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THE GUT-MUSCULOSKELETAL AXIS AS A PHARMACOLOGICAL TARGET: MICROBIOME-BASED THERAPEUTICS FOR OSTEOPOROSIS, OSTEOARTHRITIS, SARCOPENIA, AND PAIN MANAGEMENT

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ABSTRACT

The gut-muscular system axis has become a key paradigm to explain the systemic interactions between gut microbial communities and the skeletal muscle, pain regulation and bone and joint diseases. This narrative review will discuss the potential role of gut dysbiosis in osteoporosis, osteoarthritis, sarcopenia and chronic musculoskeletal pain via disruption of the intestinal barrier, microbial translocation, immune activation, nutrient handling modification, endocrine disturbance and changes in microbial metabolites. The role of short-chain fatty acids, bile acids, indole derivatives, lipopolysaccharides as mediators of bone remodelling, cartilage degeneration, muscle protein metabolism, mitochondrial function, insulin sensitivity, and nociceptive signalling is highlighted. Experimental studies support gut–bone, gut–joint, gut–muscle and gut–brain interactions mechanistically, with human evidence further supporting interactions but being heterogeneous. Adjuncts to conventional pharmacological treatment are being explored such as probiotics, prebiotics, synbiotics, postbiotics, dietary interventions, microbial metabolites, faecal microbiota transplantation, bacteriophages and next-generation live biotherapeutics. The clinical application of their use is currently restricted due to interindividual microbiome variability, inconsistent formulations, lack of certainty in dosing, short follow-up, and weak causal evidence. To validate efficacy, safety and treatment durability, standardised methodologies, disease-specific biomarkers, integration of multi-omics and large multicentre trials are needed. While the potential for microbiome-directed strategies to aid in the management of musculoskeletal degeneration and pain in a more precise and integrated manner is possible, the therapies should be considered complementary and not replacements for current therapies.

KEYWORDS: Municipal biowaste; wastewater reclamation; nutrient recovery; soil health; circular agriculture; resilient food production

1. INTRODUCTION

MSDs such as osteoporosis, osteoarthritis and sarcopenia, and chronic musculoskeletal pain, are a leading cause of disability and lower quality of life globally. Population ageing, metabolic disease and chronic inflammation are compounds that are increasing their burden. Such conditions can be considered individually as bone dysplasia, cartilage dysplasia, skeletal muscle disorder or a pain pathway disorder. However, there are indications that they have mechanisms in common such as regulation of the intestinal microbiome, immune function, host metabolism, endocrine signalling and epithelial barrier integrity. This view has led to the acknowledgment of the gut–musculoskeletal axis as a new paradigm for understanding the role of intestinal microbes in musculoskeletal health, disease progression and therapeutic response. Gut microbiota, an ecosystem of bacteria, fungi, viruses and other microorganisms involved in metabolism of nutrients, maturation of immune system, intestinal homoeostasis and production of bioactive compounds. This ecosystem is vulnerable to disruption (dysbiosis) which can include decreased microbial diversity, loss of beneficial taxa, and harmful organisms and metabolites. These changes may lead to disruption of epithelial tight junctions, and allow entry of microbial molecules (e.g., lipopolysaccharides) into systemic circulation, which may lead to other consequences. This may lead to inflammation throughout the body. Recently, metabolites produced by the gut microbiota have been found to play an important role in metabolic and immune homeostasis such as in short chain fatty acids, secondary bile acids, and indole

derivatives (Agus et al., 2021). They have profound mechanistic actions on inflammatory signalling, cellular energy balance, endocrine regulation, and tissue metabolism, which underlie their role in gut-mediated regulation of bone, cartilage, muscle and pain.

This axis is even more relevant in the context of ageing. Older adults often exhibit low microbial diversity, decreased ecological stability and a loss of health associated organisms. These changes could affect immune regulation and help to lead to a chronic low-grade inflammatory state that is associated with frailty, osteoporosis, osteoarthritis, sarcopenia, and chronic pain, known as “inflammageing”. When combined with changes in the microbiome of the host, alterations in the microbiome are known to influence host immunity, particularly when compounded by exposure to drugs and changes in diet, physical activity and physiological alterations associated with ageing, as described by Bosco and Noti (2021). The gut microbiome could thus serve as a common upstream mechanism in multiple musculoskeletal diseases beyond simply being a downstream effect of disease.

One in particular, the gut–bone axis, has been studied. Bone is continually remodelling with the cooperative work of osteoblasts which deposit bone and osteoclasts which remove it. This imbalances results in osteoporosis and susceptibility to fracture. Both suppression of bone resorption and stimulation of bone formation are targeted in the conventional approaches, and natural compounds are also being studied for their anabolic effects on osteoblasts (An et al., 2016). This balance can be affected by the microbiome via the absorption of calcium, vitamin metabolism, immune-cell activity and cytokine production. The gut microbiota is known to influence mineral availability and metabolic signalling, with nutrient effects on skeletal health potentially being mediated by this microbiota, and Rizzoli (2019) highlighted that this. This widens osteoporosis from a ‘local’ skeletal disease to a systemic disease affected by intestinal and immunometabolic factors.

The interaction of these is exemplified in postmenopausal osteoporosis. Although estrogen and bone resorption have a positive correlation, estrogen may also affect the ability of the intestine to function as a barrier and to modulate inflammation. Collins et al., (2017) showed that estrogen depletion caused by ovariectomy lead to a temporal and regional shift in intestinal barrier function, expression of tight junctions and the activity of cytokine genes. These results indicate that the loss of estrogen can lead to skeletal loss either directly on the bone or indirectly via immunological system effects in the gut. Possibly, this interplay of hormonal loss, damage to the barrier and systemic inflammation could be key to postmenopausal bone loss.

The gut–joint axis also has been studied in the context of research on osteoarthritis. Osteoarthritis is no longer considered a purely mechanical wear of the cartilage, but rather it is now acknowledged to be a disease of the whole joint with synovial inflammation, subchondral bone remodelling, metabolic dysfunction and obesity-related pathways. Biver et al. (2019) suggested possible mechanisms of action of the gut microbiota in the pathogenesis of osteoarthritis, namely metabolic endotoxemia, immune activation and systemic inflammation. Boer et al. (2019) also found correlations between the composition of the intestinal microbiome, joint pain and inflammatory characteristics, which further suggests the potential link between microbial patterns and disease processes and symptom severity. Furthermore, a systematic review by Chisari et al. (2021) confirmed a significant link between gut microbiota and osteoarthritis, but also emphasized the large variability in study designs, sequencing techniques, populations and outcomes.

There is growing evidence but some important caveats. Most studies are cross-sectional, size is limited and causal pathways are unclear. Factors such as diet, age, obesity, medication use and comorbidities may also impact microbial composition and impact the interpretation. Despite this, there is a strong potential for the gut musculoskeletal axis as a pharmacological approach. Different types of probiotics, prebiotics, synbiotics, postbiotics, dietary modulation, and microbial metabolites can potentially complement the current interventions for bone loss, joint degeneration, muscle wasting and pain in the future. This review aims to explore how the gut microbiome interacts with musculoskeletal tissues and its role in osteoporosis, osteoarthritis, sarcopenia and pain management, and highlight the therapeutic potential of microorganisms for these conditions.

2. Biological Mechanisms Linking the Gut Microbiome and Musculoskeletal Health

The gut microbiome has close relationships with musculoskeletal pathways via immune, metabolic, endocrine, neural and barrier mechanisms. It impacts more than just the intestine; metabolites and inflammatory signals produced by the microbial communities are transported to the bone, cartilage, skeletal muscle and pain processing systems. Changes in microbial balance can lead to changes in metabolite production, as well as a reduction in the function of the epithelium's defence and a maintained stimulation of the immune system, which can form a biological niche that is comfortable for the development of bone loss, joint degeneration, muscle wasting, and chronic pain.

The intestinal barrier function is a key mechanism in this axis. In an uncompromised condition, epithelial cells, mucus and tight-junction proteins will block the entry of bacteria and other microbial products into the circulation. Damage to these protective structures can lead to dysbiosis, higher permeability of the intestine and allow microbial translocation. The lipopolysaccharides that are released from the gram negative bacteria can then be transported to the bloodstream and can trigger the toll-like receptor based signalling system. This leads to production of tumour necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6) and other mediators of low grade systemic inflammation. Chronic exposure to these signals could promote osteoclastogenesis, inhibit osteoblast activity, promote cartilage matrix degradation, decrease muscle protein synthesis and increase the sensitivity of nociceptors.

Regulation of the immune system is also crucial. The intestinal microbiota controls the ratio of pro-inflammatory and regulatory immunity, such as the ratios of T-helper 17 cells to regulatory T cells. In osteoporosis, the immune profile (inflammation) may be pro-osteoclasts and disrupt normal bone remodelling. Locantore et al. (2020) proposed that the immune system–microbiota interaction is a key element of the pathophysiology of osteoporosis, notably via cytokines and

lymphocytes' impact on bone turnover. This is backed up by population-based results. Microbiota collection variations among BM loss patients were found, indicating that BM loss may be associated with changes in the gut microbiota (Li et al., 2019).

A further key way of communication is through the metabolites generated by microbes. Short-chain fatty acids (SCFAs) are formed by the bacterial fermentation of dietary fibre, notably acetate, propionate and butyrate. These compounds maintain the integrity of epithelia, regulate the differentiation of immune cells and control inflammation. Butyrate has been shown to be a regulator of tight junctions and augment regulatory T-cell responses, and short-chain fatty acids may also affect osteoclast activity, muscle energy metabolism and insulin sensitivity. This impairment of production of these metabolites could then lead to diminished barrier function and increased inflammatory damage. In addition, microbial products derived from tryptophan metabolism also play a role in the maintenance of epithelial integrity, immune function, and are responsible for Aryl hydrocarbon receptor signalling, which could have implications for pain regulation and tissue maintenance.

The bile acids are now emerging as signalling molecules of the microbiome. Liver-made primary bile acids are converted to secondary bile acids in the gut by bacteria with effects on the systemic metabolism and immune system. Collins et al. (2023) demonstrated the effects of interactions between bile acids and the microbiota on inflammation, glucose regulation, lipid metabolism, and disease processes. Bile acids can influence energy expenditure, insulin sensitivity and inflammatory signaling via two distinct receptors: the farnesoid X receptor and Takeda G protein-coupled receptor 5. These pathways are important in the context of obesity and musculoskeletal aging in the form of osteoarthritis, sarcopenia and osteoporosis, as these are 3 conditions that often drive musculoskeletal decline.

The microbiome also affects digestive and hormonal functions. Bioavailability of calcium, magnesium, vitamin K, vitamin D-related compounds, amino acids and other nutrients that are essential for bone and muscle maintenance can change via microbial activity. Dietary supplements and probiotics have been shown to alter the activity of microbes and gut–bone axis by De Sire et al. (2022). The microbiome may also have interactions with pathways of estrogen, insulin-like growth factor-1, serotonin and glucocorticoid. These hormonal connections have the potential to influence bone remodelling, the anabolism of muscle, stress and pain.

The gut–musculoskeletal axis is enriched with a neuroimmune axis by pain regulation. Changes in metabolites, cytokines and microbial products are able to sensitise peripheral nociceptors and affect central pain processing via the gut–brain axis. Persistent nociplastic pain can be caused by neuroinflammation, changes in neurotransmitter metabolism and activation of the stress-axis. Faecal microbiota transplantation (FMT) has been investigated as a possible treatment for nociplastic pain and, as a result of its growing interest in the field of pain management, it was the subject of study by Martín Pérez et al. (2025).

Combined, these pathways indicate that the gut microbiome impacts musculoskeletal health in a synergistic manner as opposed to any single pathway. All of these can interact and reinforce each other with a failure to the barrier, translocation of microbes, activation of the immune system, alteration of metabolites, alteration of nutrient handling, endocrine disruption, and neuroimmune signalling. The integrated model offers a solid biological basis for the development of dysbiosis as a possible mechanism contributing to bone strength, joint integrity, muscle function, and pain sensitivity as well as its potential as a pharmacological and nutritional target for the microbiome.

3. Gut Microbiome Dysbiosis in Osteoporosis

Osteoporosis is currently regarded as a systemic disease driven by the interplay of bone cells, immune pathways, hormones, nutrition and the intestinal microbiome. Disturbance of the gut microbiome can affect the skeletons through various mechanisms, such as decreased integrity of the epithelial barrier, change in metabolite production, nutrient absorption impairment, and low-grade inflammation. These changes may alter the relationship between osteoblastic bone formation and osteoclastic bone resorption, and thus lead to an increase in bone loss and fracture risk.

In healthy conditions, the intestinal microbiota maintains intestinal barrier and exerts immune tolerance. Usually, dysbiosis can impair the tight junctions, cause intestinal permeability, and allow entry of microbial products – lipopolysaccharides – into the circulation. This microbial translocation stimulates the activation of the toll-like receptor signalling pathway and triggers the release of inflammatory mediators such as tumour necrosis factor-alpha, interleukin-1 beta and interleukin-6. These cytokines promote osteoclastogenesis and survival, but inhibit osteoblast activity and bone matrix production. D'Amelio and Sassi (2018) have suggested that this microbiota–immune–bone axis is a key pathway by which gut dysbiosis can alter bone remodelling. Thus, chronic immune activation can induce a resorption-biased state leading to gradual decreases in BMD.

These are further exacerbated by estrogen deficiency. Once menopause, a decrease in estrogen directly stimulates osteoclast activity and immunomodulation. Loss of estrogen can also alter intestinal microbiota and lead to barrier impairment, thereby enhancing the contact with gut microbial products that trigger inflammation. Ding et al. (2020) noted that dysbiosis, immune imbalance and microbial metabolites are significant factors involved in osteoporosis, especially in ageing and oestradiol deficiency. The overall hormonal changes, gastrointestinal and systemic inflammatory conditions might thus be responsible for postmenopausal bone loss in addition to the bone mechanisms. The gut dysbiosis can be a driver for osteoporosis by disrupting the intestinal barrier, inducing systemic inflammation, changing immune signalling and by skewing the bone formation (osteoblast) versus bone resorption (osteoclast) mechanisms, as shown in Figure 1.

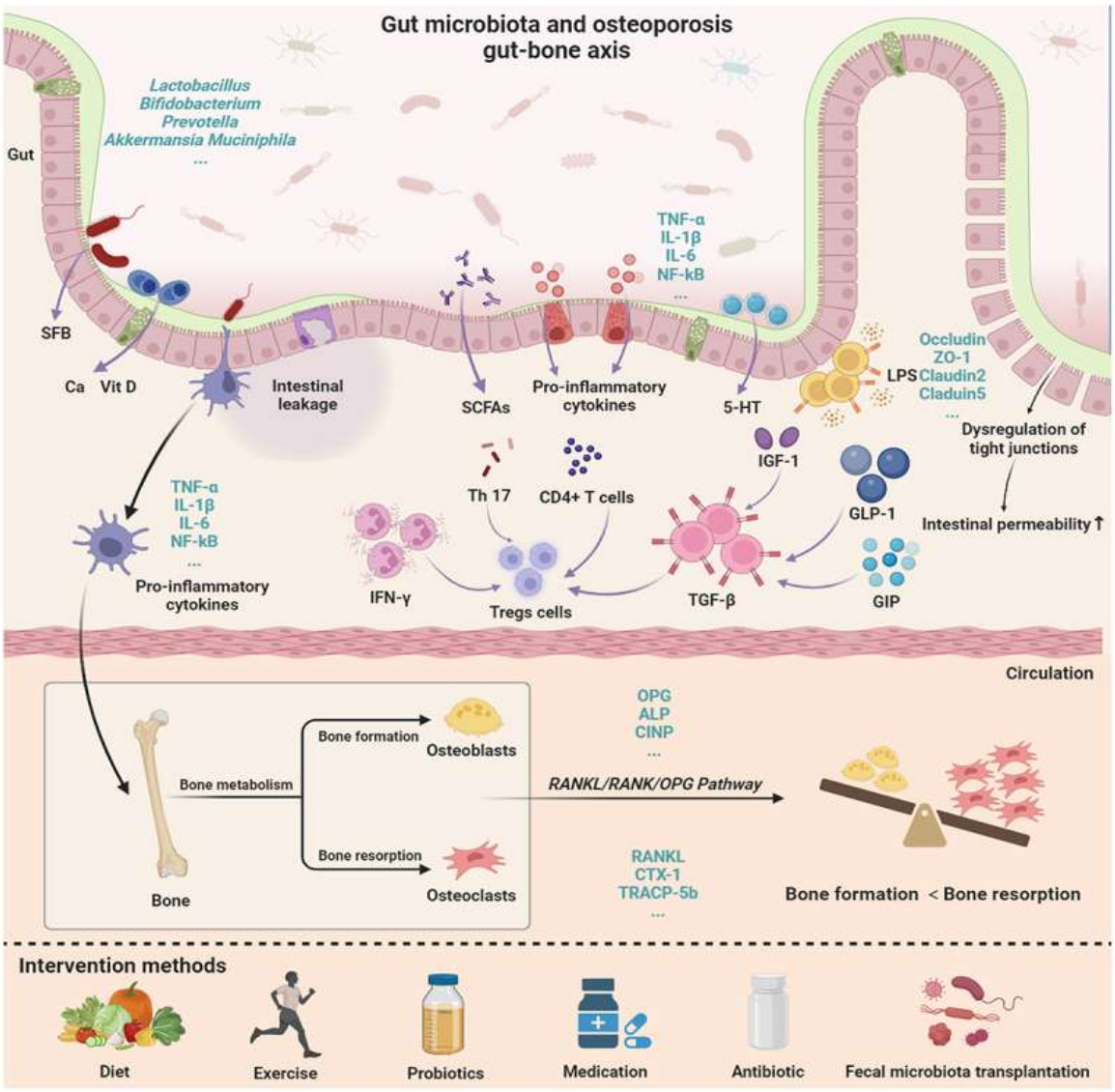

Figure 1. Microbiota-Driven Alterations in Bone Remodelling

Source: Adapted from Zhang et al. (2024).

The microbiome also affects calcium and vitamin metabolism. Dietary fibre is fermented to produce short-chain fatty acids which decrease the pH in the intestine and could potentially increase calcium solubility and absorption. In addition, microbial activity has the potential to alter the synthesis of vitamin K and/or vitamin D-mediated signaling, magnesium availability and nutrient for collagen synthesis and mineralisation. These beneficial functions may be diminished during dysbiosis, which can affect the available substrates for bone development. The microbial diversity and nutrient-handling may be further compromised in older adults by poor diet, decreased physical activity, polypharmacy and repeated exposure to antibiotics, which may contribute to increased skeletal fragility.

This correlation is well supported by experimental studies that show that this relationship is mechanistic. In their study, Schepper et al. (2019) showed that probiotic Lactobacillus reuteri was able to inhibit post-antibiotic bone loss in mice by protecting intestinal barrier function and preventing intestinal dysbiosis. This study identified that disrupting the microbiome can have measurable skeletal effects, and that potentially restoring the microbiota could help to safeguard bone. These effects on inflammatory signalling, osteoclastogenesis and bone mass have also been seen in other animal models fed antibiotics, raised in germ-free environments or provided probiotics. These models are useful in highlighting causal pathways but the microbial ecology, diet and skeletal physiology differ between the model and humans, so direct extrapolation is not possible.

There is human observational evidence, which supports but isn't quite as clear. Lower bacterial diversity and/or abundance has been reported to be associated with lower bone mineral density. These results indicate that the microbial signatures could be linked to or indicative of the deterioration of the skeleton, but do not provide direction. Major other confounders are age, BMI, menopausal status, medications, diet, activity and comorbid disease. Human studies with probiotics, prebiotics and dietary changes have provided positive indications, but the studies have been small and results have been inconsistent.

Dysbiosis may also be associated with an increase in the overall musculoskeletal phenotype, which includes frailty and muscle loss, that is also linked to age. Ticinesi et al. (2017) correlated the ageing microbiome to nutrition, physical frailty and to sarcopenia, suggesting an interplay between inflammatory and metabolic mechanisms between both bone and

muscle. While dealing with probiotics and depression, Huang et al. (2016) provides another good example of how the modulation of the microbiome can occur beyond the gut. Overall, evidence at present favors the hypothesis of dysbiosis as a potential biological cause of osteoporosis. Studies with larger longitudinal cohorts and proper clinical trials are required to establish whether there is a specific microbial signature that can predict bone loss, fracture risk, or bone loss to anti-osteoporotic treatment, or any of these. Sequencing, dietary assessment and clinically relevant skeletal endpoints will also play a crucial role in moving microbiome research into clinically relevant prevention and treatment.

4. Gut–Joint Interactions in Osteoarthritis

Osteoarthritis is now known to be a whole joint disorder that is influenced by mechanical stress, metabolic imbalance, immune activation and subchondral bone remodelling. In this context, gut microbiome has come to the fore as a potential upstream regulator of disease progression. Gut dysbiosis can lead to changes in the integrity of the intestinal barrier, which can lead to increased systemic levels of microbial products and amplify inflammatory pathways that impact synovium, cartilage, subchondral bone and pain-processing systems. The gut–joint axis is thus a means by which gut disturbances can impact on the development of osteoarthritis beyond the load.

One of the key mechanisms that are hypothesized to explain this correlation is metabolic endotoxemia. Dysbiosis can lead to breakdown of epithelial tight junctions, leading to lipopolysaccharide (LPS) from gram negative bacteria entering the blood. Exposure to these products leads to activation of toll-like receptors (TLRs) and release of tumour necrosis factor (TNF), interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6) and other pro-inflammatory mediators. These cytokines within the joint can trigger synovial inflammation, induce matrix metalloproteinase activity and promote degradation of the collagen and aggrecan. They can also influence the chondrocyte homeostasis, inhibit the repair of the extracellular-matrix and stimulate catabolic reactions, which consequently damage the articular cartilage over time.

This gut–joint interaction is additionally enhanced by obesity. Obesity is linked to changes in the composition of the gut microflora, dysregulated barrier functions and chronic low-grade inflammation due to adipokines and microbial products. This could help to explain why obesity is associated with an increased risk of developing osteoarthritis in joints other than weight-bearing, as well. Jackson et al. (2018) reported the link between gut microbiota profiles and common diseases and prescription drug usage in population-based cohorts. Thus, obesity, comorbidity, and drug exposure should be taken into consideration when unpacking the associations between the microbiome and OA, as each of these factors can impact microbiome composition and systemic inflammatory state.

Another important aspect of the gut–joint axis is subchondral bone. In OA, there are abnormal changes occurring under the cartilage, such as changes in mineralisation, sclerosis and changes in the trabecular structure. Experimental studies have shown that microbiome has the potential to affect the quality and quantity of bones. In a mouse model, Guss et al. (2019) observed alterations in bone tissue composition when they reduced skeletal strength in mice with the help of their microbiome. Further, Hernandez et al. (2016) have provided evidence on immune, endocrine and metabolic pathways by which microbial communities from the gut could participate in the regulation of bone. These studies did not specifically study osteoarthritis but suggest that dysbiosis may have an effect on the behaviour of the subchondral bone and lead to mechanical instability in the joint. The gut-derived endotoxins and microbial metabolites, such as short-chain fatty acids, can have effects on the pathogenesis of osteoarthritis via inflammatory signalling, immune regulation and disruption of bone remodelling, as shown in Figure 2.

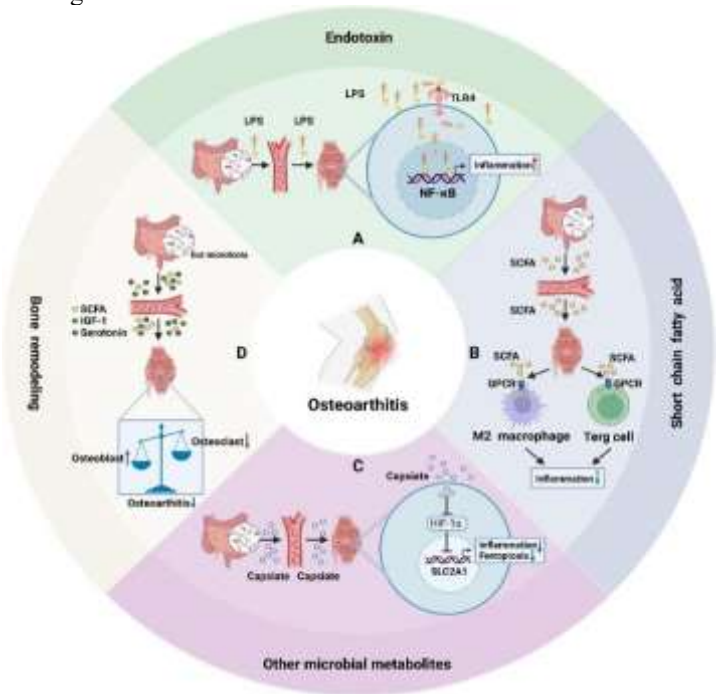

Figure 2. Microbial Pathways Influencing Osteoarthritis Progression

Source: Adapted from Sun et al. (2025).

This can be also regulated by hormones. The maintenance of epithelial integrity, immune balance and microbial diversity is dependent on estrogen receptors. Ibrahim et al. (2019) showed that the diversity of the gut microbiota was influenced by intestinal epithelial estrogen receptor beta in an inflammatory disease model. This is important, as both ageing and estrogen deficiency have been linked to changes in the microbial environment, and to increased risk of osteoarthritis. Microbial translocation, systemic inflammation and joint degeneration may be exacerbated by disrupted barrier function in the joint, which is dependent on estrogens, especially in the elderly.

There is another dimension of neuroimmune signalling. In osteoarthritis, the severity of pain is often more than is suggested by the degree of structural damage, suggesting involvement of peripheral and central sensitisation. Cryan et al. (2020) demonstrated that the gut microbiome can impact neurological function via immune mediators, microbial metabolites and gut–brain communication. These pathways can affect the excitability of nociceptors, neuroinflammation, stress responses and pain perception in osteoarthritis. The microbiome can thus play a role in tissue degradation and the maintenance and intensification of the pain.

Experimental evidence relates the occurrence of dysbiosis with barrier dysfunction, systemic inflammation, cartilage catabolism, and skeletal change. Human evidence is not as positive. Most clinical studies are observational and lack of the ability to eliminate confounding variables such as diet, age, physical activity, medications and comorbid disease. Additionally, directionality of the relationship is unclear. There are three different possible scenarios: Microbiome changes can occur before osteoarthritis, can happen due to the disease, or can happen while the disease is occurring.

The gut–joint axis is a coherent model spanning from metabolic endotoxemia, obesity-related inflammation, synovitis, cartilage degradation, subchondral bone remodelling to chronic pain. Existing evidence is compelling but more longitudinal studies are needed as are controlled interventions to prove causation and therapeutic relevance. Future research will require standardised methods for the microbiome and clinically relevant outcomes as structural, inflammatory and patient reported.

5. The Gut–Muscle Axis in Sarcopenia

Sarcopenia is a progressive musculoskeletal disorder characterized by a decrease in skeletal muscle mass, strength and physical performance. It is the result of the combination of ageing, poor nutrition, lack of exercise, hormonal changes, mitochondrial dysfunction, insulin resistance and chronic low-grade inflammation. The gut microbiome has been highlighted for its role in regulating nutrient digestion, immune homeostasis, intestinal barrier function, energy metabolism and production of bioactive metabolites. These functions can be disrupted, impairing the muscle homeostasis and promoting gut–muscle axis aging.

Experimental evidence indicates that intestinal microbes and skeletal muscle have a causal relationship. Lahiri et al. (2019) demonstrated that mice lack microbial diversity in their gut, leading to decreased muscle mass, muscle strength and performance of locomotory activity. Changes in mitochondrial function and energy metabolism were also observed in these animals. Reintroduction of the gut microbiome had a beneficial effect on various muscle metrics, indicating a direct role for microorganisms in muscle physiology as well as a correlation with the host. This study provided a mechanistic link between microbial metabolites, neuromuscular signalling and host energy balance and skeletal muscle maintenance.

One of the most relevant mediators of this relationship are short-chain fatty acids. The microbial fermentation of dietary fibre produces acetate, propionate, and butyrate, all of which play a role in maintaining the integrity, regulation of the immune system and metabolism of the epithelia. Decreased short-chain fatty acid production can lead to increased intestinal permeability and systemic inflammation, but butyrate can enhance mitochondrial efficiency, decrease oxidative stress and increase insulin sensitivity. This inflammatory environment contributes to anabolic resistance in older adults through increased proteolysis, decreased satellite-cell activity and decreased muscle protein synthesis.

Dysbiosis, in turn, is associated with insulin resistance, which leads to muscle deterioration. Skeletal muscle is one of the largest tissues that consume glucose, and insulin's ability to stimulate glucose uptake is decreased, along with its anabolic effects, and could lead to increases in protein degradation. Lee et al. (2020) explained gut microbial imbalance in obesity and insulin resistance by endotoxemia, bile acid metabolism and inflammatory signalling. These processes can lead to loss of muscle quality even if there is a lack of loss in muscle mass. They work together to exacerbate sarcopenia especially in elderly people suffering from obesity or type 2 diabetes. Inflammatory response, insulin resistance, decreased microbial diversity and altered metabolite production were identified as some of the mechanisms associated with sarcopenia involving the microbiome (Table 1).

Table 1. Microbiome-Related Mechanisms Contributing to Sarcopenia

Pathway	Microbiome-related change	Effect on muscle
Microbial diversity	Loss of beneficial bacteria	Reduced muscle mass and strength
Short-chain fatty acids	Reduced acetate, propionate, and butyrate	Impaired mitochondrial and metabolic function
Inflammation	Increased gut permeability and endotoxemia	Muscle catabolism and poor regeneration
Insulin resistance	Altered microbial and bile acid signalling	Reduced glucose uptake and anabolic response
Physical inactivity	Reduced exercise-related microbial adaptation	Lower physical performance
Pain and fatigue	Altered microbial composition	Reduced mobility and functional decline

Another major pathway is related to age-associated inflammation. The resulting loss of diversity of microorganisms, absence of beneficial microorganisms and/or impaired barrier function can lead to an increase in the levels of lipopolysaccharides and pro-inflammatory mediators in the circulation. Cytokines (such as tumour necrosis factor alpha and interleukin 6) can trigger catabolic pathways, disrupt muscle repair and cause mitochondria damage. Using bone as the tissue of interest, Yan et al. (2020) found that the microbiome can have beneficial or detrimental effects in musculoskeletal tissue, depending on the immune and metabolic context. The same goes for muscle – a microbial stability may be beneficial in maintaining muscle elasticity as we age.

The gut–muscle axis is significantly influenced by diet and exercise. Protein will influence the amount of amino acids available for muscle building, while dietary fibre will influence microbial fermentation and production of short-chain fatty acids. Low diversity of foods in the diet may be sufficient to decrease microbial diversity and increase anabolic resistance. Exercise immediately stimulates muscle growth and can also help to promote a good bacteria balance. Microbial composition is also modifiable by exercise: Morita et al. (2019) showed that exercise (brisk walking) boosted the number of intestinal Bacteroides in healthy older women.

This can be exacerbated by an interaction between frailty and this relationship. These older people tend to have lower microbial diversity and inflammatory susceptibility, particularly those who have diminished appetite, limited mobility, a history of recurrent antibiotic exposure, chronic disease and poor mobility. Inactivity and/or discomfort may additionally lead to less activity and less quality diet, perpetuating a vicious circle of dysbiosis and functional decline. Minerbi et al. (2019) found that the gut microbiota of people with fibromyalgia (a condition characterized by pain, fatigue and decreased physical function) is altered. These results add to the evidence of the interconnections between microbial imbalance, limited mobility, and musculoskeletal symptoms, despite the fact that fibromyalgia is a different condition from sarcopenia.

In conclusion, the gut–muscle axis offers a logical framework to explain the potential role of dysbiosis in the pathogenesis of sarcopenia via mechanisms of protein metabolism, mitochondrial dysfunction, insulin resistance, inflammation, poor nutrition and inactivity. While there is strong animal evidence, there is also some human research, which is quite variable, but mostly observational. To assess the potential of probiotics, prebiotics, dietary interventions and exercise to maintain the physical performance and muscle strength of the aging population, more research is needed, specifically: longitudinal studies and randomised trials.

6. Microbiome-Mediated Mechanisms in Musculoskeletal Pain

Musculoskeletal pain occurs via a combination of inflammatory, nociceptive, neuropathic and nociplastic mechanisms. Growing evidence indicates that the gut microbiome can affect all of these pathways through the effects on the integrity of the intestinal barrier, the systemic immune system, production of microbial metabolites, neural excitability, and gut–brain communication. Dysbiosis can thus be a factor in chronic pain not only in causing inflammation in the tissues, but also in its persistence, escalation, and/or differences in response among individuals.

Loss of integrity of the intestinal barrier is a central mechanism. A disturbed microbial balance can lead to a deterioration of the function of tight junctions, which can be bound to the entry of lipopolysaccharide and other microbial products into the bloodstream. These molecules stimulate the production of tumour necrosis factor alpha, interleukin 1 beta, interleukin 6 and other inflammatory mediators and interact with toll-like receptors. These cytokines can sensitize peripheral nociceptors, decrease pain thresholds and extend the responses to mechanical and chemical stimulation. Rios-Arce et al. (2020) found that post-antibiotic dysbiosis can lead to lymphocyte-dependent skeletal effects, thus proving that disruption of the microbes could alter pathways of immune system activity in a systemic manner, in addition to effects in the intestine. These immune mechanisms could exacerbate pain that is caused by bones, joints, and skeletal muscle. The major gut microbiome–driven pathways involved in the initiation and persistence of musculoskeletal pain are summarised in Table 2.

Table 2. Gut Microbiome–Driven Modulation of Musculoskeletal Pain Pathways

Mechanism	Microbiome-related alteration	Effect on pain	Supporting reference
Intestinal barrier dysfunction	Increased permeability and microbial translocation	Promotes systemic inflammation and nociceptor sensitisation	Rios-Arce et al. (2020)
Immune activation	Increased TNF-α, IL-1β, and IL-6 signalling	Intensifies inflammatory and nociceptive pain	Rios-Arce et al. (2020)
Short-chain fatty acid imbalance	Reduced acetate, propionate, and butyrate production	Weakens mucosal defence and anti-inflammatory control	Yang et al. (2020)
Microbial metabolites	Altered bile acids, indoles, and tryptophan metabolites	Affects joint inflammation and neuronal excitability	Zhang et al. (2026)
Peripheral sensitisation	Persistent inflammatory stimulation of nociceptors	Lowers pain threshold and prolongs pain responses	Zhang et al. (2026)
Central sensitisation	Neuroinflammation and altered neurotransmitter pathways	Contributes to neuropathic and nociplastic pain	Zhang et al. (2026)
Gut–brain communication	Disturbed vagal, immune, and stress-axis signalling	Influences sleep, mood, stress, and pain perception	Zhang et al. (2026)
Skeletal deterioration	Reduced microbial diversity associated with bone loss	Increases fracture-related and chronic musculoskeletal pain	Wang et al. (2017)

Also in this connection are microbial metabolites. The short-chain fatty acids (SCFAs) including acetate, propionate and butyrate play an important role in maintaining the integrity of the epithelial barrier, immune-cell differentiation and controlling hyper-inflammatory responses. Yang et al. (2020) demonstrated that short-chain fatty acids produced by the microbiota control the production of the cytokine IL-22 and the intestinal immunity. Having adequate levels of these metabolites may protect against peripheral sensitisation by reducing inflammation and cytokine release, while reduced production of these metabolites could lead to a decrease in mucosal defence and rise in inflammatory signalling.

Other metabolites produced in the gut can have direct effects on the tissues of the joints and pain pathways. Immune receptors, nociceptors and central neurotransmitter system can be activated by bile acid derivatives, indoles, and microbial lipids. Zhang et al. (2026) proposed that gut-derived metabolic messengers are central mediators in osteoarthritis, which are interconnected with microbial influence, synovial inflammation, cartilage degradation, subchondral bone remodelling and expression of the symptoms. The results point to a role of the microbiome for the modulation of pain, both structurally in the tissue and directly on the excitability of neurons.

With repetitive nociceptive input, peripheral sensitisation can be followed by central sensitisation, where the processing of nociceptive input in the spinal cord or supraspinal is changed. Chronic exposure to inflammatory mediators may lead to an increase in microglial activation, excitatory neurotransmission and decrease in inhibitory pain control. These are significant changes that are particularly important for nociplastic pain, where pain can become widespread and/or disproportionate to what can be seen in the tissues. Dysbiosis may be involved in this process via neuroinflammation, as well as changes in the tryptophan metabolism, which impacts on serotonin, kynurenine and glutamatergic pathways involved in pain modulation.

Another connection between the microbiome and the gut–brain axis involves stress, mood, sleep, and pain perception. Immune mediators, circulating metabolites, vagus nerve and the hypothalamic–pituitary–adrenal axis are all involved in the conduction of signals. Disruption of the microbiome can make you more susceptible to stress, disrupt sleep and exacerbate anxiety or depressive symptoms. All these factors may exacerbate pain and diminish coping capacity which can also contribute to chronicity. Both directions go: Intestinal microbes and changes in diet or activity, sleep habits, and medications can affect pain levels, and pain, sleep disturbance and psychological stress can also affect the composition of microbes and the motility of the intestines.

The diversity of microbes could also affect pain by degrading the skeleton. Wang et al. (2017) found that there was a difference in diversity of gut microorganisms for osteoporosis and osteopenia patients. While not the main outcome, there can be an alteration of bone quality that will make them more prone to fracture, to compression of the vertebral body and to chronic axial pain. Microbial dysbiosis and skeletal fragility thus may share inflammatory mechanisms, and lead to a burden of pain.

In summary, the microbiome can influence the musculoskeletal pain via barrier dysfunction, metabolic endotoxemia, immune activation, changes in the level of microbial metabolites, peripheral sensitisation, central neuroinflammation, and disruption of gut–brain signalling. The evidence is more and more compelling and the clinical evidence is still diverse and frequently descriptive. Future studies will need to be well-designed longitudinal studies or randomised interventions to ascertain if microbiome-targeted therapies decrease pain intensity, sleep and mood, and pain trajectory. Classification of the participants by pain phenotype, metabolic status, medications used and microbial profile at baseline will be necessary in future studies to allow a more targeted and clinically relevant application of microbiome-based pain management.

7. Microbiome-Based Therapeutics, Translational Challenges, and Future Directions

More and more studies are investigating the potential of microbiome-based therapeutics as complementary treatments for osteoporosis, osteoarthritis, sarcopenia and chronic musculoskeletal pain. Probiotics can help to restore beneficial taxa, enhance barrier integrity, mitigate endotoxemia and modulate inflammatory pathways. Prebiotics promote the growth of health beneficial bacteria, and synbiotics are made up of microbial strains together with fermentable substrates to enhance the metabolic activity and survival of the microbes. Bioactive compounds from postbiotics or purified microbial metabolites might be more stable and safe, as they do not include any living organisms. Yet the therapeutic effects are very strain-specific, dose-dependent, formulation-dependent, and require lengthy treatment periods, the host diet, and exposure to the medication, and depend on the baseline composition of the host's microbial community.

To date, dietary manipulation, the most practical and easily accessible method of microbiome manipulation in clinical settings, has been attempted. Adequate protein levels can facilitate muscle protein synthesis, fibre rich foods can help to produce short chain fatty acids and improve epithelial integrity and inflammation. Prokopidis et al. (2021) stated that the gut–muscle axis could be affecting the anabolic resistance via changes in nutrient handling, changes in microbial metabolites, systemic inflammation, and changes in muscle protein metabolism. The mechanisms outlined indicate that nutrition support could be combined with resistance exercise and protein supplementation to older adults with a risk of sarcopenia and directed by the microbiome. Picca et al. (2019) also found specific microbial, inflammatory and metabolic signatures in older individuals who were physically frail and also sarcopenic, suggesting that a treatment strategy that would be effective for correcting microbial imbalance and host metabolic dysfunction would be required.

Faecal microbiota transplantation, engineered microbes and next generation live biotherapeutic products, as well as bacteriophages are more advanced intervention options. FMT may lead to global changes in the gut microbiota, though its practical implementation is hindered by the fact that donor ecologies vary, pathogens can be transmitted, the effects may be short-lived, and the impact on the recipient metabolism and immune system is hard to predict. In addition to engineered microbes that can be engineered to produce anti-inflammatory compounds or beneficial metabolites, bacteriophages provide a more targeted solution and can attack specific bacteria. The technologies are still in the

experimental stage and should be thoroughly tested for consistency of manufacturing, ecological stability, containment and long term safety.

Manipulation of the microbiome is also being explored as a potential in chronic pain. Minerbi et al. (2025) suggested that the gut microbiome is a novel area of interest in fibromyalgia, as dysregulated microbial communities may impact inflammation, neurotransmitter metabolism, tiredness, sleep and pain amplification. However, there is limited causal evidence and the role of dysbiosis in causing symptoms, being the consequence of disease or being in a bidirectional relationship with medication use, diet and stress is unclear.

Conventional drug therapy may be more effective when combined with other drugs; however, drug–microbiome interactions make interpretation difficult. Microbiotics (antibiotics, non-steroidal anti-inflammatory drugs, opioids, bisphosphonates, nutritional supplements) can change composition and metabolism of the microbes. Future studies should thus be reported using standardized dose, formulation, viability, adherence, diet, medication exposure, sequencing methods and clinically relevant outcomes.

Limited translation into routine care is also hampered by inter-individual variations and uncertain definitions of dysbiosis, weak causal evidence and small study sizes. The regulation also varies between probiotics, postbiotics, faecal preparations and engineered organisms. Future trials should incorporate metagenomics, metabolomic and inflammatory markers and functional outcomes including bone density, joint symptoms, muscle strength, mobility, sleep and pain interference. Further long-term follow-up and large multicentre randomized studies are required to uncover the safety, responders, dosage and potential of the microbiome-driven approach to becoming a reliable part of musculoskeletal pharmacotherapy.

8. CONCLUSION

The gut–musculoskeletal axis provides a solid foundation to understand how the intestinal microbial community can contribute to osteoporosis, osteoarthritis, sarcopenia and chronic musculoskeletal pain. Gut dysbiosis may contribute to the deterioration of the intestinal barrier, enhanced microbial translocation, production of metabolites, and maintenance of low-grade inflammation. The changes may throw off bone remodelling, cartilage homeostasis, muscle protein metabolism, mitochondrial function, and pain regulation. The therapeutic potential of interventions that involve the microbiome, such as probiotics, prebiotics, synbiotics, postbiotics, dietary change, microbial metabolites, faecal microbiota transplantation, bacteriophages, and next generation live therapeutics, are explored. Nevertheless, the current evidence is weak due to small sample sizes, short follow-up periods, inconsistent formulation, differences in doses, and inconsistent evidence of causality in humans. The interpretation and standardisation of treatments is further complicated by age, diet, geographical differences, medication, disease phenotype, and baseline microbiome composition. Future studies should delve deeper into the description of dysbiosis and discover microbial functions specific to the disease, validated biomarkers and clinically relevant therapeutic targets. The large scale, multicenter randomized trials should incorporate metagenomics, metabolomics, immune profile and meaningful outcomes, including bone density, joint function, muscle strength, mobility, sleep and pain interference. The long-term effects, durability and interaction with conventional medications are also crucial to consider. Microbiome-directed therapy has the potential to offer a valuable complementary approach to existing pharmacological therapies, and could help to improve the accuracy of prevention and management of musculoskeletal decline, as evidenced by stronger mechanistic evidence and standardised clinical methods. It might be more useful in addition to, rather than as an alternative to, conventional treatments, and in targeting common inflammatory and metabolic pathways in different musculoskeletal conditions in patients.

REFERENCES

1. An, J., Yang, H., Zhang, Q., Liu, C., Zhao, J., Zhang, L., & Chen, B. (2016). Natural products for treatment of osteoporosis: The effects and mechanisms on promoting osteoblast-mediated bone formation. Life sciences, 147, 46-58.
2. Rizzoli, R. (2019). Nutritional influence on bone: role of gut microbiota. Aging clinical and experimental research, 31(6), 743-751.
3. Biver, E., Berenbaum, F., Valdes, A. M., de Carvalho, I. A., Bindels, L. B., Brandi, M. L., ... & Rizzoli, R. (2019). Gut microbiota and osteoarthritis management: An expert consensus of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Ageing research reviews, 55, 100946.
4. Boer, C. G., Radjabzadeh, D., Medina-Gomez, C., Garmaeva, S., Schiphof, D., Arp, P., ... & van Meurs, J. B. (2019). Intestinal microbiome composition and its relation to joint pain and inflammation. Nature communications, 10(1), 1-9.
5. Bosco, N., & Noti, M. (2021). The aging gut microbiome and its impact on host immunity. Genes & Immunity, 22(5), 289-303.
6. Chisari, E., Wouthuyzen-Bakker, M., Friedrich, A. W., & Parvizi, J. (2021). The relation between the gut microbiome and osteoarthritis: A systematic review of literature. PloS one, 16(12), e0261353.
7. Collins, F. L., Rios-Arce, N. D., Atkinson, S., Bierhalter, H., Schoenherr, D., Bazil, J. N., ... & Parameswaran, N. (2017). Temporal and regional intestinal changes in permeability, tight junction, and cytokine gene expression following ovariectomy-induced estrogen deficiency. Physiological reports, 5(9), e13263.
8. Agus, A., Clément, K., & Sokol, H. (2021). Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut, 70(6), 1174-1182.
9. Li, C., Huang, Q., Yang, R., Dai, Y., Zeng, Y., Tao, L., ... & Wang, Q. (2019). Gut microbiota composition and bone mineral loss—epidemiologic evidence from individuals in Wuhan, China. Osteoporosis International, 30(5), 1003-1013.
10. Locantore, P., Del Gatto, V., Gelli, S., Paragliola, R. M., & Pontecorvi, A. (2020). The interplay between immune system and microbiota in osteoporosis. Mediators of Inflammation, 2020(1), 3686749.

11. Martín Pérez, S. E., Abdel Lah, H. A. L., García, N. H., Reyes Carreño, U. A., & Martín Pérez, I. M. (2025). Effectiveness of fecal microbiota transplantation in nociplastic pain management: A systematic review. Gastrointestinal Disorders, 7(1), 5.
12. Collins, S. L., Stine, J. G., Bisanz, J. E., Okafor, C. D., & Patterson, A. D. (2023). Bile acids and the gut microbiota: metabolic interactions and impacts on disease. Nature Reviews Microbiology, 21(4), 236-247.
13. De Sire, A., De Sire, R., Curci, C., Castiglione, F., & Wahli, W. (2022). Role of dietary supplements and probiotics in modulating microbiota and bone health: the gut-bone axis. Cells, 11(4), 743.
14. Schepper, J. D., Collins, F. L., Rios-Arce, N. D., Raehtz, S., Schaefer, L., Gardinier, J. D., ... & McCabe, L. R. (2019). Probiotic Lactobacillus reuteri prevents postantibiotic bone loss by reducing intestinal dysbiosis and preventing barrier disruption. Journal of Bone and Mineral Research, 34(4), 681-698.
15. Ticinesi, A., Lauretani, F., Milani, C., Nouvenne, A., Tana, C., Del Rio, D., ... & Meschi, T. (2017). Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut–muscle axis?. Nutrients, 9(12), 1303.
16. Ding, K., Hua, F., & Ding, W. (2020). Gut microbiome and osteoporosis. Aging and disease, 11(2), 438.
17. D'Amelio, P., & Sassi, F. (2018). Gut microbiota, immune system, and bone. Calcified tissue international, 102(4), 415-425.
18. Huang, R., Wang, K., & Hu, J. (2016). Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. Nutrients, 8(8), 483.
19. Guss, J. D., Taylor, E., Rouse, Z., Roubert, S., Higgins, C. H., Thomas, C. J., ... & Hernandez, C. J. (2019). The microbial metagenome and bone tissue composition in mice with microbiome-induced reductions in bone strength. Bone, 127, 146-154.
20. Hernandez, C. J., Guss, J. D., Luna, M., & Goldring, S. R. (2016). Links between the microbiome and bone. Journal of Bone and Mineral Research, 31(9), 1638-1646.
21. Ibrahim, A., Hugerth, L. W., Hases, L., Saxena, A., Seifert, M., Thomas, Q., ... & Williams, C. (2019). Colitis-induced colorectal cancer and intestinal epithelial estrogen receptor beta impact gut microbiota diversity. International journal of cancer, 144(12), 3086-3098.
22. Cryan, J. F., O'Riordan, K. J., Sandhu, K., Peterson, V., & Dinan, T. G. (2020). The gut microbiome in neurological disorders. The Lancet Neurology, 19(2), 179-194.
23. Jackson, M. A., Verdi, S., Maxan, M. E., Shin, C. M., Zierer, J., Bowyer, R. C., ... & Steves, C. J. (2018). Gut microbiota associations with common diseases and prescription medications in a population-based cohort. Nature communications, 9(1), 2655.
24. Lahiri, S., Kim, H., Garcia-Perez, I., Reza, M. M., Martin, K. A., Kundu, P., ... & Pettersson, S. (2019). The gut microbiota influences skeletal muscle mass and function in mice. Science translational medicine, 11(502), eaan5662.
25. Yan, J., Charles, J. F., & McCabe, L. R. (2020). Gut microbiome and bone: To build, destroy, or both? Current Osteoporosis Reports, 18, 273–284.
26. Lee, C. J., Sears, C. L., & Maruthur, N. (2020). Gut microbiome and its role in obesity and insulin resistance. Annals of the New York Academy of Sciences, 1461(1), 37-52.
27. Minerbi, A., Gonzalez, E., Brereton, N. J., Anjarkouchian, A., Dewar, K., Fitzcharles, M. A., ... & Shir, Y. (2019). Altered microbiome composition in individuals with fibromyalgia. Pain, 160(11), 2589-2602.
28. Morita, E., Yokoyama, H., Imai, D., Takeda, R., Ota, A., Kawai, E., ... & Okazaki, K. (2019). Aerobic exercise training with brisk walking increases intestinal bacteroides in healthy elderly women. Nutrients, 11(4), 868.
29. Zhang, R., Zhang, L., Wang, Y., Kang, X., & Zheng, J. (2026). Metabolic messengers from the gut to the joint: Toward precision management of osteoarthritis. International Journal of Molecular Medicine, 58(2), 226.
30. Rios-Arce, N. D., Schepper, J. D., Dagenais, A., Schaefer, L., Daly-Seiler, C. S., Gardinier, J. D., ... & Parameswaran, N. (2020). Post-antibiotic gut dysbiosis-induced trabecular bone loss is dependent on lymphocytes. Bone, 134, 115269.
31. Wang, J., Wang, Y., Gao, W., Wang, B., Zhao, H., Zeng, Y., ... & Hao, D. (2017). Diversity analysis of gut microbiota in osteoporosis and osteopenia patients. PeerJ, 5, e3450.
32. Yang, W., Yu, T., Huang, X., Bilotta, A. J., Xu, L., Lu, Y., ... & Cong, Y. (2020). Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. Nature communications, 11(1), 4457.
33. Minerbi, A., Khoutorsky, A., & Shir, Y. (2025). Decoding the connection: unraveling the role of gut microbiome in fibromyalgia. Pain Reports, 10(1), e1224.
34. Picca, A., Ponziani, F. R., Calvani, R., Marini, F., Biancolillo, A., Coelho-Júnior, H. J., ... & Marzetti, E. (2019). Gut microbial, inflammatory and metabolic signatures in older people with physical frailty and sarcopenia: results from the BIOSPHERE study. Nutrients, 12(1), 65.
35. Prokopidis, K., Chambers, E., Ni Lochlainn, M., & Witard, O. C. (2021). Mechanisms linking the gut-muscle axis with muscle protein metabolism and anabolic resistance: implications for older adults at risk of sarcopenia. Frontiers in Physiology, 12, 770455.
36. Zhang, Y. W., Song, P. R., Wang, S. C., Liu, H., Shi, Z. M., & Su, J. C. (2024). Diets intervene osteoporosis via gut-bone axis. Gut microbes, 16(1), 2295432. https://doi.org/10.1080/19490976.2023.2295432
37. Sun N, Zhao Y, Zhang A and He Y (2025) Gut microbiota and osteoarthritis: epidemiology, mechanistic analysis, and new horizons for pharmacological interventions. Front. Cell. Infect. Microbiol. 15:1605860. doi: 10.3389/fcimb.2025.160586