roager et Licht, 2018)
Metabolite imbalance	Decreased production of beneficial metabolites such as short-chain fatty acids (SCFAs: acetate, propionate, butyrate); increased generation of harmful metabolites including ammonia, phenols, and secondary bile acids	Reduced anti-inflammatory signaling; increased expression of matrix metalloproteinases (↑ MMP-1, MMP-3, MMP-13); decreased synthesis of type II collagen (↓ collagen II); impaired extracellular matrix integrity; acceleration of cartilage breakdown	(Bonaz et al, 2018; Shen et al, 2020)
Endotoxemia	Increased levels of lipopolysaccharides (LPS) due to Gram-negative bacterial overgrowth and enhanced intestinal permeability (“leaky gut”)	Systemic endotoxemia leading to activation of TLR4/CD14 signaling pathways; macrophage activation; increased production of inflammatory mediators; synovial inflammation and joint swelling; contribution to osteoarthritis and rheumatoid arthritis progression	(Bercik et al, 2011; Bravo et al, 2011)
Joint microbiome theory	Presence of microbial DNA, bacterial fragments, or viable microbes within synovial fluid and joint tissues; possible translocation from gut or oral microbiome	Local immune activation within joints; activation of innate and adaptive immune responses; increased cytokine production; degradation of extracellular matrix; loss of cartilage integrity and joint function	(Tracey, 2009)

5.2 Rheumatoid Arthritis (RA)

The level of proliferation in the microbiome is another signature of the rheumatoid arthritis disease and it has been linked to the early onset of the disease and severity (Lin et al, 2022). *P. copri* causes severe Th17-mediated inflammation, increases the levels of IL-17 and GM-CSF, as well as triggers autoimmunity (Ji et al, 2018). Instead, the commensal bacteria like Bacteroides fragilis that promote the production of IL10 are weakened, which aggravates the state of inflammatory imbalance. The gut microbiome also facilitates the citrullination process and the production of anti-citrullinated protein antibodies (ACPAs). Dysbiotic microorganisms induce peptidyl-arginine deiminase-like enzyme which simulates the process of autoantigen modification thus enhancing the production of ACPA and effecting the induction of synovial autoimmunity. The effects of these antibodies are bone erosion, formation of pannus and eventual breaking of the joints over a long period of time. The microbiota-synovial immune axis is also reinforced by the fact that the microbial metabolites can regulate the synovial fibroblast activation, macrophage polarization and the osteoclast precursor growth (S. K. Kim et al, 2022b; Minerbi et al, 2019a). These suppressed RA-like inflammation are observed in germ-free mice, and restoring the disease phenotype is observed when RA-associated microbes are colonized once more.

Table 2. Microbiome-Immune Interactions in Rheumatoid Arthritis (RA)

Key Factor	**Microbial Role**	**Impact**	**References**
Prevotella copri expansion	Overgrowth of *Prevotella copri* in the gut microbiome; promotes pro-inflammatory immune responses; stimulates differentiation of naïve T cells into Th17 cells; alters gut barrier function and antigen presentation	Increased production of IL-17 and other pro-inflammatory cytokines (IL-6, TNF-α); amplification of Th17-mediated immune responses; enhanced synovial inflammation; increased severity and progression of rheumatoid arthritis (RA)	(Schwarzer et al, 2016; Yan et al, 2016)
Citrullination	Certain gut and oral microbes express peptidyl arginine deiminase (PAD)-like enzymes; microbial-induced post-translational modification of proteins leading to citrullinated peptides; molecular mimicry between microbial and host proteins	Increased formation of anti-citrullinated protein antibodies (ACPA); breakdown of immune tolerance; autoimmune activation targeting joint tissues; initiation and progression of RA pathology	(Guss et al, 2017)
Synovial immune axis	Microbial metabolites (e.g., SCFAs, indoles, LPS) and translocated microbial components influence synovial microenvironment; activation of immune cells and synovial fibroblasts via pattern recognition receptors (TLRs)	Activation of synovial fibroblasts and macrophages; increased secretion of inflammatory cytokines and matrix-degrading enzymes; bone erosion via osteoclast activation (RANKL pathway); progressive joint destruction	(Lu et al, 2021)
Loss of tolerogenic microbes	Reduction in beneficial immunoregulatory microbes such as *Bacteroides fragilis*; decreased production of anti-inflammatory molecules like polysaccharide A (PSA); impaired induction of regulatory T cells (Treg)	Decreased IL-10 production and impaired immune tolerance; imbalance between Treg and Th17 cells; persistent chronic inflammation; exacerbation of autoimmune responses and joint damage	(Blanton et al, 2016; Zhang et al, 2021b)

5.3 Osteoporosis (OP)

The gut microbiota has been known to regulate calcium, phosphate and vitamin D metabolism, which are the major regulators of bone mineral density in a number of reasons, which are interlinked. The population with a short-chain fatty acid (SCFA)-producing bacteria improves the absorption of calcium and amplifies the synthesis of IGF-1, which stimulates osteogenesis(Qin et al, 2010b). Conversely, dysbiotic communities lower the levels of SCFA, interfere with the expression and activity of calcium transportation proteins including TRPV6 and PMCA1b, and, subsequently, dysregulate mineral homeostasis (Zierer et al, 2018b).

SCFAs also have an osteoprotective effect by suppressing osteoclastogenesis by regulating the RANKL -OPG axis. One of the significant SCFA is butyrate, and this suppresses the activation of NF-bourgstin within the pre-osteoclasts, resulting in a reduction in bone resorption (Alpizar-Rodriguez et al, 2019). Under the condition of dysbiotic environment, increased production of pro-inflammatory cytokines increases the action of osteoclasts, which changes the balance in favor of net bone loss. In addition, the gut microbiota regulates the expression of vitamin DNA receptor (VDR) and bile acid metabolism, both factors which are critical to skeletal integrity(Vieira-Silva et al, 2019a).

Table 3. Microbiome Pathways in Osteoporosis (OP)

Mechanism	**Microbial Link**	**Bone Effect**	**References**
Mineral metabolism	Presence of SCFA-producing bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium*; fermentation of dietary fibers leading to production of SCFAs (especially butyrate and acetate) which lower intestinal pH and enhance mineral solubility	Increased calcium (Ca^{2+}) and magnesium absorption in the intestine; improved mineral bioavailability; enhanced bone mineral density (BMD); promotion of bone formation and skeletal strength	(Allegretti et al, 2019; Rothschild et al, 2018)
RANKL–OPG axis	Microbial metabolites such as butyrate and propionate regulate immune and bone cell signaling; SCFAs promote regulatory T cell (Treg) expansion and suppress pro-inflammatory cytokines; modulation of osteoblast–osteoclast crosstalk	Decreased osteoclastogenesis via downregulation of RANKL and upregulation of osteoprotegerin (OPG); inhibition of bone resorption; maintenance of bone homeostasis and prevention of osteoporosis	(Sinha et al, 2017)
Hormonal signaling	Gut microbiota modulate endocrine pathways including glucagon-like peptide-1 (GLP-1), parathyroid hormone (PTH),	Reduced bone resorption through hormonal regulation; improved bone remodeling balance; enhanced	(Gilbert et al, 2018a)

	and serotonin metabolism; microbial metabolites influence enteroendocrine cells and systemic hormone levels	osteoblast activity and reduced osteoclast activity; overall preservation of bone mass	
Dysbiosis inflammation	Expansion of pro-inflammatory bacteria such as *Proteobacteria*; increased intestinal permeability leading to translocation of endotoxins (LPS); activation of immune pathways (TLR4/NF-κB)	Increased osteoclast activation and differentiation; elevated inflammatory cytokines (IL-1β, TNF-α, IL-6); enhanced bone resorption and risk of osteoporosis; impaired bone formation	(Markowiak et al, 2017)

Lastly, there is bone -gut hormone crosstalk that further gives a connection between dysbiosis and osteoporosis. The microbial modulations affect the signalling of glucagon-like peptide-1 (GLP 1), parathyroid hormone (PTH), fibroblast growth factor-23 (FGF 23) and serotonergic signal pathways, which in stimulating the function of osteoblast and osteoclasts (Brenchley et al, 2006). Collectively, these mechanisms highlight the extent to which miRNA show a vast role in the pathogenesis of bone deficiency in the context of gut microbiome composition.

5.4 Sarcopenia et Muscle Wasting Disorders

Mitochondrial energetics, nutrient catabolism and systemic inflammatory milieu are the critical causes of the gutmusculoaxis. Disturbances of the gut microbiota reduce the generation of short-chain fatty acid (SCFA), which in turn suppresses muscle mitochondrial biogenesis and adenosine triphosphate synthesis through the inhibition of peroxisome proliferator-activated receptor 7 coactivator-1A (PGC-1) and AMP protein kinase (AMPK) signaling (McCabe et al, 2015; Roberfroid et al, 2010). The changes are in form of reduced muscle strength and increased fatigue. Microbiota derived SCFAs also stimulate skeletal muscle protein synthesis by acting on the mechanistic target of rapamycin (mTOR) signaling and by providing gluconeogenic activity enzymes(Sanders et al, 2018). The reduction in the beneficial microbial taxa suppresses SCFA-mediated anabolic signaling thus contributing to anabolic resistance which is a hallmark of sarcopenia. Chronic dysbiotic inflammation increases interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and reactive oxygen species (ROS) leading to yet again increased muscle catabolism. In addition, activation of satellite cells is disturbed by exposure to lipopolysaccharide (LPS), thus negatively affecting muscular regeneration (Sokol et al, 2018).

Table 4. Microbial Influences in Sarcopenia et Muscle Wasting

Mechanism	Microbial Contribution	Outcome	References
Mitochondrial dysfunction	Reduced abundance of SCFA-producing bacteria (e.g., *Faecalibacterium*, *Roseburia*); decreased levels of SCFAs (especially butyrate) impair mitochondrial biogenesis and function; reduced activation of key regulators such as PGC-1α	Decreased ATP production and impaired oxidative phosphorylation; reduced muscle endurance and energy metabolism; increased muscle fatigue and susceptibility to sarcopenia	(Cardona et al, 2013)
Anabolic signaling	SCFAs (particularly butyrate and acetate) activate anabolic pathways including mTOR signaling; modulation of insulin sensitivity and IGF-1 signaling; improved nutrient sensing and amino acid utilization	Increased muscle protein synthesis; enhanced muscle mass and strength; improved muscle repair and maintenance of skeletal muscle homeostasis	(Barbaresko et al, 2014)
Inflammation et ROS	Dysbiosis leads to increased levels of lipopolysaccharides (LPS) and pro-inflammatory microbial metabolites; activation of immune pathways (TLR4/NF-κB); increased production of reactive oxygen species (ROS)	Chronic systemic inflammation and oxidative stress; activation of muscle proteolysis pathways (e.g., ubiquitin–proteasome system); muscle wasting and atrophy; progression of sarcopenia	(Zeevi et al, 2015a)
Satellite cell impairment	Endotoxemia caused by increased gut permeability and LPS translocation; disruption of muscle stem cell niche; altered signaling required for satellite cell activation and differentiation	Decreased muscle regeneration capacity; impaired repair of damaged muscle fibers; delayed recovery and progressive muscle loss	(Mathur et al, 2017)

All these pathophysiological occurrences together highlight the great role of the microbes in the etiology of the wasting of the muscles

5.5 Spondyloarthropathies (SpA), Gout, and Fibromyalgia

There is a strong correlation between the expression of HLA-B27 and the compositional changes in the gut microbiota in the occurrence of spondyloarthropathies. HLA -27 regulates mucosal immunity resulting in augmented colonisation by inflammatory Entero-bacteriaceae which consequently provoke IL -23/IL -17 axis activation and resultant inflammatory responses in joints (S. Wang et al, 2021b; Woodworth et al, 2017). Dysbiosis additionally decreases gastro-intestinal barrier integrity thus promoting systemic responses to inflammation.

In gout, there is a disruption in microbial pathways whose role is in the uric acid breakdown. A decrease in the abundance of Akkermansia, Faecalibacterium, and Lactobacillus is associated with increased levels of serum urate and urate crystal deposition in the joints(Silva et al, 2020). This caused by loss of purine-degrading bacteria also helps in the formation of hyperuricaemia.

Table 5. Microbiome Links to SpA, Gout et Fibromyalgia

Disorder	**Microbial Mechanism**	**Outcome**	**References**
Spondyl oarthropathies (SpA)	Alteration of gut microbiota associated with HLA-B27 expression; reduced microbial diversity and expansion of pro-inflammatory taxa; disruption of gut barrier integrity leading to translocation of microbial antigens; activation of innate and adaptive immune pathways	Increased IL-23/IL-17 axis activation; Th17 cell expansion; chronic inflammation at entheses and joints; progression of ankylosing spondylitis and related SpA conditions	(Lam et al, 2021)
Gout	Loss or reduced abundance of uric acid–degrading bacteria (e.g., *Lactobacillus*, *Bifidobacterium*); impaired microbial purine metabolism; dysbiosis affecting intestinal uric acid excretion and metabolism	Increased serum uric acid levels (hyperuricemia); deposition of monosodium urate crystals in joints; activation of inflammatory pathways (NLRP3 inflammasome); acute gouty arthritis and recurrent flares	(Charbonneau et al, 2020a)
Fibromyalgia	Dysbiosis leading to imbalance in microbiota–gut–brain axis; altered production of neurotransmitters (↓ serotonin, ↓ GABA) and metabolites; increased intestinal permeability and systemic inflammation; neuroimmune dysregulation	Enhanced central sensitization and pain perception; increased fatigue, mood disturbances, and chronic widespread musculoskeletal pain; altered stress response and reduced quality of life	(Chowdhury et al, 2019)

Microbiota-neuroimmune interaction has been attributed to fibromyalgia. Dysbiosis alters the supply of neurotransmitter precursors (serotonin and GABA) and increases inflammatory metabolites and the signalling of the vagal nerves and thus is a contributor to chronic pain hypersensitivity (O'Toole et al, 2017).

6. GUT MICROBIOTA IN PAIN BIOLOGY AND MUSCULOSKELETAL NOCICEPTION

6.1 Neuromodulatory Metabolites and Pain Signalling

The mucosal flora generate a broad range of neuromodulatory metabolites that have a direct effect on nociceptive. SCFA like butyrate and propionate mediate changes in excitability of dorsal root ganglion (DRG) neurons through the GPR41 and GPR43 receptors and influence noise and inflammatory threshold. Such metabolites also promote availabilities of serotonin and dopamine precursors as well, which connects microbe metabolism profiles with central pain processing. Tryptophan nanotransformed indoles would work by the aryl hydrocarbon receptor (AhR), modulating the spinal neuroinflammation and either leading to analgesic or hyperalgesic effects depending on the balance of the microbes (Franzosa et al, 2014; Mimee et al, 2016a).

Dysbiosis diminishes the beneficial production of neuromodulatory metabolites and leads to the increased nociceptive sensitivity. Decreased levels of SCFA disrupt anti-inflammatory signaling and enhance sodium and calcium channels activation of the nociceptive neurons, and reduce pain thresholds (Gilbert et al, 2018b). Additionally, products of microbial metabolism have an effect on microglial activation, which changes cytokine profiles in the spinal cord and the brainstem that control central sensitization. Mechanistic connection between Musculo-skeletal chronic pains and the altered microbial metabolism is achieved through this crosstalk.

Recent research indicates that the decrease of hyperalgesia in pain models of inflammatory pain and neuropathic pain, as well as dysbiotic microbiota, is better mediated in the presence of colonization with pain protecting microbial strains (Zierer et al, 2018a). These results highlight that neuromodulatory metabolites are potent controllers of pain pathways and part and parcel of musculoskeletal nociception.

6.2 Microbiota-Vagus Nerve Crosstalk

The Vagus nerve is a significant two-way communication path by which gut micro biota affect the biology of musculoskeletal pains. Vagal afferents detect microbial metabolites, neurotransmitters (GABA, serotonin) and inflammatory mediators released by the gut mucosa which are transmitted to the brainstem centers of pain processing. Some of the probiotics also provoke vagal discharging that leads to analgesia that occurs through limbic and hypothalamic systems (Chang et al, 2021b; Kuntal et al, 2019).

The gut-vagus communication is unregulated in dysbiosis as it enhances the generation of pro-inflammatory metabolites, decreases vagal tone, and mediated cholinergic anti-inflammatory signals. Attenuated vagal activation facilitated peripheral inflammation, synovial sensitization and stimulation of nociceptive fibres in joint and muscle tissues (Topçuoğlu et al, 2020). Alteration of the activity of vagus nerve is also linked to the changes in the output of hypothalamic-pituitary-adrenal (HPA) axis, enhancing stress hormones that enhance pain sensitivity.

Experimental literature demonstrates that vagotomy eradicates the analgesia of various protective microbes, which results in the fact that the vagus nerve is one of the central creators of microbiota-mediated analgesia, which involves the regulation of microbiota (Vieira-Silva et al, 2019b). On the other hand, vagus nerve is stimulated and this suppresses systemic inflammation, reduces the levels of IL a and TNF a and suppress musculoskeletal pain. Microbiota -vagus nerve crosstalk would, therefore, be a vital process that links intestinal health to pain physiology.

6.3 Dysbiosis Role in Chronic pain sensitization

Intestinal dysbiosis is increasingly related to chronic musculoskeletal pain disorders including fibromyalgia, chronic low back pain, osteoarthritis pain, as well as, neuropathic pain states. Sustained low -grade inflammation Dysbiosis fosters low-grade inflammation TLR4 products via LPS activation contributing to peripheral sensitization of nociceptive fibers (Charbonneau et al, 2020b). An increase in the levels of circulating cytokines like IL-1b, IL-6 and TNF-a alters the synapse plasticity in the spinal dorsal horn leading to a condition of long-term central sensitization which increases the intensity of pain reactions (Mimee et al, 2016b). Oxidative stress, decreased neuroprotective metabolite production, and mitochondrial dysfunction of neuronal and muscle fibers is also elevated by microbial imbalance. All of these components enhance neuronal excitability and lead to the amplification of persistent pain(Zeevi et al, 2015b). Dysbiosis is also linked to decreased biosynthesis of neurotransmitter like GABA and serotonin which undermine endogenous analgesic pathways.

These mechanistic results have support in clinical studies, in which patients having chronic widespread pain, fibromyalgia, and chronic musculoskeletal pain have distinct microbial signatures characterized by low Faecalibacterium and Bifidobacterium abundance and high pain-related bacteria taxa(Narulla et Diwan, 2025b). These bacterial changes are associated with the degree of pain and fatigue and sensory hypersensitivity. In turn, dysbiosis is a primary cause of peripheral and central pain sensitization and makes the gut microbiome an agent of chronic pain disorder treatment.

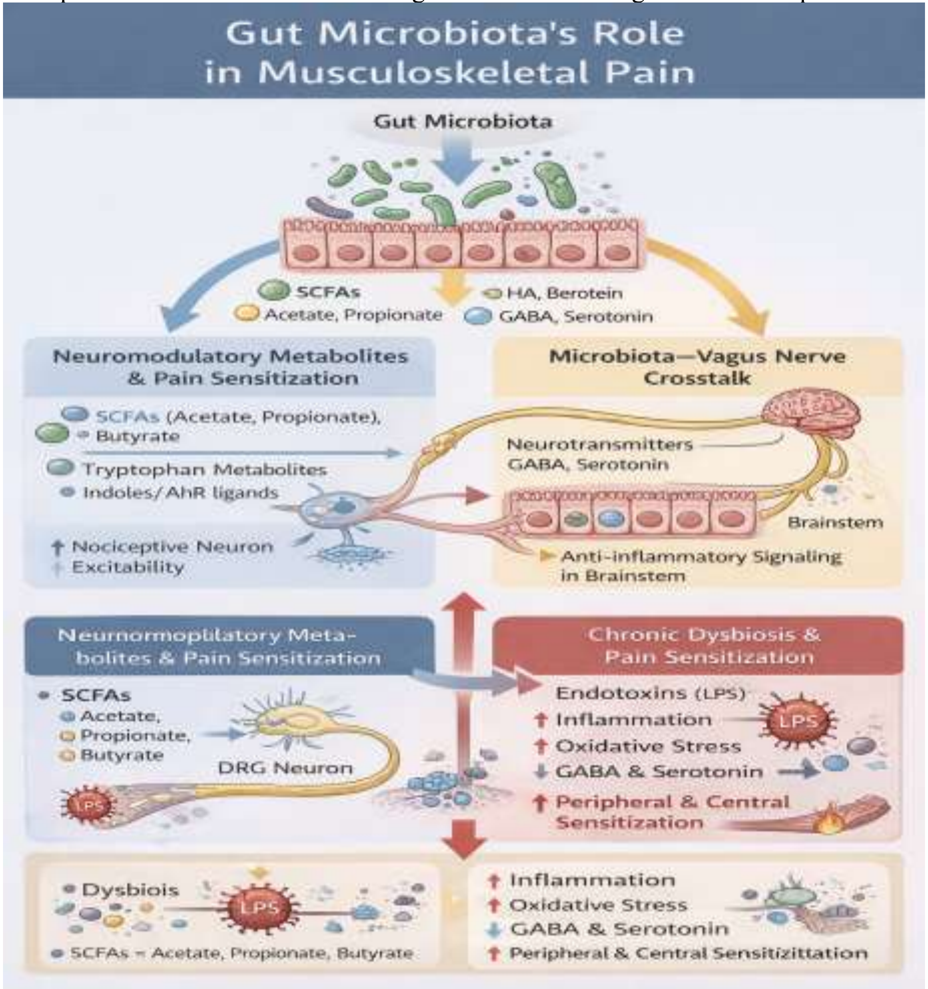

Fig 3: Gut Microbiota–Pain Interaction Pathways in Musculoskeletal Nociception

The figure 3 shows how the intestinal microbiota modulates musculoskeletal pain in metabolic, neural and immune pathways. The helpful commensal bacteria produce fatty acids in the short chain; acetate, propionate and butyrate, and neurotransmitter-related compounds, including 7-aminobutyric acid (GABA) and serotonin; and tryptophan-derived indoles. The roles of these metabolites include the control of nociceptive perception through the reduction of excitability of nociceptors and inhibition of inflammatory mechanisms. Besides, the microbiota can also communicate with the central nervous system via the gut-brain axis and especially via vagal afferents, where microbial metabolites can alter the neurotransmitter signalling and promote anti-inflammatory actions in the brainstem.

On the contrary, dysbiosis leads to higher concentration of harmful bacteria products including lipopolysaccharide (LPS), which trigger systemic inflammatory effects, oxidative damage and loss of neuroprotective mediators like GABA and serotonin. The resultant imbalance enhances the peripheral and central sensitisation of the pain pathways, thus adding to the occurrence of chronic musculoskeletal pain. Therefore, the number highlights the two-sided effect of the gut microbiota, i.e., a balanced microbial community alleviates pain, and dysbiosis contributes to the aggravation of inflammation and pain sensitization.

The experimental and clinical evidence supporting the gut–musculoskeletal axis are summarized in the Table 6.

Table 6. Consolidated Experimental and Clinical Evidence Supporting the Gut–Musculoskeletal Axis

Section	**Key Evidence / Findings**	**Model / Study Type**	**Mechanistic Insights**	**Implications for Musculoskeletal Diseases**	**References**
6.1 Animal Model Insights	Germ-free mice show ↓ bone mass, altered immunity, impaired muscle development	Germ-Free (GF) Models	Lack of microbes → ↓ SCFAs, ↓ IGF-1, Th17/Treg imbalance	Essential role of microbiota in skeletal + muscular homeostasis	(G et al, 2025c; Roberts et al, 2025a)
	Antibiotic dysbiosis causes bone loss, cartilage degradation, ↑ osteoclast activity	Antibiotic-Induced Dysbiosis	Dysbiosis → ↑ LPS, ↑ inflammation, ↑ ROS	Mimics human inflammatory musculoskeletal disorders	(Sun et al, 2025a; Y. Xu et He, 2025b)
	FMT transfers bone et immune phenotype (healthy ↔ diseased)	FMT Models	Microbial communities determine phenotype expression	Strong causal evidence for gut–musculoskeletal axis	(Gilat et al, 2025b)
6.2 Human Cohort, Metagenomics et Metabolomics	↓ *Faecalibacterium*, ↓ *Roseburia*, ↑ *Prevotella*, ↑ Proteobacteria in OA, RA, OP, sarcopenia	Multi-Center Cohorts	Dysbiosis ↔ ↑ IL-6, ↑ TNF-α	Microbial abundance correlates with disease severity	(Y. Wang et al, 2025a)
	Metagenomics: ↓ butyrate genes, ↑ LPS genes, altered bile acid metabolism	Shotgun Metagenomics	Functional pathway disruption → chronic inflammation	Confirms mechanistic signatures	(MusculoskeletalKey, 2025)
	Metabolomics: ↓ SCFAs, ↑ aromatic toxins, ↑ secondary bile acids	Serum/Fecal Metabolomics	Reflects metabolic shift promoting degeneration	Biomarkers predict progression	(Z. Li et al, 2024c)
6.3 Microbiome as Predictors of Severity et Progression	Microbial signatures predict early RA, OA progression, osteoporosis risk	Longitudinal Cohorts	*P. copri*, *Klebsiella*, *Ruminococcus* → immune activation	Early microbiome markers aid prediction	(Hong et al, 2024a)
	AI/ML models classify severity using microbiota + metabolite profiles	Machine-Learning Studies	Integrates taxa + cytokines + metabolites	Useful for precision medicine	(A et al, 2024a)
	High LPS–LBP levels correlate with pain severity, bone loss, and muscle wasting	Biomarker Studies	Endotoxemia → chronic nociception et inflammation	Predicts symptom burden	(Reynders et al, 2024b)

6.4 Translational Challenges	High inter-individual variability reduces reproducibility	Global Human Studies	Geography, diet, lifestyle affect microbiome	Need for personalized interventions	(Simorgh et al, 2024a)
	Non-standardized sampling et sequencing pipelines limit comparability	Research et Clinical Labs	Technical noise → inconsistent outcomes	Requires global harmonization	(I. Review, 2024)
	Ethical et safety issues with FMT / microbial therapeutics	Translational Research	Donor risk, pathogen transfer	Regulation required for clinical use	(Bastiaanssen et al, 2023b)
	Mechanistic complexity makes causality difficult in humans	All Models	Multifactorial host–microbe interactions	Need interventional et longitudinal trials	(G et al, 2025a)

7. THERAPEUTIC MODULATION OF THE GUT MICROBIOME FOR MUSCULOSKELETAL HEALTH

7.1 Probiotics, Prebiotics, Symbiotic: Evidence et Limitations

Lactobacillus, Bifidobacterium, and Clostridium butyricum strains of probiotics have a positive effect on musculoskeletal health, as augmenting the generation of short-chain fatty acids (SCFAs), which strengthens intestinal barriers, and balancing the Th17/Treg axis. These strains suppress the production of pro-inflammatory cytokines (IL 6, TNF 061), inhibit the activation of osteoclasts and improve the mineral density of bones in animal models and can also be seen in the initial phase of studies carried out on humans. Synbiotics (combinations of prebiotics and probiotics) synergistically ensure the colonization of microbes and the production of SCFA, and produce stronger musculoskeletal effects than its individual components do(Roberts et al, 2025c).

Prebiotics, including inulin, fructo-oligosaccharide (FOS), and galacto-oligosaccharide (GOS), enhance the SCFA-producing bacteria (Faecalibacterium, Roseburia) and enhance calcium absorption, which occurs as a result of colonic acidification. The mechanism promotes mineralization of the bones and promotes the metabolism of the cartilage and muscle. However, the activity of the probiotics is strain-specific and many of the commercially available preparations have not been shown to have validated musculoskeletal activity. The shortcomings of probiotic intervention are that its survival in the gastrointestinal tract is inconsistent, there is microbiome heterogeneity amongst individuals, and clinical responses are unpredictable. The literature on long-term supplementation is limited and the findings do not often replicate across population since the foods and genetics are not homogeneous. As a result, though the therapeutic prospect is significant, the approach based on probiotics requires careful selection and personalization of the strategy to remain focused and achieve steady muscle skeletal improvement (Sun et al, 2025c).

7.2 Food-Based Interventions to Reduce Muscle/bone Outcome

Dietary modulation is one of the most effective and readily available means of the restructuring of the gut microbiome to foster musculoskeletal wellbeing. Diets high in resistant starches, whole grains, legumes, fruits, and vegetables are associated with the increase in the production of SCFA, which leads to the improvement of bone formation, mitigation of cartilage erosion, and augmentation of efficiency of mitochondria in muscle tissues. Foods high in polyphenols (berries, green tea, turmeric) are also prebiotic-like substances, which promotes the growth of anti-inflammatory taxa (Bifidobacterium, Lactobacillus) (Z. Li et al, 2024b).

The diets of Mediterranean type have proven to significantly lower inflammation levels, ameliorate the synovial fluid status, and reduce the severity of musculoskeletal pain in the conditions related to chronic inflammation. The omega-3 fatty acids also promote anti-inflammatory cytokine phenotypes and combine with SCFA pathways to inhibit bone resorption. Well, modern eating habits of high saturated fat, fast foods, refined sugars promote dysbiosis, increase the burden of lipopolysaccharides LPS, and cause oxidative stress, all of which worsen the course of musculoskeletal diseases. This makes diet one of the key components of the yield of the gut-musculoskeletal axis. Individualized nutrition that is based on microbiome results is on the rise, but clinical validation is still in its early stages (W. J. G. Review, 2024).

7.3 Fecal Microbiota Transplantation (FMT)

FMT is the most immediate way of restoring a normal gut flora. In Preclinical FMT using skeletally or metabolically healthy donors demonstrates the transfer of beneficial phenotypes beneficial bone density, less inflammatory, and better muscle mass to dysbiotic recipients (Lyu et al., 2023). FMT replenishes SCFA concentration, increases mucosal immunity, and rebounds pro-inflammatory Toll-like receptor signaling, and thus promotes the musculoskeletal regeneration. The evidence provided by initial human case-series suggests that FMT suppresses systemic inflammation, reduces chronic pain and controls bone turnover markers in dysbiosis-related disorders e.g., rheumatoid arthritis and fibromyalgia. Still, these results are preliminary and should be subjected to highly controlled tests (R. Li et al., 2021). Among the risks, such factors as the transfer of pathogenic organisms, antibiotic-resistant genes, and unassailable immunological reactions should be named. FTM is a biological therapeutic approach that is classified by regulatory bodies

(FDA/EMA) as one, and its use in musculoskeletal condition
is still experimental. Donor screening and stool processing standardization as well as dosing before FMT is extensively applied in musculoskeletal therapeutics is necessary.

7.4 Postbiotics and Next-Generation Microbials Therapeutics

Postbiotics are non-viable microbial components and metabolites (butyrate, propionate, indole derivatives, peptide compounds of microbial cell walls) with specific beneficial actions, but which have none of the risks present in live bacteria. Butyrate supplementation is also reported to suppress osteoclast differentiation, enhance osteoblast differentiation and decreases apoptosis in chondrocytes. Indole derivatives control the spinal neuroinflammation and offer potential analgesic effects to musculoskeletal pain disorders (Hao et al., 2024).

Next-generation microbial therapeutics (NGMTs) are engineered microbial consortia of highly defined microbial types that are used to produce particular metabolites. Other strains like *Akkermansia muciniphila*, Clostridium XIVa, and *Bacteroides fragilis* are being studied because of their immune-regulatory and bone and muscle anabolic effect on the body.

These techniques are more reproducible, stable and precise, but require significant clinical validation. The regulatory pathways of NGMTs are not simple since these therapeutics find an interplay between probiotics, biologic, and engineered microbial drugs.

The reducing technique involves using adolescent cells, which are transferred to petri dishes containing bacterial cultures known as microbiomes. Microbiome Editing (CRISPR/ Microbial Gene Therapy Prospects): This reducing method involves the use of adolescent cells transferred to petri dish bacterial cultures (microbiomes) as well.

The novel technology of CRISPR-based microbiome editing provides the ability to accurately edit microbial genomes to eradicate undesirable taxa or to increase the production of advantageous metabolites. CRISPR-Cas systems are capable of selective depletion of pro-inflammatory bacteria (e.g., LPS producing Proteobacteria) or inoculation/ inoculation of the commensal strains with beneficial metabolic pathways. This strategy will enable the correction of dysbiosis (F. Wang et al., 2024).

The efforts of microbial gene therapy are to genetically engineer strains that can maintain known proportions of SCFAs, anti-inflammatory cytokines analogues, or bone supportive peptides. The preclinical evidence shows that engineered Lactococcus strains expressing therapeutic molecules in the directly accessible environment of the gut lumen have the capacity to regulate systemic inflammation and bone turnover.

Nevertheless, health concerns that have been raised such as off-target effects, horizontal gene transfer, and ecological imbalance are major limitations. Regulation and ethical considerations relating to modified microbes should be developed before the process of genetically modified microbes is translated in human musculoskeletal applications(Mehta et al., 2023).

8. EMERGING TECHNOLOGIES ET RESEARCH FRONTIERS

8.1 Multi-Omics Integration (Metagenomics, Metatranscriptomics, Metabolomics)

Multi-omics systems are transforming our understanding of the gut-musculoskeletal axis, making it possible to achieve the exhaust and profiling of microbial organisation, activity and metabolic production. Metagenomic studies show changes in microbial taxa and functional gene groups, which are related to bone loss, joint inflammation, muscle degeneration, etc. Metatranscriptomic data also reveal active microbial processes, particularly those associated with short-chain fatty acid (SCFA) production, bile acid metabolism, and inflammatory signaling that are strongly associated with disease phenotypes. The study of metabolism introduces a connection between metabolic features in microbial metabolites (SCFAs, indoles, bile acids, aromatic toxins) and systemic musculoskeletal biomarkers, which makes it possible to associate pathways between dysbiosis and affected bone turnover, chondrocyte metabolism and mitochondrial functioning in muscles. Multi-omics data when combined result in a single molecular signature, which contains information on both the microbial dynamics and host responses (Bose et al., 2024).

Integrative omics has today made it possible to generate so-called microbiome fingerprints that link subtypes of diseases, forecast progression, and reveal targets of therapy. This multi-layered strategy is essential both in the accuracy of microbiome studies and the creation of masterful musculoskeletal diagnostics of the next generation (Rahman et al., 2023).

8.2 Gut-muscular and Skeleton networking Systems Biology Models

The systems biology provides the capacities to build the computational models of mapping the complicated interactions between the microbes, immune pathways, signalling molecules, and musculoskeletal tissues. These models are based on network biology, dynamic simulation and mathematical formulations to discover regulatory nodes of the gut-bone-cartilage-muscle axis (Z. Li, Zhou, et al., 2024)

Analysis of networks vertically indicates the interaction of microbial metabolites with cytokines, osteoblast / osteoclast signalling and neuromuscular signal transduction. Examples of such models are how small changes in microbial composition can lead to large scale physiological consequences, e.g. the T17/Tregs imbalance, RANKL- OPG deregulation or mitochondrial dysfunction.

Systems-level research also identifies so-called control hubs that may act as points of therapy access. These are SCFA signalling, LPSTLR pathways, bile acid receptors (FXR/TGR5), and neuro-modulatory metabolites. Finally, rational design of therapeutic versions of microbiomes and their ability to predict the overall effect on the body requires systems-biology frameworks.

Aiming to keep pace with microbiome-specific disease prediction and disease diagnosis, this paper will use Artificial Intelligence/Machine Learning to create a model for making predictions. The development of artificial intelligence (AI) and machine learning (ML) have been found to be very effective in identifying patterns in high-dimensional microbiome data. With metagenomic, metabolomic, inflammatomic, and clinical variables, deep-learning models can predict the development of musculoskeletal disease, feebleness of pain, and treatment reaction bloodiness, consistently surpassing traditional statistics (Yu et al., 2024).

ML classifiers, including random forests, support vector machines and neural networks, single out microbial taxa, including Prevotella, Faecalibacterium and Roseburia, as strong predictors of rheumatoid arthritis severity, osteoarthritis progression and osteoporosis risk exposure (167. Vieira-Silva S, et al. Microbiome–Disease Classifiers Using AI. Gut. 2019;68:62–70., n.d.). The approaches based on multi-omics and AI can improve the accuracy of predicting phenotypes, including bone mineral density, muscle mass loss, and inflammatory phenotypes.

Microbiome profiling by the use of AI is also used to inform personalized interventions. Algorithms indicate which probiotic varieties, dietary interventions or microbial therapies have the highest chance of being effective depending on an individual microbiome structure and this represents a major breakthrough towards clinical translation of microbiome science (Ticinesi et al., 2025).

8.3 Microbial Bioengineering in Recombinant Therapy

With synthetic biology and microbial engineering, accurate manipulation of the gut bacteria to accomplish therapeutic molecule delivery, control immunology, or manipulate metabolite synthesis is now achievable. Anti-inflammatory cytokines, SCFAs, or bone-anabolic peptides have been engineered into engineered strain of Escherichia coli Nissle, lactococcus lactis and bacteroides spp. to secrete them into the host.

The CRISPR-based systems allow targeted deletion and insertion of pathogenic genes or therapeutic features into gut microbes correcting dysbiosis, inhibiting the production of lipopolysaccharides or directly increasing the production of SCFA. Synthetic consortia of known microbial communities with particular metabolic capabilities have managed therapeutic effects better than traditional probiotics conventional probiotics hold crucial functions in defining microbial systems of human bodies and metabolic processes including the production, excretion, and recycling of vitamins and nutrients (Liu et al., 2025; Sun, Li, et al., 2025).

Regardless of their promise, safety, and off-target impacts, as well as horizontal gene transfer, and long-term ecological stability remain an issue. However, microbial engineering is one of the most sophisticated future orientation of musculoskeletal treatment.

8.4 Microbiome Medicine of Musculoskeletal Diseases on individual basis

Personalised microbiome medicine aims to consider interventions on an individual basis formed of microbial signature, the ability of an individual to metabolise, and the genetic history of an individual. Microbiome profiling of the stool in combination with host genomics and metabolomics can currently be used to selectively choose probiotics, prebiotics, dietary habits, or even designed microbial therapies personally (Tian et al., 2025). This will fit the inter-individual variability that is one of the factors plaguing existing microbiome therapies.

These interventions can also be of great benefit in clinical outcomes in osteoarthritis, rheumatoid arthritis, osteoporosis and sarcopenia as heterogeneity of disease plays an important role (Hwang et al., 2025).

Digital health innovation, wearable sensor developments, and real-time microbiome monitoring will be used to create dynamic and adaptive treatments that adapt together with the microbiome of the patient. Individualized microbiome medicine is the future of precise musculoskeletal medicine, which is no longer focused on the one-size-fits-all paradigm (Ribeiro et al., 2024).

9. RESEARCH GAPS AND FUTURE DIRECTIONS

9.1 Requirement of Causal Investigations and Longitudinal Human Research

Most evidence on the gut microbiome has been associative despite significant progress associating the gut microbiome with musculoskeletal diseases. One of the critical gaps is the lack of human studies that can be done over the long run and can trace changes in the microbiome with musculoskeletal outcomes (bone density, cartilage degeneration, pain progression, muscle functions). Efforts It was found that animal models provided strong mechanistic understanding but did not completely mirror the dietary variety, way of life, comorbidities, or even the genetic variety of humans. Coming up with definitive causal mechanisms requires large, highly-controlled longitudinal cohorts and intervention-based clinical trials that directly interfere with human microbiome but also quantitatively assess musculoskeletal responses under the influence of such interventions over time.

9.2 Standardisation of Problems with Microbiome Sampling and Analysis

One of the underlying constraints of the existing studies is the inconsistency of methods. Diverse approaches to stool collection, diverse protocols to extract the DNA, and alternative sequencing platforms, data-analytical pipelines, and frameworks of data-interpretation have significant technical noise. Such inconsistencies make it unfeasible to compare studies across studies and lead to less reproducibility. The lack of standardised practices and unified workflow analysis to analyse a sample makes it impossible to come up with globally accepted microbial biomarkers or therapeutic principles in musculoskeletal illnesses. Unifying the results of different laboratories and clinical sites is therefore a priority goal.

9.3 Mechanistic Uncertainty: Relating Microbes to Tissues Biology

Despite the fact that it is apparent that gut microbes drive and shape bone, cartilage, muscle and pain pathways, the exact molecular and cellular pathways have not been fully charted. The major unresolved questions are the mechanisms of entry of microbial metabolites into distal tissues, the interaction of immune-signaling in the gut with the joint or bone-marrow setting, and the mechanisms connecting gut physiology to nociception and muscle flux. New sophisticated tools will be needed including the use of single-cell sequencing, space transcriptomics, microbes metabolic tracing, and organ chipson-chip to achieve fine-scale mechanistic resolution.

9.4 Inter-individual Diversity and Individualised Therapies

Human gut microbiomes differ tremendously in each person since they depend on diet, genetics, environment, lifestyle, geography and exposure to medications. This variability determines personal interventions towards probiotics, diet interventions, fecal microbial transplantation, and genetically engineered microbial therapeutics. Creating a successful microbiome-based therapy will thus have to focus on individualised approaches as opposed to a one-fit-fits-all approach. Precision-medicine systems comprising of the microbiome profiles with other factors such as host genetics, metabolic measurements and clinical phenotypes are vital in the development of tailored intervention concerning musculoskeletal disorders.

9.5 Regulatory considerations in microbiome-based interventions

The increasing rate of probiotics, postbiotics, characterized microbial consortia, and genetically engineered microbes put the regulatory system in a challenging position. These treatments simply do not fall in the special purview of drugs, biologics, or dietary supplements. There are additional safety issues, such as the microbial translocation, immunological responses, and horizontal gene transfer. Urgent control mechanisms, definitive standards of safety and stringent long-term surveillance measures are necessary to move the microbiome-based therapies in musculoskeletal medicine into clinical use.

10. Conclusion

One of the most outstanding and the fastest-growing spheres of biomedical science is the gut-musculoskeletal axis. Experimental, clinical, and systems-level evidence has shown that the gut microbiome has significant effects on the inflammation, immune regulation, metabolic signalling, neuromodulation and tissue remodelling of the musculoskeletal system. Dysbiosis turns out to be a central cause of the pathogenesis of osteoarthritis, rheumatoid arthritis, osteoporosis, sarcopenia, chronic pain syndromes, and other disorders.

Future approaches of utilizing the microbiome against disease that hold promise include therapeutic modulation of the microbiome through the use of probiotics and prebiotics, dietary interventions, fecal transplantation of the microbiome, engineered bacterial strains and microbial metabolite therapies. Such modalities have a hope of reestablishing homeostasis, interfering with inflammation, promoting tissue repair, and completed pain management in musculoskeletal illnesses.

Nevertheless, there are still serious problems. Uncertainties in a mechanistic nature, the inter-individual variance and absence of generalised procedures as well as the complexity in regulations impairs its general utilisation in clinics. The future will be based on longitudinal human studies, incorporation of multi-omics, personalised therapeutic design, and latest technology such as microbial engineering and AI-based prediction models.

It is necessary to have a multidisciplinary research roadmap with coordination between microbiology, musculoskeletal biology, immunology, and data science and clinical medicine. The gut microbiome can evolve to be a fundamental musculoskeletal health and regenerative medicine platform, through the promotion of mechanistic insights and precise therapeutics.

Conflicts of interest

The authors have no competing interest to declare that are relevant to the content of this article.

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