Gut microbial dysbiosis as a limiting factor in the management of primary and secondary sarcopenia: an Asian Indian perspective

Gut microbial dysbiosis as a limiting factor in the management of primary and secondary sarcopenia: an Asian Indian perspective

Shinjini Bhattacharya[a,*], *Rohini Bhadra*[a,*], *Annemie M.W.J. Schols*[b], *and Sucharita Sambashivaiah*[c]

Purpose of review
The article summarizes recent research advances on the role of gut microbiome in primary and secondary sarcopenia. This article also explores the potential contribution of gut dysbiosis to suboptimal sarcopenia management with special focus on factors contributing to gut dysbiosis among Asian Indians.

Recent findings
Aging and chronic diseases contribute to gut dysbiosis and intestinal barrier dysfunction allowing enhanced microbial translocation that may negatively affect muscle strength, physical function, and frailty. Gut microbiome of Asian Indians has shown a unique composition that is affected by multiple factors, such as socioeconomic status, poor hygiene, high rate of infection and infestations, antibiotic overuse and transition towards a westernized eating pattern. Current management approach for sarcopenia (exercise and/or protein supplementation) fails to address gut dysbiosis and intestinal barrier dysfunction. Incorporating a prebiotic or probiotic element to the intervention strategy may improve gut dysbiosis, inflammation and muscle function.

Summary
Gut dysbiosis and intestinal barrier dysfunction appear to be a significant limitation in sarcopenia management, thus gut centric intervention may be perceived as a (co)intervention strategy to be tested in appropriate clinical trials.

Keywords
aging, gut microbiome, gut-centric intervention, muscle strength, sanitation

INTRODUCTION

Sarcopenia is characterized by the progressive loss of skeletal muscle mass and function with advancing age. It is one of the major causes of age-associated frailty, disability and mortality. Prevalence of sarcopenia varies greatly among various populations around the world [1]. Its prevalence in India varies from 1.6 to 36.6% among different communities [2]. Sarcopenia is of two types, distinguishable based on its chief etiology. Primary sarcopenia is mainly age-related with no other cause, whereas secondary sarcopenia is associated with factors other than (or in addition to) aging, such as malnutrition, reduced physical activity and chronic disease [3]. Several mechanisms may contribute to muscle loss, including decreased protein synthesis or anabolic resistance, increased protein breakdown or impaired muscle regeneration because of multiple causes including chronic low-grade inflammation, oxidative stress and mitochondrial damage [4,5]. The effect of these factors may be enhanced when combined with physical inactivity, malnutrition and the presence of one or more chronic diseases, all commonly prevailing in the elderly population. Gut dysbiosis and associated inflammation have been speculated as being a contributory factor in the development of sarcopenia. Gut dysbiosis is defined as the presence of

[a]St John's Research Institute, St John's Medical College, Bengaluru, India, [b]NUTRIM School of Nutrition and Translational Research in Metabolism, Department of Respiratory Medicine, Maastricht University, The Netherlands and [c]Department of Physiology, St John's Medical College, Bengaluru, India

Correspondence to Sucharita Sambashivaiah, MD, PhD, Professor, Department of Physiology, St John's Medical College, Bengaluru 560034, India. Tel: +91 80 49466324; e-mail: sucharita@stjohns.in

*Shinjini Bhattacharya and Rohini Bhadra have equally contributed and share joint first authorship.

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KEY POINTS

- Gut dysbiosis and altered intestinal membrane permeability may accelerate the process of sarcopenia associated with aging and chronic diseases.
- Multiple environmental factors are responsible for negative modulation of gut microbiome in Asian Indians, which includes poor sanitation, increased infection, infestation, antibiotic overuse and dietary variation.
- Gut dysbiosis may be recognized as the potential contributor to sub-optimal management of sarcopenia.
- Gut microbiome represents a promising intervention site for management of sarcopenia.

an imbalanced, low-diversity, intestinal microbiota [6]. The microbiota of the elderly, in general, shows decreased diversity [6]. The association between gut microbiota alteration and modulation of whole-body lean mass was first established in a pioneering animal study by Bakhed *et al.* [7]. A decrease in whole body lean mass and increase in fat mass was observed in germ-free mice following colonization with fecal samples of conventionally raised mice [7], indicating sarcopenia and sarcopenic obesity. Increasing literature evidence identifies the gut microbial composition as a key contributor to skeletal muscle mass, metabolism and function during aging, and thus might be an important determinant in development of sarcopenia [5], giving rise to the concept of the gut–muscle axis. Various studies have indeed shown that increase in microbial production of short-chain fatty acids, such as butyrate, is a potential modulator of muscle strength and physical function in humans [8▪▪,9]. The gut–muscle axis has also become an area of interest for researchers focusing on the development and management of sarcopenia. In the past year, several studies have been conducted in this area, worldwide. Remarkably, in India, direct studies have been scarce although there is evidence of various factors affecting gut health among Indians, which might be linked to muscle health as well. This review will, therefore, summarize the recent literature evidence on the above-mentioned areas to explore the contribution of gut dysbiosis to suboptimal sarcopenia management, with a specific focus on factors that might be contributory to gut dysbiosis among Asian Indians.

AGING GUT AND SARCOPENIA

Gut microbiota has been causally linked to systemic low-grade inflammation that is observed in both aging and chronic disease. Enhanced production of pro-inflammatory cytokines, such as IL-6, TNF-α and IL-1β by intestinal epithelial cells is increased with advanced age. This, in turn, could cause increased intestinal epithelial tight junction permeability giving rise to intestinal barrier dysfunction. Indeed, a study by Sovran *et al.* [10▪] has reported a reduction (or even complete absence) in colon mucus layer of older mice (19 months) than younger controls (10 months), thus indicating a decreased intestinal barrier function with aging.

The gastrointestinal tract acts as the major barrier in the translocation of microbial products in both animals and humans. The barrier is composed of various physical, biochemical, immunological and microbial elements. Defects in these barrier elements, a phenomenon common in aging, can result in an elevated immune reaction and inflammation by causing an increased translocation of microbial products into the systemic circulation. This barrier dysfunction-induced systemic inflammation might have significant clinical implications in the form of metabolic syndrome, decreased muscle strength and physical function [11▪]. This is supported by the observation of Stehle *et al.* [11▪] where a significant decrease in physical function and grip strength was reported among healthy older adults with a simultaneous increase in plasma levels of lipopolysaccharide binding protein (LBP), as a biomarker of microbial translocation and hence, intestinal barrier dysfunction. Ambulatory (<60 min/week moderate structured physical activity) community dwelling elderly individuals of 60–79 years of age, having a BMI between 28 and 40 kg/m^2 with either cardiovascular disease or cardiometabolic dysfunction and a self-reported limitation in mobility, demonstrated a significantly strong association between baseline markers of microbial translocation and inflammatory markers. The microbial markers measured by LBP-1 and sCD-14 levels were strongly associated with IL-6 and IL-8. Furthermore, a negative association between LBP-1 levels and physical function [assessed by the short physical performance battery (SPPB) and 400 m walk test] was found in the above-mentioned study group [11▪]. Lifestyle interventions (diet and exercise) were shown to have no effect on intestinal barrier function and inflammation despite successful weight reduction among the study group [11▪]. This suggests that diet and exercise are possibly not universally beneficial for restoring intestinal barrier competency, and hence alternative or additional strategies might need to be explored for reducing microbial translocation and inflammatory burden in older adults. Other studies conducted previously have also shown chronic inflammation (measured

by IL-6, TNF-α and CRP levels) elicited by microbial translocation to be negatively associated with physical function (measured by SPPB, 4 m walk and repeated chair stands) in older adults with multiple comorbidities [11▪].

Decreased intestinal barrier function was shown by Sovran *et al.* [10▪]. Evidence of altered fecal microbial composition and expression of immunity in intestinal mucosal tissue with aging was demonstrated [10▪]. The gut-based study among centenarian has found high proteobacteria, a pathobiont (pathogenic in certain circumstances), shown to cause negative health effects in susceptible hosts [20]. Therefore, maintaining gastrointestinal barrier integrity is important for the microbial homeostasis.

Association of gut microbial profile with physical frailty and sarcopenia was shown in a study by Picca *et al.* where microbial alpha diversity (the variance within the sample) between sarcopenic and nonsarcopenic groups did not show any significant difference, however, analysis of differential abundance of microbial taxa showed increased Peptostreptococcaceae and Bifidobacteriaceae at the family level and depletion of *Slackia* and *Eubacterium* in participants with sarcopenia. The taxa linked to sarcopenia in this study were also associated with biological aging and frailty in other studies conducted previously [8▪▪].

An overall shift towards butyrate-producing bacteria, which may be comparable to that observed in higher functioning people was observed in this study [8▪▪]. Butyrate, itself, has been shown to have a beneficial effect on the intestinal barrier function by reinforcing intestinal epithelial tight junction and preventing microbial translocation and reducing systemic inflammation, as well as, improving muscle bioenergetics and restricting myosteatosis by promoting fatty acid oxidation. This characteristic of butyrate shift among frail individuals may suggest a positive role of butyrate-producing microbes in muscle function [8▪▪]. One possible reasoning for this may be a compensatory mechanism to counteract the loss of muscle mass, strength and function associated with sarcopenia but this warrants further investigation for confirmation.

Reduced SCFA production may also trigger insulin resistance and result in increased fatty acid deposition within the muscle, lowering muscle quality, thus having an indirect effect on muscle quality. The ensuing lower muscle quality may further promote insulin resistance, feeding a vicious circle that contributes to the onset and progression of sarcopenia, frailty and possibly even sarcopenic obesity [8▪▪].

GUT DYSBIOSIS ASSOCIATED WITH CHRONIC DISEASES AND SARCOPENIA

Chronic organ dysfunction including liver disease, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) may contribute or even accelerate the development of sarcopenia. Gut dysbiosis and systemic inflammation have also been a consistent finding in many of these conditions that impair muscle functionality.

Altered gut microbiome composition has been reported in predialysis CKD patients with a higher relative abundance of genera *Lactobacillus*, *Coprobacillus*, *Anaerotruncus* and *Citrobacter* species and lower *Prevotella*, *F. prausnitzii* and *Roseburia* (the saccharolytic and butyrate-producing species). This alteration in gut microbiota was further associated with frailty most likely mediated through production of toxic bacterial metabolites [12].

Similarly, patients with liver disease have shown marked alteration in the gut microbiome and/or inflammatory profile. Gut microbiome analysis of nonalcoholic steatohepatitis (NASH) patients revealed an abundance of *Escherichia coli* [13]. It is noteworthy, that the abundance of genus *Escherichia* is associated with production of alcohol that induces inflammation. A recent publication used *E. coli* lipopolysaccharide for immune system stimulation in a porcine model and reported a decrease in whole-body protein synthesis, a reduced muscle fiber cross-sectional area and a switch in muscle fibers towards a slow-twitch oxidative type (type I) with lower fast-twitching glycolytic fibers (type II) [14▪▪]; all the observations indicative of muscle atrophy. Furthermore, it has been reported that chronic alcoholics having significantly lower mean handgrip strength than controls reported to have gut microbiome profile skewed towards pro-inflammatory direction [15]. Surprisingly, incorporating gut-based intervention, that is, multistrain probiotic supplementation in dynapenic (loss of muscle strength) cirrhosis patient failed to demonstrate significant improvement in muscle strength after 12-week probiotic supplementation, despite improvement in intestinal barrier function and inflammatory response [16]. However, the study did not include objective measures of muscle mass. Furthermore, the study lacked exercise or nutrition support, considered to be crucial for the improvement in muscle quality. Thus, the study outcome might not reflect the true impact of gut-based (co)-interventions on muscle health.

Increased small intestinal permeability has been reported in COPD patients during acute exacerbations as reflected by an increased inflammatory response and higher urinary lactulose/L-rhamnose ratio during hospitalization [17]. The underlying

mechanisms are not yet known, however, authors speculated that inflammation and hypoxic damage as the cause of intestinal barrier disruption. The contribution of altered gut microbiome being a strong predictor of intestinal barrier integrity requires further investigation. The available evidences on COPD patients including experimental COPD models are pointing towards an accelerated and stepwise decline in the muscle mass, which is suggested to be related to the frequency of acute exacerbations [18].

Studies conducted on patients of metabolic syndrome have shown the beneficial effect of probiotic supplementation on the improvement in inflammatory markers and insulin resistance. However, the direct impact of the changes in gut microbiome on muscle health was not examined [19,20]. Therefore, this might be a potential pathway to explore for exhibiting the favorable effect of gut microbiota on muscle functionality in metabolic syndrome or diabetes.

The recent evidences point towards the altered gut microbial profile in chronic organ dysfunction. There is a decrease in commensal microbes, abundance of pathogenic bacteria, increase in intestinal permeability and inflammatory response. These factors can alter the muscle physiological and biochemical properties in a catabolic direction thereby accelerating the development and progression of sarcopenia.

GUT MICROBIAL PROFILE IN INDIANS

Gut microbiome metagenomic studies have illustrated that there are population-specific signatures in microbial composition. Studies on gut microbiome of adult Indians with no comorbidity have shown a distinctive composition with a predominance of *Prevotella* as the most discriminatory genus [21▪,22,23]. *Prevotella* belongs to phylum Bacteroidetes typically associated with production of SCFA. However, literature suggests, among *Bacteroidetes*, *Prevotella* shows the lowest genetic potential of producing SCFA. Further it is frequently linked with chronic inflammation [21▪]. Gut microbiome composition of rural Indians have demonstrated a difference in bacterial abundance with age. A higher abundance of *Ruminococcus* has been reported in healthy older adults (age $\geq$50 years) [23]. Gut microbiome analysis of Indian centenarians has shown a higher species richness and biodiversity of family Ruminococcaceae, accompanied with a decrease in *Prevotella* species [24]. These findings are indicative of the beneficial role of Ruminococcaceae to facilitate healthy aging, also indicating the negative association of *Prevotella* with longevity and well being. It is noteworthy that the members of Ruminococcaceae family were reported to be a major butyrate producer, which is indicative of its potential role in preventing inflammation and immunosenescence [24]. These evidences primarily concentrate on gut microbial profile of healthy Indians while the changes with aging, chronic disease or sarcopenia is still lacking. Therefore, it is difficult to conclude the discriminative alterations in gut microbiome of elderly Indians with sarcopenia or chronic disease.

Although there is paucity in literature linking aging, chronic disease and the gut–muscle axis published in the past year for the Indian population, we have come across several population-specific causes of gut dysbiosis in Indians, which might have a subsequent implication on muscle health. Environmental factors, such as diet, lifestyle and hygiene have shown a strong influence on microbial composition in many of the studies that might have a profound effect on the gut–muscle axis. Identification of these factors is instrumental to establish therapeutic and preventive measures for sarcopenia.

Poor sanitation, related infections and antibiotic resistance

Over the past few decades, researchers have emphasized the 'hygiene hypothesis', which implies insufficient exposure to microbes in developed countries with high levels of hygiene may restrict the spectrum of bacterial colonization, thus reducing microbial enrichment and biodiversity. Considering this hypothesis, the population in developing countries should be expected to have better microbial composition because of increased exposure to a wide variety of microbes. However, low socioeconomic status in developing countries contributes to poor sanitation and inadequate healthcare infrastructure, which results in a prominent increase in infection rates. This leads to rampant use of antibiotics that can eliminate the sensitive bacterial strains and favor the growth of antibiotic-resistant strains thereby supporting the spread of antibiotic-resistant genes in gut microbiota. The depletion of commensal bacterial strains because of antibiotic treatment was associated with a reduction in SCFA production and increased gut inflammation in mice during oral *Candida albicans* infection, which was resolved following SCFA administration [25]. Furthermore, certain antibiotics, such as a combination of cefoperazone, clindamycin, and vancomycin may eliminate Lachnospiraceae and Ruminococcaceae families. Ruminococcaceae, as mentioned above is associated with healthy aging, and loss of this family is indeed detrimental to aging health. Also, both

Lachnospiraceae and Ruminococcaceae are associated with the production of secondary bile acids in intestinal lumen that restricts the growth of pathogen *Clostridium difficile, a* Gram-positive anaerobe associated with diarrheal disease. Thus, loss of the above-mentioned microbial families because of antibiotic treatment may increase the risk of *C. difficile* infection [25]. A recent study on Indian population investigating the burden of antimicrobial resistance and diarrheal diseases, particularly *C. difficile*, in rural and urban population of central India, reported a higher burden of *C. difficile* in the urban and peri-urban populations with higher exposure to antibiotics, many of which carried antibiotic resistance genes to virtually every class of antibiotic [26▪].

Parasitic infestation

Parasitic disease, a secondary consequence of poor sanitation, widely prevalent in developing countries, such as India, might have specific interaction with the subset of microbial population. For instance, *Entamoeba histolytica*, a protist parasite that causes amoebiasis, was associated with phagocytosis of beneficial bacteria. *E. histolytica* exhibited preferential phagocytosis to Lactobacillales, Erysipelotrichales, Clostridales, and Bifidobacteriales family, which are essential for maintaining healthy gut microbial population [27▪]. Thus, wiping out the favorable bacterial families may trigger gut dysbiosis and associated inflammatory response.

Dietary habits and lifestyle

India is experiencing a steep rise in urbanization and westernization in line with the global trend. There is a drastic increase in sedentarism in urbanized population, which is accompanied with a transition towards ready-to-eat, factory-processed eating pattern that has replaced the naturally produced unprocessed staples. This major shift in diet and lifestyle affects the intestinal microbial population to a great extent. Westernized eating pattern has been shown to shift the microbial population towards Bacteroides dominance [28], which is linked to adiposity and metabolic disease. In the Indian population, a higher abundance of taxa belonging to Bacteroidetes was reported in urban inhabitants following a western-type diet, typically high in protein and fat [29▪]. An overall higher gut microbial diversity has been observed in the tribal population compared with the urban [29▪]. However, Kaur *et al.* reported a higher proportion of Bacteroidetes in Ladakh ethnic tribes and abundance of *Actinobacteria* and *Firmicutes* in Jaisalmer and Khargone participants respectively. Also, healthy population from Ladakh had alpha diversity as low as the US population [30]. It is noteworthy that the dietary pattern of Ladakh ethnic group was predominantly nonvegetarian with increased intake of fat and protein, whereas the majority of Jaisalmer participants were vegetarians and Khargone participants had a mixed eating pattern.

The challenges of exploring the gut microbial composition of Indians lie mainly in the vast diversity of the population in relation to their geographic locations, genetic make-up and dietary habits among others [31]. Environment has been shown to extensively affect the microbial population, richness and biodiversity in addition to aging and chronic disease. In a developing country like India, environmental components, such as infection, antibiotic overuse, parasites, dietary variation in line with the urbanization, appear to be the major source of gut dysbiosis. As, gut dysbiosis has the potential to cause deterioration of muscle health with aging and given the already established prevalence of sarcopenia among Indians, despite scarcity of recent literature on the Indian gut–muscle axis, therapeutic strategies targeting gut microbiome is extremely important in Asian Indians and may be indispensable to overall wellbeing.

GUT-CENTRIC INTERVENTION AS A NOVEL THERAPEUTIC APPROACH TO SARCOPENIA MANAGEMENT

The conventional therapy for the management of sarcopenia and ensuing frailty that remains most explored includes exercise and protein supplementation [32]. Various studies have been conducted over the years with mixed results. Significant increase in handgrip strength and improvement in the physical function was observed in prefrail and frail older adults following a 12-week resistance exercise with protein supplementation compared with a control group receiving only resistance exercise (both groups received a weight maintenance diet) [32]. Assessment of the effect of a 13-week Vitamin D and leucine-enriched whey protein intervention on chronic low-grade inflammatory profile (CLIP) in sarcopenia, found an overall significant increase in CLIP, demonstrated by an increase in IL-6 and IL-1RA [33].

To date, resistance exercise and high protein intake have been advocated in the management of sarcopenia. However, recent literature suggests that high protein intake itself might have a negative impact on gut microbiota by shifting the gut bacterial metabolism towards amino acid degradation and fermentation [8▪▪]. Furthermore, age-related alteration in the gut microbial composition and associated inflammation can contribute to anabolic

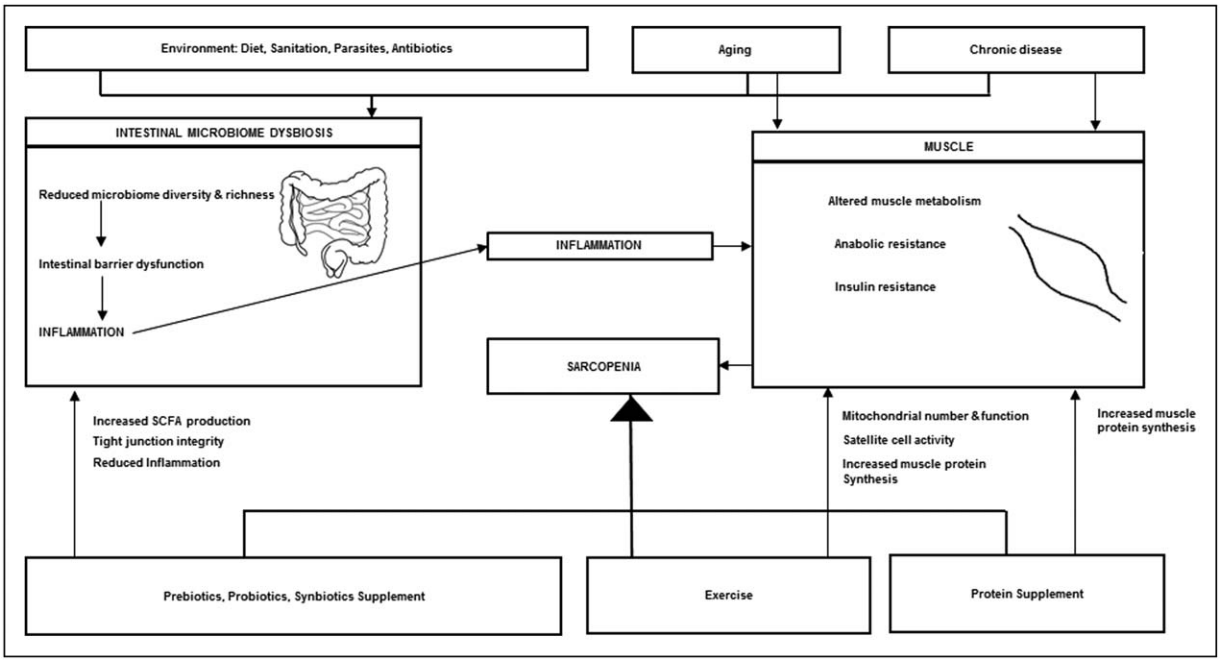

FIGURE 1. Illustration of gut-muscle axis and potential gut-based (co)intervention to ameliorate sarcopenia: aging and chronic disease are potential contributors to muscle degradation, and when accompanied with environmental factors, it mediates intestinal dysfunction inducing inflammation, a key mechanism for sarcopenia development. Hence, incorporating a gut-centric supplementation to the current management might bring about a more wholesome perspective to the management strategy by overcoming the pitfalls of the current approach.

resistance as it affects the absorption and utilization of protein in small intestine that results in a higher requirement of proteins for muscle protein synthesis [4]. Therefore, the role of gut bacteria in nutrient signaling to the host might need to be monitored and applied in the nutritional management of sarcopenia.

Gut-based intervention seems to be a promising site of (co)intervention to improve muscle mass, physical performance and frailty indices as evidenced by multiple literature. Supplementation of high-dose probiotic has been associated with an increase in muscle mass and a significant improvement in exercise performance in healthy adults [34▪▪]. Frailty index score was significantly reduced in nondemented elderly individuals on prebiotic supplementation [35]. Supplementation of heat-killed *Bifidobacterium breve* B3 has shown to increase the weight of the soleus muscle in mice. HK-B3 also promoted muscle mitochondrial biogenesis through the AMPK-PGC-1 signaling pathway and significantly increased expression of peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α, which is known to shift muscle fiber distribution to a more oxidative fiber type (type II). The HK-B3 group was also characterized by increase in muscular strength measured by handgrip [36]. Supplementation of inulin or inulin propionate ester supplementation (IPE) improved markers of systemic inflammation and insulin resistance in adults between 18 and 65 years of age, both of which are detrimental to muscle quality [37]. Thus, probiotic or prebiotic supplementation appears to positively modulate age-related muscle loss and frailty, but the relative improvement compared with exercise or in combination with exercise needs further investigation.

Given the evidences to date, gut microbiota and metabolites appear to be a potential target for intervention in the context of sarcopenia and frailty. Thus, gut-centric intervention may be a novel therapeutic approach worth exploring in mitigating sarcopenia (Fig. 1).

CONCLUSION

Gut microbiota plays an active role in the development of both primary and secondary sarcopenia. Though, human trials on the gut–muscle axis is still in the early phase, there is clear evidence suggesting an association between the gut microbial composition, membrane permeability and inflammation with measures of muscle strength and physical function. The conventional method of sarcopenia management involves exercise and protein supplementation; however, exploration of the gut-centric approach could emerge as a novel intervention therapy for effective multimodal sarcopenia management.

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Conflicts of interest

There are no conflicts of interest.

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