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Mini-Review

Mini-Review: the gut microbiota-muscle axis and its role in aging research

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HIGHLIGHTS

- Aging-related gut microbiota changes affect muscle atrophy pathways.
- The link between gut microbiota and physical function in older adults is unclear.
- Physical training alters gut microbiota, aiding in muscle atrophy prevention.
- Probiotics enhanced microbial diversity, boosting muscle mass and reducing body fat.
- The gut microbiota-muscle axis is an emerging field in aging research.

ABBREVIATIONS

CRP	C-Reactive Protein
IL-6	Interleukin-6
MIP-1 α	Macrophage Inflammatory Protein-1 alpha
MuRF1	Muscle Ring-finger protein-1
MyoD	Myogenic Differentiation 1
SCFA	Short-Chain Fatty Acids
TNF-α	Tumoral Necrosis Factor Alpha

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BACKGROUND: Aging is a multifactorial process, one of whose key consequences is the decline in muscle strength and mass, which directly impacts the functional capacity of older adults. One possible mechanism involved in this process is the role of gut microbiota in muscle atrophy.
AIM: To explore the role of the gut microbiota-muscle axis during aging, investigating its relationship with functional outcomes and the potential for intervention.
METHOD: A mini-review of the literature was conducted using the PubMed, Scopus, and Embase databases with the keywords "microbiota", "microbiome", "gut-muscle axis", "aging" and "muscle".
RESULTS: Aging affects the gut microbiota, notably its bacterial composition (with increases in *Proteobacteria*, *Clostridium*, and *Enterococcus*), along with an increased release of lipopolysaccharides and a reduction in short-chain fatty acid production. These changes are linked to signaling pathways involved in muscle atrophy. Despite evidence showing how the gut microbiota-muscle axis influences muscle mass loss during aging, the direct relationship with functional capacity remains limited. However, physical training and diet are non-pharmacological interventions that can modify the gut microbiota.
CONCLUSION: The mechanisms underlying the gut microbiota-muscle axis present opportunities for further investigation into aging health and motor performance, particularly concerning nutrition and physical training.

KEYWORDS: Gut-muscle axis | Muscle atrophy | Aging | Functional capacity

INTRODUCTION

The aging process is characterized by numerous biological changes, including alterations in muscle structure. Notably, a reduction in cross-sectional area [1] can adversely impact muscle function, particularly in terms of force production [2]. This decline in muscle parameters is closely tied to diminished performance in functional tasks, leading to impaired functional capacity [3]. While this process is influenced by multiple factors, emerging mechanisms offer promising avenues for developing strategies to mitigate its effects. One such mechanism involves the role of gut microbiota in muscle atrophy [4].

The gut microbiota is primarily composed of bacteria, with the Bacteroidetes and Firmicutes phyla making up approximately 90% of the dominant taxonomic groups, particularly in the large intestine [5]. Key functions of a healthy gut microbiota include genes involved in glycosaminoglycan degradation, the production of short-chain fatty acids (SCFAs) through the fermentation of complex polysaccharides, the synthesis of specific lipopolysaccharides, and the biosynthesis of essential amino acids and vitamins [6].

During aging, changes in bacterial composition occur, including an increase in Proteobacteria (which produce pro-inflammatory bacteriophages [7]), an increase in Clostridium and Enterococcus (bacteria with high pro-inflammatory potential linked to various systemic infections [6]), an increased release of lipopolysaccharides into the bloodstream, serving as an intermediate marker of muscle atrophy [5,8], and a reduction in SCFA production (which may prevent skeletal muscle atrophy [9]). The role of these changes on skeletal muscle was

observed through the association between alterations in gut microbiota composition, increase in pro-inflammatory markers and reduced muscle mass in both animals and humans [10], which may also impact performance in functional tasks [3].

The gut microbiota-muscle axis is an emerging concept under investigation for its potential influence on age-related muscle loss [11]. A systematic review has shown that changes in gut microbiota can directly affect muscle phenotypes, with some therapies, such as probiotics and prebiotics, showing promise in enhancing muscle mass [12]. However, the effects of gut microbiota modifications on functional capacity in older adults are not yet well understood. This mini-review aims to explore the role of the gut microbiota-muscle axis during aging and its implications for physical function. We hypothesize that age-related changes in gut microbiota contribute to muscle atrophy and the decline in physical function commonly observed with aging, highlighting opportunities for targeted interventions on this axis.

METHODS

A mini-review of the literature was conducted using the PubMed, Scopus, and Embase databases with the keywords "microbiota", "microbiome", "gut-muscle axis", "aging" and "muscle". Studies of all types published in English, Portuguese, and Spanish since 2018 were included. The search strategy used in PubMed was as follows: "Microbiota"[Mesh] OR “microbiome” OR “gut-muscle axis” AND "Aging"[Mesh] AND "Muscles"[Mesh].

Box 1. Key definitions adapted from MeSH library.

Bacteroidetes and Firmicutes: the two bacterial phyla that constitute the majority of the human gut microbiota.

Dysbiosis: Changes in quantitative and qualitative composition of microbiota. The changes may lead to altered host microbial interaction or homeostatic imbalance that can contribute to a disease state often with inflammation.

Gut: gastrointestinal tract

Lipopolysaccharides: Lipid-containing polysaccharides which are endotoxins and important group-specific antigens. They are often derived from the cell wall of gram-negative bacteria and induce immunoglobulin secretion.

Microbiota: the full collection of microbes (bacteria, fungi, virus, etc.) that naturally exist within a particular biological niche such as an organism, soil, a body of water, etc.

Prebiotics: Non-digestible food ingredients mostly of a carbohydrate base that improve human health by selectively stimulating the growth and/or activity of existing bacteria in the colon.

Probiotics: Live microbial dietary supplements which beneficially affect the host animal by improving its intestinal microbial balance

Short-Chain Fatty Acids (SCFA): Short-chain fatty acids of up to six carbon atoms in length. They are the major end products of microbial fermentation and are produced when gut microbiota ferments undigested carbohydrates, such as dietary fibers, in the colon. The main SCFAs produced are acetate, propionate, and butyrate.

RESULTS AND DISCUSSION

The results will be presented under the following topics: (i) changes in gut microbiota during aging; (ii) the gut microbiota-muscle axis and functional capacity in aging; and (iii) interventions targeting the gut microbiota-muscle axis. The main selected studies are summarized in Table 1.

Changes in Gut Microbiota During Aging

Aging is associated with a reduction in microbial diversity [15], including a decrease in *Bifidobacteria* (SCFA producers) and an increase in *Prevotella*, which inhabits both the oral cavity and gut and contributes to inflammatory processes across the gastrointestinal tract [6]. Additionally, there is an increase in *Clostridium* and *Enterococcus*, bacteria with significant pro-inflammatory potential linked to various systemic infections [6]. It is important to note that aging also leads to physiological and functional changes throughout the gastrointestinal tract, from the mouth to the anus, which directly influences bacterial composition and gut diversity [17].

Table 1. Summary of Gut Microbiota Changes and Their Effects on Skeletal Muscle During Aging.

Study	Population	Gut microbiota change	Biochemical change	Skeletal muscle change
Nikkhah et al. (2022) [13]	Individuals with sarcopenia or cachexia	Reduction in SCFA-producing bacteria Increase in *Enterobacteriaceae* (pro-inflammatory)	Increase in pro-inflammatory cytokines (IL-6 and TNF-α). Reduction in butyrate and vitamin B12.	Decrease in the size and number of muscle fibers
Giron et al. (2022) [14]	Studies in older humans and animal models with sarcopenia	Decreased butyrate-producing bacteria in sarcopenic populations. Increase in *Enterobacteriaceae* in cases of severe frailty.	Increase in pro-inflammatory markers (IL-6 and CRP). Reduction in insulin sensitivity.	Loss of muscle mass and strength, with a decrease in type I fibers in some models
Grosicki et al. (2018) [15]	Older individuals with sarcopenia, sarcopenic obesity, and animal models on obesogenic diets	Reduced microbial diversity. Increased in *Enterobacteriaceae* Decreased butyrate-producing bacteria	Elevated circulating of lipopolysaccharides Elevated circulating of pro-inflammatory cytokines (IL-6 and TNF-α).	Loss of muscle mass due to increased atrogenesis (MuRF1, Atrogin-1). Fat infiltration, and changes in muscle fiber distribution
Liu et al. (2021) [12]	Preclinical and clinical studies, including rat models and older humans	Dysbiosis with reduced *Lactobacillus* and *Bifidobacterium*. Lower microbial diversity.	Increased in pro-inflammatory markers (IL-6 and TNF-α) Disruptions in amino acid and SCFA metabolism.	Reduced muscle mass, muscle fiber atrophy, Impaired mitochondrial function.
Picca et al. (2020) [16]	BIOSPHERE study with frail and non-frail older individuals	Increase in *Peptostreptococcaceae* and *Bifidobacteriaceae*. Reduction in SCFA-producing bacteria.	Increase in pro-inflammatory markers (MIP-1α and IL-6)	Decrease in appendicular lean mass

Legend: BIOSPHERE: BIOmarkers associated with Sarcopenia and Physical frailty in Elderly persons; CRP: C-Reactive Protein; IL-6: interleukin-6; MIP-1 α: Macrophage Inflammatory Protein-1 alpha; MuRF1: Muscle Ring-finger protein-1; SCFA: Short-Chain Fatty Acid; TNF-α: Tumoral Necrosis Factor Alpha.

In the stomach, delayed gastric emptying associated with aging can affect appetite regulation and pH, impacting the richness and abundance of mucus-producing bacteria [11]. Additionally, there is a notable reduction in the secretion of stomach acid and mucus [18]. This decline in pH regulation alters the gut's bacterial composition, particularly favoring pathogenic bacteria, which disrupts the digestion and absorption of macronutrients and micronutrients, leading to issues such as increased bowel movements, constipation, and diarrhea [18]. These changes lead to increased secretion of pro-inflammatory products, reduced energy substrates for intestinal epithelial adhesion cells, and heightened intestinal permeability to and from the bloodstream [19]. Dysfunction of the intestinal barrier is linked to mucosal atrophy and damage to adhesion proteins in intestinal cells (such as occludins, zonulins, and claudins), weakening the connections between enterocytes and colonocytes. This dysfunction of the intestinal barrier activates the immune system in older adults, triggering a low-grade inflammatory response and contributing to immunosenescence [19].

Another notable change in the gut microbiota during aging is a reduction in diversity, accompanied by an increase in *Enterobacteriaceae*, a family of bacteria known for their pro-inflammatory effects [13-15], along with a decrease in SCFA-producing bacteria [13-16] such as *Ruminococcus obeum*, *Roseburia intestinalis*, *Eubacterium ventriosum*, *Eubacterium rectale*, and *Eubacterium hallii*, all belonging to *Clostridium cluster* XIVa [9]. These fatty acids (SCFA) help protect against the overgrowth of pathogens, such as Escherichia coli (which is strongly associated with hospital infections in older adults), stimulate the growth of beneficial bacteria [20], and inhibit the production of inflammatory mediators linked to muscle atrophy [12]. Therefore, changes in gut microbiota may also impact skeletal muscle due to potential pro-inflammatory response, potentially impairing muscle function.

Gut Microbiota-Muscle Axis and Functional Capacity in Aging

Some metabolites produced by gut bacteria are associated with pathways involved in muscle synthesis or atrophy, serving as intermediate markers. This has led to the proposal of the 'gut microbiota-muscle axis' concept to explore this relationship [21]. Butyrate, a SCFA that declines with aging [13-16], binds to a specific receptor in skeletal muscle and helps attenuate muscle mass loss through signaling pathways involving Atrogin-1 and Myogenic Differentiation 1 (MyoD) [22]. Likewise, lipopolysaccharides appear to signal a catabolic state [8], primarily by inducing pro-inflammatory conditions [15] and their release into the bloodstream tends to increase with aging [5,8,15]. Therefore, aging-related changes in the gut microbiota are linked to protein synthesis and degradation processes [21]. Notably, an increase in the richness of the *Lachnospiraceae* family (within the *Firmicutes phylum*) appears to mitigate age-related sarcopenia, as this family includes SCFAs producing bacteria [13]. Conversely, a higher richness of *Enterobacteriaceae* (from the *Proteobacteria phylum*) seems to contribute to increased muscle catabolism due to its pro-inflammatory effects [13-15].

The impact of gut bacteria on muscle health is influenced by their metabolic capacity to affect the nitrogen balance of skeletal muscle [13]. Greater diversity and richness of SCFA-producing bacteria are associated with a more beneficial effect on skeletal muscle, as these bacteria produce metabolites that interact with muscle receptors and transporters, promoting protein synthesis and mitochondrial biogenesis [9,12-15]. Conversely, lower bacterial diversity and richness lead to an increased presence of Gram-negative bacteria (e.g *Enterobacteriaceae* family [13-15]), which can enhance intestinal permeability and elevate the levels of inflammatory metabolites. These metabolites also interact with muscle receptors, triggering increased muscle catabolism and mitochondrial apoptosis through pro-inflammatory pathways [9,12-15].

In a systematic review with meta-analysis including 1,239 participants, the gut microbiota of frail and non-frail older individuals was compared. The main findings indicated no significant difference in alpha diversity (which measures richness and abundance within an individual) or beta diversity (which assesses similarity or differences between bacterial groups among individuals) between the groups [23]. However, sensitivity analysis revealed that certain bacterial strains had a more substantial impact on skeletal muscle and frailty, supporting the previously noted associations with morphological parameters [13].

Given the established relationship between muscle parameters and functionality in aging [3], it is possible that alterations in the gut microbiota could affect the functional capacity of older adults. However, few studies have explored the relationship between gut microbiota composition and functional parameters in aging. A recent cross-sectional study with 740 older men (age: 84 ± 4 years) found that faster walking speed and less decline in walking speed were associated with a higher abundance of SCFA-producing bacteria and possess anti-inflammatory properties [24]. Therefore, understanding the role of gut bacteria in the signaling pathways of skeletal muscle and performance in functional tasks, it's possible to improve gut microbiota and enhance skeletal muscle function?

Interventions targeting the gut microbiota-muscle axis

The role of physical training and level of physical activity on gut microbiota was explored in previous meta-analyses [25,26]. One meta-analysis observed the effects of physical training on gut microbiota compared to a control group. The authors found that exercise interventions (primarily consisting of endurance or high-intensity interval training) decreased Bacteroidetes and increased Firmicutes, with more significant changes observed in females and older adults [25]. While these changes can influence signaling pathways involved in muscle atrophy and contribute to its prevention, as previously discussed, the extent to which modifications in gut microbiota induced by physical training impact functional capacity remains poorly understood. To date, two randomized clinical trials have explored the effects of physical training on gut microbiota in older adults, offering valuable insights. In one study, 8 weeks of concurrent training (4x per week) led to increased bacterial diversity, which was associated with greater strength gains and improved performance on the unilateral balance test [27]. In another study, 12 weeks of resistance training sessions (3x per week) combined with chicken meat consumption improved muscle function and whole-body lean mass without affecting gut microbiota composition [28].

Diet is another factor consistently mentioned as key to altering gut microbiota [29]. However, randomized clinical trials examining various diets' effects on gut microbiota and their potential to improve skeletal muscle structure or function are still lacking. A previous study found that six weeks of high-dose probiotic supplementation with *Lactobacillus plantarum* TWK10 increased microbial diversity and resulted in more significant gains in muscle mass and reductions in body fat [30]. Additionally, combining probiotic supplementation with *Lactococcus lactis* LY-66 and *Lactobacillus plantarum* PL-02 with resistance training led to increases in microbial diversity, strength, power, and muscle endurance [31].

CONCLUSION

Aging affects the gut microbiota, particularly its bacterial composition, leading to increased release of lipopolysaccharides and a reduction in short-chain fatty acid production. These changes are associated with signaling pathways involved in muscle atrophy. While evidence demonstrates how the gut microbiota-muscle axis influences muscle mass loss during aging, the direct relationship with functional capacity remains underexplored. However, the mechanisms discussed and the initial evidence are promising for further investigation into aging health and motor performance. These mechanisms underscore the need for new longitudinal studies focusing on non-pharmacological interventions, particularly those involving nutrition and physical training.

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