REVIEW

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Influence of Exercise on Musculoskeletal Disorders Associated with Gut Microbiota: A Narrative Review

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SUMMARY
The gut microbiota, a collection of populations of gut microbes, is responsible for a range of metabolic, immunological, structural and neurological functions, such as maintenance of metabolic homeostasis, development and maturation of the immune system, resistance to infection and production of neurotransmitters, microbial dysbiosis, defined as a negative alteration in the diversity, structure or function of the gut microbiota, appears to contribute to the onset and maintenance of various disease states. The gut microbiota appears to be involved in the initiation and progression of some inflammatory diseases, and microbial dysbiosis has emerged as a poorly understood risk factor inducing the production of proinflammatory cytokines and bacterial metabolites. These may persist and fuel the pathophysiological mechanisms of numerous diseases.
The aim of this study is to provide an overview of musculoskeletal disorders associated with gut microbiota dysbiosis and the possibility of treatment through physical exercise.

KEY WORDS
Gut microbiota; dysbiosis; osteoporosis; osteoarthritis; rheumatoid arthritis; exercise.

INTRODUCTION

The gut microbiome (GM) is a microbial community, composed nearly one hundred trillion microbes (1) also called "the second largest human genome" (2). In healthy people, microbiome, host, and environment are in a stable dynamic equilibrium; when this equilibrium is lost, pathologies can occur.
The normal gut hosts four main classes of microbes:
1. Actinobacteria;
2. Firmicutes;
3. Bacteroides;
4. Proteobacteria;

with Bacteroidetes and Firmicutes comprising over 90% of the phylogenetic categories (3). Examples of gut microbiota composition are represented in **figure 1**.
Every condition that induces GM dysbiosis, such antibiotics or inappropriate diet, can expose the host to an increased risk of bone loss, inflammatory bowel disease, diabetes, and obesity (4, 5).
The symbiotic relationship between the gut microbiota and the host is regulated by a complex network of interactions

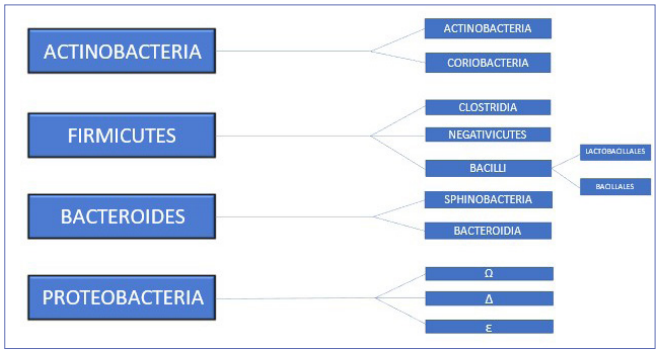

Figure 1. Composition of major component of GM.

that include metabolic, immune, and neuroendocrine crosstalk between them. This crosstalk is potentially mediated by microbial-synthesized metabolites which exhibit pleiotropic effects, including acting as signaling molecules in regulating host neuro-immune-inflammatory axes that could physiologically link gut with other organs and systems (5, 6).
Many metabolites can contribute to gut microbiota (**table I**).
Dysbiosis may influence the course of several musculoskeletal conditions: osteoporosis, osteoarthritis, sarcopenia, and rheumatoid arthritis (18-21).
Gut microbiota dysbiosis is related to lower muscle mass and poor physical function (20), the microbiota is closely related to bone metabolism and the absorption of nutrients and minerals essential to the health of the skeleton (22-23).
The role of microbiota in bone health may bridge the gap between bone physiology, gastroenterology, immunology, and microbiology (24).
The aim of this study is to provide an overview of the correlation between gut microbiota and musculoskeletal disorders; if there is a possibility of positively influencing the putative "gut-joint" axis through exercise, to induce a rebalancing of intestinal dysbiosis to influence the development of pathologies and associated risk factors.

MATERIALS AND METHODS

Search strategy

- The literature search of the present narrative review was conducted according to this protocol:
- gut microbiota.
- Linkage about gut microbiota dysbiosis and pathologies.
- Musculoskeletal disorders associated to gut microbiota.

Literature search

In December 2022 the following databases were accessed: Pubmed, Embase, Scopus, Web of Science, Google Schol-

Table I. Functions of metabolites contributed Gut Microbiota.

Metabolites	Functions	References
Short Chain Fatty Acids		
Acetate	Regulate host metabolic pathways	Chambers *et al.* (7)
Butyrate	via G-protein-coupled receptor;	Blottiere *et al.* (8)
Proprionate	immunomodulatory effect, gut immunity;	Hinnebusch *et al.* (9)
	histone deacetylase (HDAC) inhibitor-	Siavoshian *et al.* (10)
	regulation of intestinal cell proliferation	
Phenolic derivatives		
4-OH phenylacetic acid	Antimicrobial effects; ability to denature	Larrosa *et al.* (11)
propionic acid	proteins, bind (through hydrogen bonds)	Rogovskii *et al.* (12)
2-(3,4-dihydroxyphenyl)acetic acid	to bacterial proteins, altering their	Larrosa *et al.* (13)
5-(3,4-dihydroxyphenyl)valeric acid	structure and compromising their natural	Monagas *et al.* (14)
Urolithins	activity; protective effect against oxidative	
	stress; estrogen-modulating effect	
Vitamins		
Thiamine (B1)	Enzymatic cofactor for diverse biochemical	Forster *et al.* (15)
Riboflavin (B2)	reactions; immune functioning; DNA	Boughanem *et al.* (16)
Niacin (B3)	regulation, production of nucleotides	Lerner *et al.* (17)
Pantothenic acid (B5)	vitamins and amino acids	
Pyridoxine (B6)		
Biotin (B7)		
Folate (B11-B9)		
Cobalamin (B12)		
Menaquinone (K2)		

ar. The following keywords were used in combination: gut microbiota, musculoskeletal disorders, osteoporosis, rheumatoid arthritis, osteoarthritis, dysbiosis, probiotics, prebiotics, exercise, sarcopenia, frailty syndrome, human genome, immune system, postmenopausal disorders, SCFAs, inflammatory mediators. If title and abstract matched the topic, the full text was accessed. The bibliographies of the full-text articles were also screened for inclusion. Disagreements were solved by a third author (FO). All the articles that investigate possible association between gut microbiota and musculoskeletal pathologies were considered. According to the authors language capabilities, articles in English, French, German, Italian, and Spanish were considered.

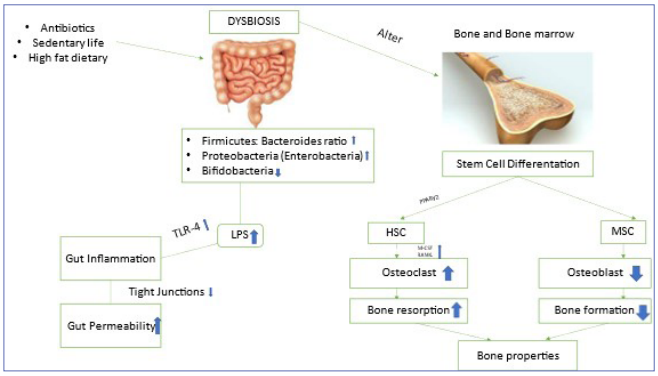

Figure 2. Major alterations inducted by GM dysbiosis on bone and bone marrow.

DISCUSSION

Based on the published literature, a review has been carried out on the various musculoskeletal (MSK) pathologies associated with gut microbiota. Studies on composition of gut microbiota have shown a more or less marked role on development of MSK pathologies. Osteoporosis and osteoarthritis seem to be the two major musculoskeletal pathologies associated with alterations of gut microbiota, given the role on immune system.

Immune system and bone

The immune system is central to bone mineral density control under abnormal conditions. Approximately 8%-20% of bone marrow mononuclear cells are lymphocytes, with a T cell/B cell ratio of 5:1 (25). Approximately 1% of the bone marrow mononuclear population are plasma cells, which can produce antibodies. Approximately one-third of $CD4^+$ T cells are $CD4^+CD25^+$ regulatory T (Treg) cells (26), and the CD4/CD8 ratio in the bone marrow is 1:2, which is inverted as compared to both peripheral lymph nodes and the blood (27-19). In addition to T cells, there are 1%-2% $CD11c^+$ dendritic cells (30) and 0.4%-4% natural killer T (NKT) cells in bone marrow (31, 32). Therefore, bone marrow contains substantial amount of immune cells. Altogether, bone marrow is a lymphoid organ which may play a key role in immunity.

Dysbiosis is associated with gut barrier alterations that promote the dissemination of bacteria and of the factors they produce. The gut barrier is altered in both inflammatory joint disease and estrogen deficiency (33-35). In both situations, the alterations are accompanied by enhanced $CD4^+$ T-cell activation and increased production of the proinflammatory and osteoclastogenic cytokines IL-17, TNF-α, IL1-β and RANKL (33, 36). By modulating the gut immune response, dysbiosis also alters monocyte and lymphocyte migration to tissues, including the bone marrow (**figure 2**).

Osteoporosis and gut microbiota

Osteoporosis is a pathology characterized by the loss of bone density, an increase in osteoclast function, which subsequently increases bone resorption, with a corresponding decrease in bone formation and a major risk of bone fracture (37-39).

The most prevalent causes of osteoporosis are menopause and age, as the bone remodeling process is regulated by estrogen, parathyroid hormone, inflammatory cytokines, and vitamin D (40-43).

Human gut microbiota and bone are in a close relationship, due to various activity promoting by GM:

- GM mediated the proliferation of colonocytes and enterocytes that mediates gut homeostasis and support mineral absorption (44).
- Primary role on restoring and maintaining of GM epithelium barrier (45, 46).
- Osteo-immunity is supported through SCFAs (microbiota metabolites). SCFAs inhibiting activation of NFκB, reducing autoimmune inflammation. Furthermore, propionate and butyrate (SCFAs) through downregulation TRAF6 and NFATc1 metabolically reprogram osteoclast, to inhibit osteoclastogenesis and bone resorption (47, 48).
- In dysbiosis state, the immune system's reaction to microbiota stimulation leads to an increase in circulating osteoclastogenic cytokines through the action of T-cells (49, 50).

Osteoarthritis and gut microbiota

Osteoarthritis (OA) is a chronic degenerative disorder, characterized by loss of articular cartilage and periarticular bone remodeling (51). OA causes joint pain, typically worse with weight-bearing and activity as well as can manifest with stiffness after inactivity (52, 53). It can present as localized, generalized or as erosive osteoarthritis (54, 55).

EBM suggest a correlation between OA and gut microbiota, through proinflammatory mediators such as LPS (lipo-

polysaccharides) in animals with OA (56) and in humans too (57, 58).
Huang *et al.* (57) support a role for LPS in the pathogenesis and severity of structural abnormalities and symptoms of knee OA, linked by activation of macrophages in knee joint capsule and synovium via high levels of serum and synovial fluid LPS.
In Rotterdam study III (59), 1444 patients were enrolled, and an association between abundance of microbes in the proinflammatory Streptococcus taxa and increased WOMAC score was identified (60) (**figure 3**).

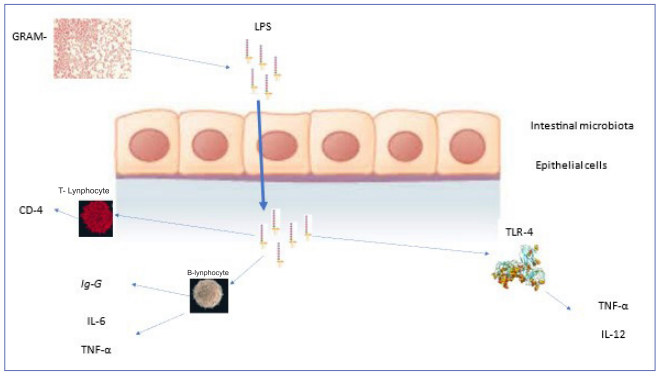

Figure 3. Interaction between Lipopolysaccharide and Gut Microbiota in Gut dysbiosis.

Rheumatoid arthritis and gut microbiota

Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disease characterized by painful, swollen joints impacting physical function and quality of life (61, 62).
RA has a multifactorial etiology; both genetic and environmental factors are known to be involved in pathogenesis. Various inflammatory pathways can lead to an altered immune system and onset of disease (63, 64). The presence of autoantibodies prior to the onset of RA suggest that an autoreactive immune response occurs much before the clinical symptoms appear.
Gut microbiota seems to play a key role in the development and progression of RA. In concert with the gut-associated lymphoid tissue, the gut microbiome is involved in maintaining immune homeostasis and acts as an indicator of the health status of the host (21, 65).
Kohashi *et al.* (66), in 1970, supported a link between microbiota and pathology of arthritis, germ-free-condition-raised rats developed severe arthritis with 100% incidence, whereas conventionally raised rats developed less-severe arthritis with an incidence of only 20%.
Gut dysbiosis in RA patients correlates with the depletion of Gram-negative bacteria and enrichment of Gram-positive bacteria (67, 68).
Chen *et al.* (67) suggest a role of genus Collinsella in pathogenesis of RA and in its severity, genus Collinsella playing an important role in the cumulative inflammatory burden within established RA (68).

Sarcopenia and gut microbiota

Sarcopenia is characterized by a progressive loss of muscle mass, function, and physical performance during aging (69, 70). The incidence of sarcopenia reaches up to 5-13% in 60-70 years old population and 11-50% in those at 80 years or above (71).
In recent years a consistent role gut microbiota involved in pathogenesis of sarcopenia and frailty is increasingly relevant (72). Alterations in the gut microbiota composition could promote chronic inflammation and anabolic resistance, ultimately conditioning reduced muscle size, impaired muscle function and adverse clinical outcomes (73, 74).
The reduction of muscle mass and strength in sarcopenia increases with age. Several factors are involved in the development of muscle atrophy and age-related sarcopenia:

- Persistent low-grade inflammatory status in the elderly, characterized by increased circulating levels of pro-inflammatory cytokines, such as TNF-alpha, IL-6, and myostatin, defined as "inflammaging", which increase the permeability of the intestinal membrane and cause both local and systemic inflammatory effects (74-76).
- Muscle wasting, with a rise in atrogenes expression, muscle skeletal proteolysis and mitochondrial disfunction.
- Physical inactivity, with a rise in bone loss and creeping fat accumulation and a reduction of VDR expression and muscle mass/strength.

The modulation of GM modulation could impact significantly on the onset of sarcopenia.
The administration of *Lactobacillus reuteri* in mouse models of cancer could inhibit the development of sarcopenia and increase in muscle weight and fiber size, through an up-regulation of the transcriptional factor Forkhead Box N1 (FoxN1) (78).
Supplement of probiotics (*Faecalibacterium prausnitzi*) modified gut microbiota composition and improved intestinal integrity, with an increased muscle mass (79).

Influence of exercise on gut microbial composition

Regarding exercise proposals in terms of intensity and frequency, regular low-intensity exercise has been found to act on the gastrointestinal tract by reducing the transit time of feces. This decreases the contact window between pathogens and the intestinal mucous layer, assumes a protective role for intestinal morphology and integrity by reducing COX-2 expression and limiting inflammatory infiltrate, and regulates protein activity in response to thermal stress by maintaining tight junction integrity and preserving intestinal barrier function (77-79).

The human microbial composition tends to remain relatively stable over time, showing resilience to perturbations or returning wholly or partially to its previous state after cessation of the stimulus, implying that the positive changes of exercise must be maintained over a long period to be effective (80).

However, alongside the documented positive effects, negative aspects related to the microbial physiology of the host have also been described, induced by high exercise intensity not supported by an adequate level of training or overtraining syndrome, subverting the role of exercise from beneficial modulator to stressor (81).

Indeed, the hormonal effects of reactive oxidative species (ROS) (82) generated by exercise and by specific commensals of the gut microbiota at physiologically normal levels promote positive effects by participating in specific signaling pathways, while at higher concentrations, reached in the presence of toxic or pathological conditions, they exert harmful effects, whereby the transition from a 'beneficial' to a 'harmful' response depends on many variables, which also include the duration and intensity of the effort and the body's overall antioxidant status (83, 84). In this scenario, excessive exercise not proportional to the level of training, as well as inadequate recovery exerts a profound impact on oxidative stress, muscle damage, systemic inflammation and immune responses, causing physical and psychological stress to be interconnected to the point of performance decline, fatigue, insomnia, anxiety, inflammation and immunosuppression (85-87).

To date, there is not yet enough evidence to attest to the frequency, duration and intensity of exercise sessions to address the pathological conditions underlying intestinal dysbiotic states. Most of the studies that have obtained significant results have been in a range of 4 to 12 weeks, with a protocol favoring carefully selected aerobic exercises at an intensity of between 60% and 80% of maximum effort (88, 89).

The benefits of aerobic exercise on the gut microbiota can be divided in three distinct categories, evidencing modulation in terms of improvement in each. In particular:

- Obese adolescents evidence changes in bacterial phylum, class and genus. Exercise may modulate inflammatory pathways and upregulate the metabolic potential of the gut microbiota post-exercise, with protective effects on insulin resistance and body composition (78, 90, 91).
- In athletes, exercise results in reduction in stool transit time, decrease in the contact window between pathogens and the intestinal mucous layer, protection of intestinal morphology and integrity and enrichment of the diversity of intestinal microflora improving sports performance (79).
- Finally, in post-menopausal women, an active lifestyle appears to prevent and counteract the negative effect of the estrogenic decline associated with the climacteric period and age-related cognitive decline through an improvement in mitochondrial oxidative capacity and reduced expression of inflammatory cytokines (92).

The potential mechanisms by which exercise appears to perturb the gut microbiota in ameliorative terms can be traced back to the fact that, as the gut-associated lymphoid tissue contains the majority of the body's immune cells, exercise alters the gene expression of intra-epithelial lymphocytes, reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines and antioxidant enzymes, with the result of mediating host-microbe homeostasis (72, 93, 94).

Similarly, exercise increases core temperature, particularly when performed for long periods, and significantly reduces intestinal blood flow, whereas at rest the latter undergoes rapid reperfusion: trained athletes have lower levels of circulating bacterial endotoxins at rest than sedentary individuals and exert a greater heat shock protein response to heat stress, the increase of which within the gut prevents the breakdown of tight junction proteins between epithelial cells. It is therefore plausible that exercise may be counted as a hormonal stressor for the gut, stimulating beneficial adaptations and maintaining the long-term resilience of the intestinal barrier (95-97).

Furthermore, changes in the pool of bile acids (98), powerful regulators of the community structure of the gut microbiota, the absence of which significantly impairs its diversity, are evident with exercise, as is an increase in the rate of turnover of molecules through metabolic pathways via skeletal muscle contraction. In turn, this promotes the release of myokines, metabolites and neuroendocrine hormones that may interact with the gut directly or indirectly via a common interface with the immune system (99, 100).

Monda *et al.* (77) in their study highlighted the importance of exercise, that can be used as a treatment to maintain the balance of the microflora or to rebalance his eventual dysbiosis, thus obtaining an improvement of the health status.

In their review, Bonomini-Gnutzmann *et al.* (101) found that a large part of published literature reported adverse effects on the intestinal microbiota when performing endurance exercises, but, at same time other studies found positive effects with aerobic exercise.

Overall, therefore, the mutual interplay of these mechanisms appears to be responsible for the adaptation of the gut microbiota to training, although further research is required to determine the how reciprocal influences are exerted.

CONCLUSIONS

Gut microbiota is implicated in a diversity of physiological and pathological MSK processes.

Exercise has protective effects on musculoskeletal pathologies given its capacity to balance and return to a eubiosis state of Gut microbiota.
Future perspectives should focus on identify an association between bacterial phyla involved in a specific musculoskeletal disorder and finding out how to act on specific phyla through lifestyle changes. For this reason, more human studies are needed not only in aged and metabolically unhealthy population, but also in each person with a musculoskeletal disorder, to design microbiota-based therapeutic approaches that take advantage of the relationship between gut microbiota, metabolic diseases and aging.

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None.

DATA AVAILABILITY

N/A.

CONTRIBUTIONS

FO: writing, revising, study selection, data collection, data extraction, synthesis methods, risk of study bias assessment, final approval. AB: writing, revising, study selection, data collection, data extraction, risk of study bias assessment, final approval. EG: writing study selection, data collection. MC: writing, revising. GO: writing, revising, final approval. NM: writing, revising, final approval. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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