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The Journal of Nutrition, Health and Aging 28 (2024) 100298

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Mini-Review

Therapeutic perspectives of pre-, pro-, post-biotics in the treatment of sarcopenia

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ARTICLE INFO

Keywords:
Microbiota
Sarcopenia
Probiotic

Over the past two decades, research has increasingly indicated that the human intestinal microbiome is vital for health at all stages of life and may influence various pathophysiological mechanisms that lead to sarcopenia [1]. This mini-review aims to summarize the current understanding of the potential use of probiotics (live bacteria or yeasts that confer health benefits when consumed in sufficient quantities), prebiotics (non-digestible substances that promote beneficial bacterial growth), and postbiotics (products made from non-living microorganisms and their components) as treatments for sarcopenia, while also discussing ongoing clinical trials in this area.

Dysbiosis, characterized by an imbalance in bacterial populations, can have detrimental effects on the host. It is suspected to interact with other biological aging processes, such as inflammation and anabolic resistance, potentially contributing to sarcopenia [1]. Although the connection between the gut microbiota and sarcopenia is not fully understood, aging typically corresponds with reduced microbial diversity and a propensity toward dysbiosis. [1]. These age-related changes are more pronounced in individuals with sarcopenia compared to older adults with normal muscle mass and function [1].

Understanding the causal relationships between changes in the microbiota and the development of sarcopenia is complex, highlighting the necessity for both pre-clinical and, importantly, clinical trials that explore interventions targeting the human gut microbiota. Numerous factors influence the composition and functions of the gut microbiota. Moreover, the communication between the microbiota and the host is bidirectional, subtle, and sustained, complicating the interpretation of changes observed in purely observational studies. The potential roles of the gut microbiota in muscle health are vast and not yet fully understood. For instance, the microbiota can synthesize tryptophan—an essential amino acid that promotes protein anabolism —and convert it into a wide array of metabolites with key metabolic and immune functions [2,3]. These complex interactions within the gut-muscle axis have been extensively reviewed and continue to be a focal point for research [4]. the causal connections between the decline in human muscle strength and mass and the microbiota remain largely theoretical. Nonetheless, the scientific basis for these links is robustly supported by pre-clinical data.

Fecal microbiota transplantation (FMT) from fit older men to sarcopenic mice has led to significant improvements in muscle function [5], as has the transplantation of fecal microbiomes from young to old mice [6,7]. Similarly, FMT from conventional mice to germ-free mice, combined with the addition of short-chain fatty acids (SCFAs) to their diet, has been shown to partially restore muscle mass. These results underscore the role of both microbiota and SCFAs in muscle development. The production of SCFAs by the intestinal microbiota thus represents a

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[1] Given his role as Editor-in-Chief, Prof. Philipe de Souto Barreto had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to the co-Editor-in-Chief Prof. Jorge G. Ruiz.

http://doi.org/10.1016/j.jnha.2024.100298
Received 10 June 2024; Accepted 11 June 2024
Available online 21 June 2024

significant area of research with potential implications for sarcopenia treatment. Additionally, the recent identification of Bacterial quorum sensing peptides as potential sarcopenia inducers opens up new avenues for therapeutic exploration.

Several pre-clinical studies in mice have demonstrated that supplementation with the probiotic *Lactobacillus plantarum* TWK10 leads to increases in muscle fibers, muscle strength [8] and physical endurance [9]. Similarly, Other probiotics have shown beneficial effects; for instance, heat-killed *Bifidobacterium breve* B-3 increases muscle mass [10], while *Lactobacillus plantarum* improves endurance performance [11]. Pre-clinical trials using Lacticasei bacillus *casei* LC122 and *Bifidobacterium longum* BL986 have also yielded positive outcomes in muscle health [12]. These findings collectively underscore the potential of probiotics and fecal microbiota transplantation (FMT) in supporting mobility. Additionally, a systematic review by Lui et al. of 26 preclinical studies reported generally positive effects on muscle health from interventions with prebiotics, probiotics, and postbiotics such as short-chain fatty acids (SCFAs), highlighting their significance in this field [13].

In humans, the microbiota is essential for digestion and the synthesis of amino acid derivatives, secondary bile acids, and short-chain fatty acids (SCFAs). These compounds play roles in regulating the immune system, modulating inflammatory mechanisms [12] and influencing the release of catabolic hormones such as IGF-1. However, research on the effects of interventions targeting the gut microbiota on muscle health in humans is still limited [14]. Systematic reviews and meta-analyses have examined the impact of treatments centered on the gut microbiota [15]. The administration of a probiotic blend of Lactobacillus and Bifidobacterium has shown promising results in improving muscle mass and strength in adults [15], though outcomes in older individuals are less definitive. Only six studies, involving 676 participants with an average

Table 1

On-going trials* on Prebiotic, probiotic or postbiotic in older adults targeting muscle.

	Title and reference	Number of participants	Duration	Intervention	Population	Primary outcome
Prebiotic	Dietary Strategy to Tackle Sarcopenia in Early Elderly Subjects (FOOP-Sarc) (NCT05485402)	135	12-weeks	Fructo-oligosaccharides (FOS) and inulin	Men and women aged 60–80 years with Sarcopenia (low muscle strength or low skeletal muscle mass index (BIA) or low 4 m gait speed)	Change in muscle mass (Magnetic Nuclear Resonance)
Pre and Probiotic	Protein and Skeletal Muscle in Older Twins: Role of the Gut Microbiome (PROMOTe) (NCT04309292)	70	12-weeks	Protein supplementation plus a gut microbiome modulator (prebiotic plus probiotic) Darmocare Pre	Men and women aged 60 years or more with dietary protein intake of <1.3 g/kg/day	Change in chair rise time
	Frailty in Patients With Cirrhosis: Prognostic Value of the Phase Angle in Hospitalized Patients and Effect of Multifactorial Intervention (NCT04243148)	100	12-months	Multispecies probiotic: Vivomixx®	Men and women aged 18 years or more with cirrhosis	Mortality during hospitalization and follow-up Evolution of the Liver Frailty Index
	Biomarker Identification and Nutritional Intervention of Primary Sarcopenia Based on Gut-muscle Axis (NCT06347835)	120	12-weeks	Mixture of probiotics and prebiotics (20 g/d) and dietary pattern modification.	Men and women aged 65 years or more with sarcopenia (AWGS criteria)	Change from baseline of Appendicular Skeletal Muscle Mass index (DXA)
Probiotic	The Effect of Fermented Milk Containing Lactobacillus Casei Strain Shirota on Sarcopenia in Elderly Taiwanese: Interactions With the Nutrients Utilization, Diversity of Gut Microbiota, Microbiota-derived Metabolites and Muscle Loss (NCT04985877)	120	12-weeks	Lactobacillus casei Strain Shirota	Men and women aged 65–90 years with sarcopenia (AWGS criteria)	Muscle mass (assessed with Inbody S10), gut microbiota composition and gut microbial metabolites, ROS and protein utilization.
	OsteoPreP: Food Supplements for Postmenopausal Bone Health (OsteoPreP) (NCT05348694)	160	12-months	Pendulum WBF-038, a mixture of probiotics (Akkermansia muciniphila, Clostridium butyricum, Clostridium beijerinckii, Anaerobutyricum hallii, Bifidobacterium infantis) plus chicory inulin and magnesium stearate	Postmenopausal women, 40–65 years old, able to walk without the use of an aid.	Percentage change in total bone density (HR-pQCT), lower leg muscle area, relative change in lower leg muscle area (HR-pQCT), lean body mass, relative change in Appendicular Lean Mass (DXA), grip strength (hand dynamometer)
	Effect of Bacillus Coagulans on Skeletal Muscle Protein Synthesis in Response to Vegetable Protein Ingestion (NCT04297111)	12	6-months	Bacillus coagulans	Men and women aged 65 years or more with a BMI between 20 and 35 kg/m^2	Myofibrillar protein synthesis
Postbiotic	Efficacy and Safety of Kefir Whey Postbiotics (NCT06230302)	60	12-weeks	Whey postbiotics derived from kefir lactic acid bacteria	Men and women aged 40 years or more with CCI score of 0 and skeletal muscle mass less than 110% of the standard BIA	Hand Grip strength test

Note: *Results from *ClinicalTrialTrial.gov that target the microbiota in elderly subjects. Trials information were extracted from Clinical trial.gov with "condition or Disease": Sarcopenia and Advanced search: Prebiotic or probiotic or postbiotic or Quorum-sensing peptides /Early phase 1, phase 1, 2, 3, 4 (May 6th, 2023)*; AWGS, Asian Working Group for Sarcopenia; EWGOS, European Working Group on Sarcopenia; BMI, Body mass index; CCI, Charlson Comorbidity Index; BIA, bioelectrical impedance analysis; DXA, Dual X-ray Absorptiometry; HR-pQCT, High-Resolution peripheral Quantitative Computed Tomography; ROS, Reactive Oxygen Species.

age of 72.8 years, have tested prebiotics, probiotics, or postbiotics in older populations [16]. For instance, The Darmocare Pre®, a prebiotic, was investigated in a study of 60 frail individuals aged 65 and older and was found to enhance handgrip strength in a randomized controlled trial. Nonetheless, prolonged consumption of Lactobacillus and Bifidobacterium lactis strains has not yielded improvements in lean mass or muscle strength in the elderly. In a 2021 study, Lee et al. conducted a randomized clinical trial evaluating the effects of *Lactobacillus plantarum* TWK10 over six weeks on 55 older subjects, noting a trend towards increased muscle mass and grip strength at the conclusion of the trial [17].

In 2024, Handajani et al. conducted a meta-analysis on randomized controlled trials that explored the use of probiotics in older adults with sarcopenia. They identified seven trials that examined the effects of probiotics on older individuals with this condition [18]. For instance, a study by Rondanelli et al. in 2022 found that eight weeks of supplementation with the probiotic L. paracasei PS23 significantly improved appendicular lean mass and handgrip strength, and reduced visceral fat in older adults with sarcopenia, compared to a placebo [19]. Although The current data are not sufficient to definitively conclude a clear benefit on muscle health, the promising results from this meta-analysis encourage further confirmatory studies [20].

Table 1 lists the ongoing clinical trials targeting the microbiota in older subjects, as reported on ClinicalTrials.gov. The information was extracted using the search terms "condition or Disease: *Sarcopenia*" along with "Advanced search: *Prebiotic*, *probiotic*, *postbiotic*, or *Quorum-sensing peptides*" across various phases (Early phase 1, phase 1, 2, 3, 4) as of May 6th, 2023.

Ongoing research into the gut-muscle axis offers promising therapeutic possibilities for the prevention and treatment of sarcopenia. Among the eight ongoing randomized controlled trials, three include sarcopenic patients. These trials, which focus on older adults with sarcopenia as outlined in Table 1, are of larger scale and are expected to provide clearer insights into the causal relationships between microbiota interventions and their clinically relevant effects on strength and muscle mass in sarcopenic patients. One particular trial is examining the effects of fructo-oligosaccharides (FOS) and inulin, a fructan known for its potential benefits, including enhancing the production of short-chain fatty acids (SCFA), and involves 135 men and women with sarcopenia. Additionally, two large trials in Asia are investigating the effects of a prebiotic and probiotic mixture in one, and *Lactobacillus casei* Strain Shirota in the other, each planning to include 120 older adults with sarcopenia. Results from these studies are highly anticipated.

To date, the connection between aging-related dysbiosis and sarcopenia is strongly suspected. Further evidence from basic and preclinical research, along with findings from these extensive clinical trials, is needed before making clinical recommendations regarding the use of probiotics, prebiotics, and postbiotics.

Conflict of interest

YR: support from CHU Toulouse, University Paul Sabatier, INSERM CERPOP1295 (Employee); fees consultancy on Sarcopenia from Longeveron, Biophytis; honoraria for lectures on Pneumonia for Pfizer; shareholder of SARQOL SPRL, a spin-off of the University of Liege.

The other authors declare that they have no conflict of interest.

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