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Review

Role of Nutritional Supplements on Gut-Muscle Axis Across Age: a Mini-Review

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Abstract
Sarcopenia is a progressive skeletal muscle disorder associated with aging, resulting in loss of muscle mass and function. It has been linked to inflammation, oxidative stress, insulin resistance, hormonal changes (i.e. alterations in the levels or activity of hormones which can occur due to a variety of factors, including aging, stress, disease, medication, and environmental factors), and impaired muscle satellite cell activation. The gut microbiome is also essential for muscle health, and supplements such as probiotics, prebiotics, protein, creatine, and beta-alanine can support muscle growth and function while also promoting gut health. Chronic low-grade inflammation is a leading cause of sarcopenia, which can activate signaling pathways that lead to muscle wasting and reduce muscle protein synthesis. Insulin resistance, hormonal changes, and impaired muscle satellite cell activation contribute to sarcopenia, and high levels of fat mass also play a role in the pathogenesis of sarcopenia. Resistance exercise and dietary supplementation have been shown to be effective treatments for sarcopenia. In addition, a combination of resistance exercise and supplementation has been shown to have a more significant beneficial effect on anthropometric and muscle function parameters, leading to a decrease in sarcopenic state. Thus, understanding the relationship between the gut microbiome and muscle metabolism is crucial for developing new treatments for sarcopenia across age groups.

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Introduction

Sarcopenia is a complex age-related phenomenon that is influenced by a multitude of mechanisms that leads to decreased muscle strength and function due to impaired muscle synthesis and increased muscle catabolism [1, 2]. These mechanisms comprise inflammation, oxidative stress, insulin resistance, hormonal alterations, and hampered activation of muscle satellite cells, among others, which are considered crucial factors in the onset and progression of sarcopenia [3]. In this sense, nutritional status may significantly contribute to maintain muscle structure and its metabolism in sarcopenic subjects as factors as chronic inflammation has been linked to both muscle dysfunction and gut metabolism, and certain supplements, such as omega-3 fatty acids, can reduce systemic inflammatory markers and support both gut and muscle health [4-7]

Gut structure and microbiota changes with aging, and its imbalance has a close relationship with human health and disease [8, 9]. Nutritional supplements provide essential nutrients that are important for gut and muscle health. For example, probiotics and prebiotics can help to maintain a healthy gut microbiome by supporting the growth of beneficial gut bacteria and improving gut microbial diversity [4-6]. Additionally, certain nutrients, such as protein, creatine, and beta-alanine, have been shown to support muscle growth and function [4-6]. In addition, a recent study showed that supplementation for the balance of gut in critically ill patients can shorten the length of intensive care unit (ICU) stay, reduce muscle protein degradation, and reduce infection complications [10]. Additionally, a recent systematic review showed that gut microbiota may play a significant role on muscle homeostasis due to the gut-muscle axis [11].

Therefore, understanding the relation between gut microbiota and muscle metabolism is of paramount importance to develop new treatments for diseases, such as nutritional supplements to avoid sarcopenia across age. Thus, we conducted a literature review on Pubmed for experimental and clinical studies to elucidate the role of supplementation on the interaction between gut and muscle metabolism.

Muscle Aging and Sarcopenia

Sarcopenia, a Geriatric Giant, is a progressive skeletal muscle disorder that involves loss of muscle mass and function [12], associated with increased adverse outcomes as increased risk of falls, functional decline, frailty, and mortality in aged populations [13-15]. According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia diagnosis requires measurement of muscle mass (mid-arm muscle circumference, dual energy X-ray absorptiometry or bioelectrical impedance analysis), muscle strength (hand grip), and physical performance (mobility and balance analysis) to assess, using cut-off values, the severity of disease [15].

Regarding the mechanisms involved in muscle wasting, chronic low-grade inflammation has been linked to the development of sarcopenia as it can activate signaling pathways that lead to muscle wasting and reduce muscle protein synthesis [3]. Furthermore, oxidative stress can cause damage to muscle cells and disrupt the balance between muscle protein synthesis and degradation [3]. Additionally, insulin resistance can reduce muscle protein synthesis and increase muscle protein degradation, leading to muscle wasting [3, 12]. Moreover, hormonal changes, such as decreased testosterone levels in older men and decreased estrogen levels in older women, can contribute to sarcopenia as the reduced levels of these hormones may decrease muscle protein synthesis and increase muscle protein degradation [3]. Beyond that with aging, the activation of muscle satellite cells is impaired, leading to decreased muscle repair and increased muscle wasting [3, 12].

Body composition is another factor related to sarcopenia. In this sense, fat mass, in particular, has been shown to play a role in the pathogenesis of sarcopenia as studies have shown that increased fat mass is associated with decreased muscle mass and strength in older adults [16]. This may be due, in part, to the fact that fat mass and muscle mass are inversely related, meaning that as one increases, the other decreases. Furthermore, high levels of fat mass have been shown to impair insulin sensitivity, leading to chronic low-grade inflammation, which can further contribute to the development of sarcopenia [16, 17]. Additionally, fat mass has been shown to have a negative impact on muscle function, as it can interfere with the mechanical signaling pathways that are required for muscle growth and maintenance [16, 17]. This can result in decreased muscle mass and strength, leading to the development of sarcopenia.

As for cellular changes, the age-related loss of human skeletal muscle mass that may lead to sarcopenia is due to a decrease in myofiber size and number with the loss of both fast and slow type myofibers, although the loss of fast myofibers (glycolytic metabolism) tends to start earlier [18]. Additionally, function of the nervous system, which plays a significant role on muscle strength, declines across age due to the loss of motoneurons, demyelination of axons and withdrawal of nerve terminals from the neuromuscular junctions [1, 2]. In addition, a significant contributor for sarcopenia is an anabolic resistance of older skeletal muscle to protein nutrition, which can be ameliorated by resistance exercise and dietary supplementation [19, 20].

The search for therapeutical approaches to avoid the effects of sarcopenia is critical. In this sense, non-pharmacological treatments as nutritional supplementation with or without resistance exercise, can decrease the age-related changes on muscle structure [21]. A recent systematic review showed that strength-resistance training and its combination in programs with aerobic exercise show significantly beneficial effects on anthropometric and muscle function parameters, leading to a decrease in sarcopenic state [22]. However, the association between a routine of physical exercises and supplementation is seen, as a more effective approach as nutrition plays a major role on the muscle maintenance. A randomized controlled trial that analyzed the effects of supplementation (32.4 g of whey protein) versus a control group for 12 weeks along with a 30 minutes home-based resistance exercise program to 115 male and female subjects over the age of 60, showed that the whey supplemented group had a significant increase in grip strength, gait speed, and time to complete chair stands [23]. Additionally, a supplement with minerals, *Silybum marianum*, and yeast β-glucan of non-dairy bacterial origin which has a prebiotic effect, increased the lean mass of sedentary mice submitted to a nonfat diet [24]. As for sarcopenia, another study analyzed 112 subjects with sarcopenia that received a nutritional supplementation for 12 weeks (10 g whey protein along with 800 IU Vitamin D_3) with or without a program of resistance exercise as compared to exercise alone and a control group. The authors concluded that the combination of exercise and whey protein supplementation significantly improved appendicular muscle mass in sarcopenic adults [7].

Studies focused on the effects of nutrition showed that a higher intake of minerals, such as calcium, are related to regulatory signaling pathway for muscle fibers [25]. Thereby, a cross-sectional analysis of 396, 283 participants through the United Kingdom revealed that a higher intake of both calcium and magnesium was associated with lower odds of sarcopenia [26]. Additionally, a study found that daily calcium intake was positively correlated with appendicular skeletal muscle mass in 1339 older Korean adults [27]. These data suggest that nutritional intervention may play a critical role on age-related changes of muscle, as well as pathological changes due to sarcopenia. However, understanding the physiological changes on gut microbiota and its metabolism is of paramount importance for nutritional supplementation of older subjects.

Gut Microbiota and Muscle, what's the relation?

Although gut villus surface area declines with aging [28], bacterial cells in the gut do not age [29]. On the other hand, people growing older may experience comorbidities associated with the gut microbiota metabolism [29, 30]. This phenomenon may be related to diet as aging is often accompanied by a reduction in the amount and variety of fiber-containing foods, as well as the increased risk of malnutrition [31]. Additionally, lower fiber intake leads to a decrease in core microbiota diversity, which may be detrimental to gut health [32]. The core microbiota are those taxa that are present in the vast majority of the subjects in appreciable proportions, e.g. *Bacteroidetes* and *Firmicutes* are the core microbiota in adults [33, 34]. However, an inappropriate diet may negatively affect the gut microbiota homeostasis, leading to impaired nutrient distribution and noxious bacterial metabolites to the organism, which may contribute to the genesis of several diseases such as sarcopenia [11, 35].

The Gut-Muscle Axis had been proposed as gut microbiota-derived micronutrients and metabolites can act on muscle metabolism [36, 37]. Thereby, recent advances showed that modulating this axis via interventions (e.g. supplementation) has the potential to reverse a sarcopenic phenotype [37, 38]. Additionally, an experimental study in aged mice showed that *Lactobacillus* and *Bifidobacterium* supplements notably enhanced muscle mass, strength, and endurance capacity [39]. In addition, a randomized, double-blind clinical trial showed evidence that old people can benefit from the pathways related to the Gut-Muscle Axis through a prebiotic formulation composed of a mixture of inulin plus fructooligosaccharides [38]. Thereby, elucidating the role of nutritional supplementation on Gut-Muscle Axis may be a novel target to delay age-related muscle wasting and dysfunction.

Role of Nutritional Supplements on Gut-Muscle Axis

The gut-muscle axis is influenced by the gut microbiome. Regarding the molecular pathways in the gut-muscle axis, indoxyl sulfate and lipopolysaccharide, which are noxious bacterial metabolites in a gut with a lack of microbiota homeostasis, results in bacteria depletion [11]. This phenomenon can induce muscle atrophy through activation of phosphoinositide-3-kinase/protein kinase B (PI3K/AKT), nuclear factor kappa B (NF-κB), and mitogen-activated protein kinases [40-46]. This molecular pathway can signal to up-regulate Atrogin-1/MAFbx and Muscle RING Finger-1 (MuRF-1) genes encoding E3 ubiquitin ligases, and inflammatory cytokines [11]. Additionally, adenosine-5′-monophosphate–activated protein kinase (AMPK), forkhead box O3 (FoxO3), Atrogin-1/MuRF1 cascade (AMPK–FoxO3–Atrogin-1/MuRF1) and branched-chain amino acids (BCAA) catabolism are activated in the bacteria depletion [40-46]. This activation may lead to a decrease in expressions of insulin-like growth factor 1 (IGF1), myogenin, and myoblast determination protein 1, with an over expression of myostatin. The sum of these pathways negatively affects the neuromuscular junction and mitochondrial metabolism which results in the decrease of muscle mass [40-46]. In this scenario, the supplementation with probiotic bacteria can help to improve gut and muscle health. Thus, some of the most commonly used probiotic strains in supplementary therapy [47, 48] include:

- *Lactobacillus acidophilus*: is a commonly used probiotic strain that can help to improve gut health and enhance the immune system.
- *Bifidobacterium bifidum*: this strain is found in the gut and can help to improve digestive function and modulate the immune system.
- *Lactobacillus rhamnosus*: this probiotic strain has been shown to reduce inflammation, improve gut health, and enhance muscle recovery after exercise.
- *Streptococcus thermophilus*: has been shown to improve gut health and modulate the immune system.

Regarding nutritional supplementation, the literature shows that certain nutrients and minerals are highly related to the maintenance of the gut-muscle axis [6, 47, 48]. Thus, the most important nutrients and minerals for this axis are:

- Protein: Adequate protein intake is essential for muscle growth and recovery.
- Vitamin D: is important for muscle function and can also help to modulate the immune system.

- Magnesium: is essential for muscle function and can also help to reduce systemic inflammation.
- Omega-3 fatty acids: are essential fatty acids that have been shown to play a role in maintaining gut and muscle health. Omega-3 fatty acids have been shown to improve gut microbiota diversity and support gut barrier function, as well as improve muscle function and reduce muscle wasting.
- Prebiotics: are indigestible fiber compounds that serve as food for beneficial gut bacteria. Consuming prebiotics can help to promote the growth of beneficial bacteria and improve gut health, which can support muscle health.

These components showed the suppression of glucocorticoid receptor and excessive AMPK activation, decreased inflammatory levels, mitochondrial and neuromuscular junction repair, as well as, increased the expression of muscle growth-related genes (IGF1, myogenin, salt inducible kinase 1) to maintain muscle mass and function [39, 45, 49, 50]. Additionally, the symbiotic effect of yeast β-glucan, prebiotic, minerals and *Silybum marianum* synergistically modulated the PPAR coactivator 1α (Pgc-1α), which is involved in the mitochondrial biogenesis [51]. Overall, a balanced and varied diet that includes adequate amounts of nutrients, minerals and probiotics can help to improve the gut and muscle health and modulate the gut-muscle axis. However, further experimental and clinical investigations with different nutritional compositions and dosages are needed to positively modulate the Gut-Muscle Axis to avoid severe sarcopenic cases in the elderly population.

Conclusion

This review suggests that nutritional supplementation plays a crucial role on Gut-Muscle Axis to maintain muscle homeostasis and it is important to investigate the role of nutritional supplements on the gut-muscle axis across age for several reasons. First, aging is associated with a decline in gut and muscle health, which can have a significant impact on overall health and well-being. Understanding the role of nutritional supplements in modulating the gut-muscle axis in older adults is critical for developing effective interventions to improve gut and muscle integrity in this population. Second, the gut microbiome is a complex and dynamic ecosystem that changes throughout life, and these changes can have a significant impact on gut and muscle health. Understanding the effects of nutritional supplements on the gut microbiome across different ages is important for developing targeted and effective interventions for improving gut and muscle health. Third, the efficacy of nutritional supplements can vary depending on age and other factors, such as health status and lifestyle. For example, older adults may require higher doses of certain nutrients compared to younger adults, and certain nutrients may have different effects in older adults compared to younger adults. Investigating the role of nutritional supplements on the gut-muscle axis across age is important for understanding these differences and developing effective interventions for improving gut and muscle health in older adults. Finally, the gut-muscle axis is a complex system that is influenced by a variety of factors, including diet, exercise, and gut microbiome composition. Understanding the role of nutritional supplements in modulating this axis across age is important for developing comprehensive and effective interventions improving gut and muscle health. Thus, further investigations are needed to elucidate different supplementations, prebiotics and probiotics, as well as, the effect of its dosage on the severity of sarcopenia in both experimental studies, using molecular techniques, and clinical trials, with the aid of standardized cut-off values (e.g. EWGSOP) for muscle structure and function.

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Statement of Ethics

This study is an analysis of published data, which does not require ethics committee approval.

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Author Contributions

R. A. B. N., V. A. N. F., and A. F. M. P. contributed to the review design. R. A. B. N., W. J. F., and J. P. O. contributed to literature review. R. A. B. N., W. J. F., and A. F. M. P. contributed to the writing of the manuscript. V. A. N. F., and J. P. O. have reviewed and approved the final draft of the manuscript.

Disclosure Statement

The authors have no conflicts of interest to declare.

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