Correlation between gut microbiota and musculoskeletal diseases

Alessandro de Sire [1,2], Nicola Marotta [2,3], Roberta Zito [1], Marco Invernizzi [4,5], Antonio Ammendolia [1,2]

[1] Physical and Rehabilitative Medicine, Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy; [2] Research Center on Musculoskeletal Health, MusculoSkeletalHealth@UMG, University of Catanzaro "Magna Graecia", Catanzaro, Italy; [3] Department of Experimental and Clinical Medicine, University of Catanzaro "Magna Graecia", Catanzaro, Italy; [4] Department of Health Sciences, University of Eastern Piedmont "A. Avogadro", Novara, Italy; [5] Translational Medicine, Dipartimento Attività Integrate Ricerca e Innovazione (DAIRI), Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy

ABSTRACT

Dysbiosis of the microbiota is linked to an increase in intestinal permeability and a simultaneous reduction in antioxidant functions, contributing to the creation of a chronic inflammatory state that results in weakening and fragility of the musculoskeletal system. Dysbiosis can, in fact, negatively influence the immune system, leading to an increase in the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which can damage joint tissue.

In this regard, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recently stated that several risk factors for osteoarthritis (OA) can interact with the intestinal microbiota, which appears to be a critical determinant of metabolism and bioavailability of OA drugs. Recent scientific evidence shows that changes in the composition of the microbiota, altering intestinal permeability and thus allowing leakage of bacteria and their components into the bloodstream, can trigger a systemic inflammatory reaction capable of contributing to the progression of joint degeneration.

It is known that physical exercise can play a key role not only in improving the functioning of patients suffering from OA, but also in terms of modulating the composition of the microbiota, strengthening the immunity of the intestinal mucosa; furthermore, obesity, which is an important risk factor for the development of OA, has been linked to both dysbiosis of the gut microbiota and chronic inflammation, suggesting that complex connections exist between microbiota, obesity, and musculoskeletal pathologies.

Intestinal dysbiosis can have a negative impact on bone health by influencing the RANK/RANKL/OPG pathway; in this context, it has been hypothesized that food supplements, prebiotics and probiotics can support an adequate balance of the intestinal microbiota and consequently bone health.

In conclusion, the correlation between gut dysbiosis and musculoskeletal diseases, such as OA, sarcopenia, and osteoporosis, is still the subject of research and further studies are necessary to fully understand the underlying mechanisms.

KEYWORDS

Microbiota, musculoskeletal diseases, gut, osteosarcopenia.

Introduction

The gut microbiota, comprising a collection of gut microbe populations, plays a vital role in various metabolic, immunological, structural, and neurological functions. These include maintaining metabolic balance, fostering immune system development and maturation, bolstering resistance to infections, and generating neurotransmitters [1].

The bacterial phyla most represented in the gut microenvironment are *Firmicutes* and *Bacteroidetes*, followed by *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, and *Cyanobacteria* [2]. Microbial dysbiosis, defined as an adverse alteration in the diversity, structure, or function of the gut microbiota, contributes to various pathological states and diseases.

The gut microbiota plays a role in the onset and advancement of inflammation-related diseases, and microbial imbalance has emerged as a risk factor that triggers the release of proinflammatory cytokines and bacterial byproducts. These elements could exacerbate the pathophysiological processes of osteoarthritis (OA).

Risk factors for OA, such as aging, diet, and obesity, have been demonstrated to disrupt the gut microbiota, although there is scant evidence supporting an influence of the gut microbiota on the mechanisms of these risk factors.

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Contact

Alessandro de Sire; alessandro.desire@unicz.it

Associate Professor of Physical and Rehabilitative Medicine

Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy

Licens terms

This concise review was therefore conducted with the aim of evaluating the correlation between the gut microbiota and musculoskeletal diseases.

Osteoarthritis and the gut microbiota

Osteoarthritis is a joint condition prevalent among adults and commonly associated with persistent joint discomfort, decreased productivity, and limited mobility [3-5]. The knee is the most commonly affected joint, followed by the interphalangeal joints of the hand and the hip [6]. The development of OA is related to a plethora of factors such as age, sex, genetics, trauma, and increased mechanical load, as well as various concomitant diseases [7]. OA is a disease in which most treatments are aimed at relieving the symptoms, which reinforces the importance of early diagnosis of the condition. Achieving early detection of OA is a challenging task as the link between pain and structural degeneration is not strong. Lifestyles are known to greatly influence the prevalence of OA: unhealthy diets with a low fiber content and high fat and sugar content, along with sedentary lifestyles, are making OA more prevalent today. Several studies link nutritionally poor diets to the occurrence of low-grade inflammation in the intestinal mucosa [8].

The same risk factors are also well known to contribute to altering the gut microbiota towards potentially dysbiotic configurations associated with the disease [9]. The human microbiome, i.e., the now well-established set of microbial ecosystems populating the different niches of the organism, communicates with the different systems and organs of the human body, influencing our physiology [10]. In particular, alteration, i.e., dysbiosis, of the gut microbiota, if persistent over time, can promote excessive porosity of the epithelial barrier and thus leakage of microorganisms and their products into the circulatory system [11]. There are studies that explain the existence of low-grade intestinal inflammation in OA and suggest a potential role for the microbiome in OA-related pain [12,13]. Elevated systemic levels of lipopolysaccharide (LPS) may underlie a possible correlation between the gut microbiome and OA [14]. In addition, stress and pain could be directly responsible for modulating the microbiota, through the release of hormones and sympathetic neurotransmitters that alter gut physiology and microbial gene expression [15], thus contributing to the aforementioned increase in intestinal permeability. Although the mechanisms of action remain to be defined, the presence of inflammatory products and microbial DNA in the joint seems to point to a direct relationship between the intestine and inflammatory arthropathies [16,17]. Despite the need to design new and more effective therapeutic strategies for OA, few scientific studies are currently available in the literature [18].

Gut microbiota and sarcopenia

The intricate environment of the gut microbiota is crucial for intestinal immune and endocrine functions, nutritional well-being, energy balance, and maintenance of overall health [19]. In fact, the gut microbiota serves an intermediate role by breaking down carbohydrates, proteins, and lipids to supply energy for the host [20]. To regulate tissues beyond the gastrointestinal tract, microbial products can cross the intestinal barrier, or be further metabolized by other organs to then enter the circulatory system [21,22]. For instance, LPS and trimethylamine-*N*-oxide induce a pro-inflammatory state, while short-chain fatty acids (SCFAs) and bile acids regulate host metabolism [23].

More importantly, advanced age not only affects the muscle but also causes gut microbiome dysbiosis [24], characterized by altered microbial diversity and lower levels of beneficial bacterial metabolites [25,26]. Gut microbiota-derived micronutrients and metabolites can reach and act on muscle [27], and the concept of the "gut-muscle axis" has been raised to study this relationship [28]. According to recent advances, interventions via this axis can potentially reverse sarcopenic phenotype [27]. *Lactobacillus* and *Bifidobacterium* supplements notably enhanced muscle mass, strength, and endurance capacity in aged mice [29,30]. Hence, interventions targeting the gut-muscle axis could offer a new approach to slowing down age-related muscle loss and dysfunction [28]. There is currently a need for deeper understanding of the intricate molecular mechanisms involved in this axis.

The gut microbiota and osteoporosis

Osteoporosis is characterized by an increase in osteoclast function, which subsequently increases bone resorption, with a corresponding decrease in bone formation [31]. 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 [32]. Bone is a plastic substance that undergoes continual remodeling in response to both physiological and extracorporeal factors; increased bone resorption and concomitant bone loss, regardless of the underlying mechanisms [33,34], constitute a complex pathophysiology that can be influenced by genetic predisposition, as well as pharmaceuticals (e.g., glucocorticoids), lifestyle, and diet [32,35]. This complexity can make the underlying causes of osteoporosis particularly difficult to isolate and clinically treat; hence, many treatments address the symptoms, doing little to influence the underlying pathology.

Increasing evidence indicates that the gut microbiota influences bone metabolism and should be taken into account in efforts to understand and treat osteoporosis. Recent studies suggest that maintaining a healthy microbiome is essential for bone balance, as disruptions in gut bacteria can enhance osteoclast function and contribute to osteoporosis. According to research findings, the interaction between the human gut microbiota and key bone cells like osteoblasts, osteoclasts, and receptor activator of nuclear factor-kappa-B ligand (RANKL) plays a crucial role in regulating osteoclast formation and the development of osteoporosis. Furthermore, in many studies, micro-RNA, insulin-like growth factor 1, and immune system mediation are hypothesized as pathways of the interaction of the gut microbiome with osteoclastogenesis and bone health. Although this is a complex relationship with several proposed mechanisms of modulation, addressing the microbiome in a

treatment plan is not overly burdensome; and yet it is predominantly overlooked [36].

Microbiota modulators with an impact on bone

While there are still knowledge gaps regarding the pathophysiological mechanisms governing the relationship between the gut microbiota and bone, dietary supplements, prebiotics (indigestible dietary fibers that encourage specific bacterial growth), and probiotics (microorganisms potentially providing health advantages to the host), have been suggested to play a role in maintaining intestinal equilibrium, crucial for bone well-being [37,38]. In fact, food supplements and probiotics could play a role in the management of osteoporosis, in combination with a correct lifestyle and specific pharmacological treatments. Prebiotics can be converted into SCFAs by the intestinal microbiota, which increases their intestinal and serum levels and lowers intestinal pH [36]. Prebiotics regulate the number and function of regulatory T cells in the colon, thereby controlling inflammation [39], and modulate the IGF-1 synthesis involved in bone remodeling [40]. Therefore, saccharide supplementation could have beneficial effects on bone metabolism, although further studies are needed to confirm these findings.

Microbiota and physical exercise

Physical exercise can play a significant role in preventing and treating various chronic conditions, including OA [41]. It can have a considerable impact not only by improving patient functionality, but also by modulating the composition of the microbiota [42,43]; it is recommended by multiple guidelines as the primary therapeutic option for the management of this condition [44,45].

Recent research indicates that physical activity has the potential to alter the composition of the gut microbiota, improve immune defense within the intestinal lining, increase the ratio of *Bacteroidetes* to *Firmicutes*, alter the bile acid profile, and improve synthesis of SCFAs [46,47].

Several research studies have shown that the gut microbiota can modulate oxidative stress and inflammatory responses, leading to enhanced metabolism and energy expenditure [48].

However, the existing literature on these topics is still limited and therefore further observational studies are needed to determine whether modulation of the gut microbiota through therapeutic exercise can reduce the chronic inflammatory state (improving intestinal dysbiosis and consequent intestinal permeability) and consequently improve patient functionality.

Conclusion

Taken together, the findings published in the recent literature demonstrate that there could be a correlation between gut dysbiosis and musculoskeletal diseases (i.e., OA, sarcopenia, and osteoporosis), but this should continue to be considered a hot research topic in the near future. Further studies are mandatory to fully understand the mechanisms underpinning this link.

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