

# A Narrative Review of Gut-Muscle Axis and Sarcopenia: The Potential Role of Gut Microbiota

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**Abstract:** Sarcopenia is a multifactorial disease related to aging, chronic inflammation, insufficient nutrition, and physical inactivity. Previous studies have suggested that there is a relationship between sarcopenia and gut microbiota, namely, the gut-muscle axis. The present review highlights that the gut microbiota can affect muscle mass and muscle function from inflammation and immunity, substance and energy metabolism, endocrine and insulin sensitivity, etc., directly or indirectly establishing a connection with sarcopenia, thereby realizing the “gut-muscle axis”.

**Keywords:** gut microbiota, metabolism, inflammation, muscle

## Introduction

Recent studies put forward a relationship between sarcopenia and gut microbiota, namely, the gut-muscle axis. Although some of them explain this relationship from certain angles, most of them are one-sided and ignoring several possible special influencing factors, such as immunity and endocrine. This article will explain the gut-muscle axis in detail from the following aspects: inflammation, immunity, substance and energy metabolism, endocrine and insulin sensitivity, etc., and reveal how different kinds of Nutritional Supplements affect muscle function and mass through the gut microbiota. List the facts that different types of exercise can have different effects on muscles and gut microbiota. The following content will introduce sarcopenia and gut microbiota separately.

## Introduction to Sarcopenia

Sarcopenia is an involuntary loss of skeletal muscle mass and strength.<sup>1</sup> It is a multifactorial disease related to aging, chronic inflammation, insufficient nutrition, physical inactivity, and endocrine system disorders (such as reducing estrogen and androgens). So far, several diagnostic criteria for sarcopenia, determined by different races and different regions, have been proposed.<sup>1-3</sup> Working Group of the International Sarcopenia Conference, EWGSOP2 (European Working Group on Sarcopenia in Older People), and AWGS2019 (Asian Working Group for Sarcopenia 2019), The European Working Group on Sarcopenia in Older People (EWGSOP) established its first version of sarcopenia's diagnostic criteria in 2010, which was then further revised in 2018. Today, the definition of sarcopenia was mainly based on the decrease in muscle mass and muscle function.<sup>4,5</sup> The muscle function is commonly evaluated using handgrip strength, 5-times repeated chair stand test, and 4-meter walking speed.<sup>1</sup> Grip strength is closely related to lower

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limb muscle strength and calf muscle cross-sectional area; thus, this test has been recommended as the golden approach for diagnosis and prognosis prediction.<sup>6,7</sup>

In a large cross-sectional study, 973 participants (from a total of 11253 subjects) were diagnosed with sarcopenia using EWGSOP2, and the incidence of sarcopenia significantly increased with age.<sup>8</sup> Another cross-sectional study in the Korean community showed that among 2099 community older adults aged 70–84, sarcopenia incidence was 4.6–14.5% in men and 6.7–14.4% in women.<sup>9</sup> In general, the reduction of muscle mass and strength in sarcopenia is closely related to aging. In addition, this systemic skeletal muscle disease increases the risk of falls in the elderly, prolongs the length of hospitalization and costs, and increases morbidity and mortality. Compared with the higher arm muscle cross section ( $\geq 33.4$  cm<sup>2</sup>), the lower arm muscle cross section ( $< 23.5$  cm<sup>2</sup>) has a higher risk of death (HR 2.03; 95% CI, 1.36–3.02). Compared with those without sarcopenia, the risk of falls in men with sarcopenia was higher (OR 2.58; 95% CI, 1.42–4.73).<sup>10,11</sup>

## Introduction to Gut Microbiota

The gut microbiota can affect the host's muscle mass and function by regulating systemic inflammation and immunity, substance and energy metabolism, and insulin sensitivity. With the development of high-throughput sequencing technology and bioinformatics technology,<sup>12</sup> so far, over 9.9 million microbial genes have been detected in human feces,<sup>13</sup> including more than 1000 different bacteria,<sup>11</sup> most of which are anaerobes.<sup>14</sup> Probiotics are beneficial bacteria (eg, *Lactobacillus*, *Bifidobacterium*, *Clostridium butyricum*, *Bacillus subtilis*) that are primarily found in our digestive system. And prebiotics are mainly oligosaccharides that cannot be digested and absorbed by the host<sup>15</sup> that feed other beneficial bacteria, promoting their growth and reproduction. The preparation that mixes probiotics and prebiotics are called synbiotics.<sup>16</sup> Synbiotics unify the benefits of probiotics and prebiotics, and have been widely used in related experiments.

Gut microbiota changes with age. Healthy aging is related to changes in the structure of the gut microbiota,<sup>17,18</sup> and its imbalance has a close relationship with human health and disease. Najmeh Seifi discovered that supplementing the synbiotics for critically ill patients can shorten the length of ICU stay, reduce muscle protein catabolism, and reduce infection complications.<sup>19</sup>

This review highlighted the relationship between sarcopenia and gut from the perspective of gut microbiota,

namely, the gut-muscle axis. We found that the gut microbiota can affect muscle mass and muscle function from inflammation, immunity, substance and energy metabolism, endocrine and insulin sensitivity, etc., directly or indirectly establishing a connection with sarcopenia, thereby realizing the “gut-muscle axis”. The next content will introduce in detail.

## Search Strategy

We searched through PubMed, Scopus, Web of Science, EMBASE databases. First, a basic search was done in PubMed, then the same strategy was applied to other databases. Articles published before 1st October, 2020 were searched using the following key terms: microbiota AND muscle; microbiota AND sarcopenia; microbiota AND “muscle mass”; microbiota AND “muscle strength”; microbiota AND “muscle function”. Two researchers searched the above keywords separately and removed duplicate documents. We chose to include experimental and observational studies, including animal and human experiments. In order to avoid the limitations of English, we also expanded the search scope to Chinese. However, there are some articles in other languages that cannot be fully searched. A total of 178 articles were retrieved after screening.

## The Potential Role of Gut Microbiota in Gut-Muscle Axis Phenomenon: Gut Microbiota with Muscle Function/Muscle Mass

So far, a number of studies, including in vitro experiments and preclinical studies, have directly or indirectly proved a certain relationship between muscle mass and gut microbiota. **Table 1**. For example, Fielding et al transferred fecal samples from two older adults (HF (high-functioning groups) and LF (low-functioning groups)) into germ-free mice. The grip strength was significantly increased in HF, when compared with LF mice.<sup>20</sup> A randomized controlled double-blind study found that prebiotic increases the grip strength in elderly people over 65 years old.<sup>21</sup> There was no significant difference in grip strength between the two groups before the intervention, but after 13 weeks of prebiotic supplementation, compared with the placebo group, the grip strength of the experimental group was significantly increased ( $10.2 \pm 4.1$ kg vs  $12.4 \pm 3.2$ kg,  $p < 0.05$ ). Munukka et al found that compared with controlled group, supplement of prebiotic (*Faecalibacterium prausnitzii*) can

**Table 1** Existing Facts of Animal and Human Experiments: The Effects of Intestinal Microbiota on Muscle Function and Quantity

References	Objects	Methods	Results	Mechanisms
Fielding et al <sup>20</sup>	Germ-free mice	Transferred fecal samples from two older adults (high-functioning groups and low-functioning groups) into germ-free mice	HF-colonized mice has stronger grip strength compared with LF-colonized mice	Strengthened the intestinal barrier
Chen et al <sup>31</sup>	Older people aged 65 and over	Supplementation of probiotics: <i>L. plantarum</i> TWK10 (LP10)	Improvement of muscle strength and endurance	Reduced cytokine production; enhanced glucose utilization
Lee et al <sup>23</sup>	Mice	Supplementation of <i>Lactobacillus salivarius</i>	Improvement of muscle strength and endurance	Related to the increased BCAA pathway, BCAA can increase the microorganism <i>Methanobrevibacter smithii</i> , which can use H <sub>2</sub> in the colon to convert into SCFA and ATP, thereby providing energy for synthesis of muscle protein.
Lee et al <sup>24</sup>	Mice	Supplementation of <i>Bifidobacterium longum</i>	Increase of muscle strength, and endurance	Increased intestinal SCFA content
Kazmierczak-Siedlecka et al <sup>28</sup>	Healthy people and cancer patients	Supplementation of <i>Lactobacillus</i> (extracted from pickle)	Improvement of exercise performance, reduction of the muscle loss in cancer patients	Increased iron absorption, reduced the side effects of antibiotics on colonic fermentation
Munukka et al <sup>22</sup>	Mice	Supplement of <i>Faecalibacterium prausnitzii</i>	Increase of muscle mass	Enhanced mitochondrial respiration; reduced inflammation; improved insulin sensitivity

**Abbreviations:** BCAA, branched chain amino acid; SCFA, short-chain fatty acids; ATP, adenosine triphosphate.

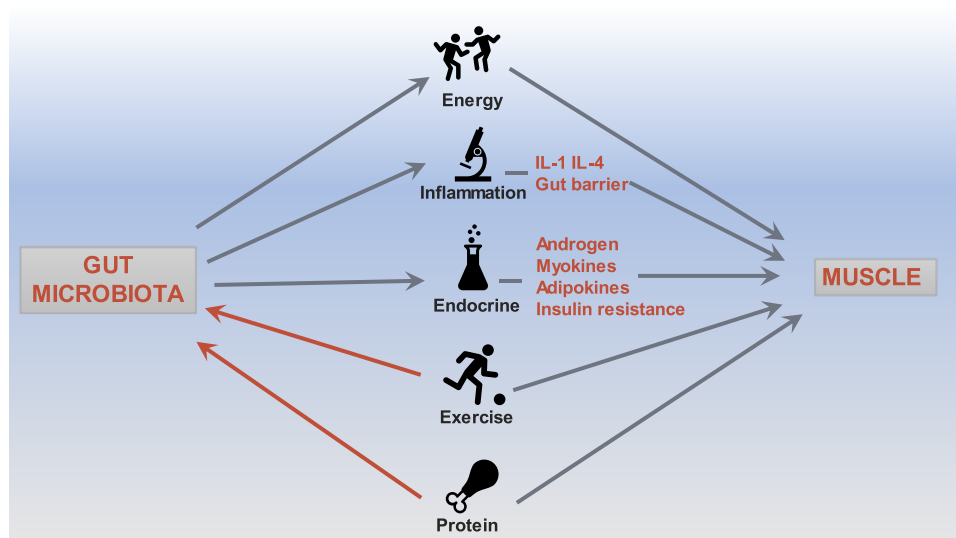
increase muscle mass (95g vs 110g,  $p < 0.05$ ) by enhanced mitochondrial respiration; reduced inflammation and improved insulin sensitivity.<sup>22</sup>

Over recent years, probiotics have been increasingly used in athletes because of their improved performance and reduced fatigue after exercise. Lee et al studied the effects of *Lactobacillus salivarius* in mice, revealing that a 4-week supplementation of *Lactobacillus* could significantly improve muscle strength and endurance, increase liver and muscle glycogen storage, blood lactic acid, BUN, and acid kinase after exercise.<sup>23</sup> Furthermore, Lee et al transferred *Bifidobacterium longum* subsp and *Bifidobacterium longum* OLP-01 (extracted from the intestines of the 2008 women's 48 kg weightlifting gold medal champion) into the mice. After 4 weeks of treatment, glycogen, liver glycogen content, muscle strength, and endurance all increased.<sup>24</sup> Moreover, after antibiotic treatment, the mice's exercise endurance was greatly reduced, which was related to the muscle's ability to use glycogen for energy production.<sup>25</sup>

In nature, fermented food is an important source of probiotics, which contain thousands of live lactic acid

bacteria (mainly *Lactobacillus*).<sup>26,27</sup> Kazmierczak-Siedlecka et al found that *Lactobacillus* (extracted from pickle) supplementation could improve exercise performance in a dose-dependent manner and significantly increases muscle mass in healthy people, and reduce the muscle loss in cancer patients.<sup>28</sup> These experiments suggest that *Lactobacillus* may become a biological agent for improving physiological function.<sup>29</sup>

In patients with cancer and chronic wasting disease, the balance of gut microbiota is of great significance. Supplementing the corresponding microbiota is also beneficial to fight the disease.<sup>28,30</sup> Therefore, probiotics are closely related to muscle strength and function and muscle mass. Although there is limited understanding of probiotics' mechanism on muscle strength and quality benefits at this stage, it is clear that gut microbiota is linked to muscles through endocrine, substance and energy metabolism, immunity and inflammation. The possible mechanisms of gut-microbiota are summarized in Figure 1.



**Figure 1** Overview of the main mechanisms of gut-muscle axis.

## Mechanism: Mitochondrial and Energy Metabolism

Skeletal muscle mitochondrial dysfunction or decline is thought to be one of sarcopenia causes.<sup>32</sup> Muscle mitochondrial function and content, as well as resting and maximal oxygen (O<sub>2</sub>) consumption, decrease with age.<sup>33,34</sup> As age increases, abnormally enlarged mitochondrial fragments can be seen under the electron microscope.<sup>35</sup> ATP that needed for muscle protein synthesis decreases.<sup>36</sup> Consequently, maintaining healthy mitochondrial mass has a vital role in combating aging-related muscle atrophy and weakness.<sup>37</sup>

Gut microbiota is connected with skeletal muscle mitochondria level through the production of insulin-like growth factor 1 (IGF-1).<sup>38</sup> Lahiri et al compared the skeletal muscle of germ-free mice that lacked a gut microbiota to the skeletal muscle of pathogen-free mice with gut microbiota and found muscle atrophy decreased IGF-1, and decreased mitochondrial function in germ-free mice without microbiota. After transplanting the microbiota in the gut, the muscle atrophy and the muscle's antioxidant capacity were significantly improved.<sup>39</sup> The liver mainly synthesizes IGF-1 as a systemic growth factor. IGF-1 can also be synthesized by extrahepatic tissues, such as skeletal muscle, which affects its own synthesis through autocrine and paracrine. Many studies have found that IGF-1 oversecretion can maintain skeletal muscle quality and function<sup>40,41</sup> and promote the synthesis of skeletal muscle cells.<sup>42,43</sup> Furthermore, Brunk et al

suggested that the vicious cycle of muscle atrophy involves the decline of muscle antioxidant capacity and the gut microbiota may maintain muscles' normal function in terms of antioxidant capacity and mitochondrial function.<sup>44</sup>

Ebner N et al found that urolithin A, a natural intestinal metabolite produced by host microbiota and metabolized by food conversion products, can restore mitochondria' function in muscles, thereby maintaining the normal progress of energy metabolism.<sup>45</sup> This may provide a certain reference for future research on improving mitochondrial function associated with aging.

## Mechanism: Immune and Inflammation

Systemic chronic inflammation is one of the most important factors associated with sarcopenia.<sup>46–48</sup> Abou-Samra M et al found that wild mice and ordinary experimental mice have different gut microbiota. Experimental mice are more susceptible to external invasion and have a similar frontal immune response to humans than wild mice.<sup>50</sup> This suggests that the difference in gut microbiota may have a regulatory effect on the immune system.

As a recurrent chronic gut inflammatory disease of the intestinal tract, inflammatory bowel disease (IBD) has obvious changes in the gut microbiota. In patients with IBD, the microbiota that produces butyrate is reduced. Butyrate is a SCFA that reduces intestinal inflammation, protects the intestinal barrier and regulates intestinal homeostasis.<sup>51</sup> Increased intestinal permeability is one of the manifestations of the destruction of intestinal barrier

function and a potential pathogenic factor for IBD. Furthermore, in IBD patients, *E. Coli* can interact with intestinal epithelial cells and induce inflammation, leading to excessive production of pro-inflammatory cytokines such as IL-1, TNF- $\alpha$ , etc., thereby promoting intestinal inflammation and destroying the intestinal barrier.<sup>52,53</sup> Studies reported that compared with normal people, IBD patients are more likely to have sarcopenia. The mechanisms underlying sarcopenia in IBD mainly include chronic intestinal inflammation, malabsorption of nutrients, lack of exercise, imbalance of gut microbiota<sup>54–56</sup> Therefore, chronic intestinal inflammation, increased intestinal permeability and malnutrition in patients with IBD may affect skeletal muscle mass, leading to sarcopenia, in which the gut microbiota plays an important role.

Cancer cachexia refers to the severe weight, fat, and muscle loss of cancer patients,<sup>57–59</sup> which is related to the increase of catabolism. Patients with cachexia have chronic inflammation and weakened immunity.<sup>54–56</sup> In addition, many pathogenic factors of cachexia overlap with sarcopenia. Patients with advanced cancer are more likely to have both cachexia and sarcopenia, especially elderly cancer patients.<sup>60,61</sup>

The composition of gut microbiota is different in patients with cancer cachexia that in healthy individuals.<sup>62–64</sup> Bindels et al found a decreased amount of *Lactobacillus* in mice with leukemia. Yet, after supplementing *Lactobacillus* to these mice with leukemia, the levels of inflammation factors such as interleukin-6, monocyte chemoattractant protein-1, interleukin-4 dropped.<sup>65</sup> Another animal experiment found a lower number of *Lactobacillus* and a higher amount of *Enterobacteriaceae* and *Parabacteroides* in mice with leukemia and colon cancer. After treating mice with *Lactobacillus*, cancer cell proliferation, as well as muscle loss and deficiency, were reduced.<sup>66</sup> Pötgens and colleagues found an increased amount of *Klebsiella oxytoca* (a type of *Enterobacter*) in mice with cancer cachexia. This bacterium has been associated with a distributed balance of gut microbiota and the destruction of intestinal defensive barriers.<sup>67</sup>

To sum up, these studies suggest a strong relationship between gut microbiota and cancer cachexia. Supplementation with probiotics can reduce the cachexia state and inflammation. Interestingly, regular physical exercise can reduce inflammation in the body and promote health by changing the gut microbiota.<sup>68</sup> Furthermore, it is known that autophagy is a key factor in the pathogenesis of SOB (sarcopenic obesity), a disease with a chronic

inflammatory state. Autophagy can remove dysfunctional organelles in senescent cells, thereby retaining normal mitochondria and ensuring normal skeletal muscle quality. AMP-activated protein kinase (AMPK) and the peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1 $\alpha$ ) signaling pathways has been involved in the activation of autophagy. These signaling pathways also appear to be involved in the gut- muscle axis. Therefore, the gut microbiota disorder may be related to the onset of SOB.<sup>69</sup>

## Gut Microbiota: The Bridge Between Exercise and Sarcopenia

Nutrition and exercise intervention are the most important interventions for sarcopenia.<sup>70–73</sup> Nutritional supplements currently proven to be useful for sarcopenia are protein,<sup>74,75</sup> essential amino acids,<sup>76</sup> Vitamin D, bisphosphonates, calcifediol and calcium. Vitamin D supplementation has a small but significant effect on muscle strength, but the specific dosage, duration of use and the underlying mechanism have not been fully explained.<sup>77,78</sup> Calcifediol has a significant effect on improving muscle function in postmenopausal women.<sup>79</sup> The combined use of calcium and phosphate can significantly improve the muscle strength of patients with hip fractures.<sup>80</sup> The role of protein in sarcopenia will be discussed in the next section.

Different types of exercise have different effects on muscles. Aerobic endurance exercise can increase the flexibility of exercise. Still, muscle strength and muscle mass improvement are not obvious and can only be used as an auxiliary exercise method. Resistance exercise can significantly improve muscle strength and affect muscle function and structure at the same time.<sup>70,71</sup>

Evans et al found different gut microbiota composition in obese mice and healthy animals. After exercise intervention, the gut microbiota of the experimental group was similar to the one found in normal mice.<sup>81</sup> Zhao et al found that gut microbiota's composition (the feces' organic acids are significantly increased, and the nucleic acid-related substances are significantly reduced) drastically changes after a long endurance run (eg, half marathon).<sup>82</sup> Exercise can also lead to the increase of muscle mass and function through gut microbiota, thereby reducing the occurrence of sarcopenia. Morita et al found that aerobic exercise 12-week training with brisk walking increased intestinal *Bacteroides*, as well as trunk muscle

strength and cardiopulmonary function in elderly women (over the age of 65).<sup>83</sup> This is due to the following reasons: firstly, exercise increases the blood flow in the guts, strengthens the contraction of abdominal muscles, and accelerates the release of gastrointestinal hormones, thereby speeding up the peristalsis of food and shortening the time to pass through the colon. Thus, the pH of the colon affects the gut microbiota.<sup>84–86</sup> Secondly, aerobic exercise increases the content of short-chain fatty acids (SCFA) in the feces, which can slightly reduce the intestines' pH, leading to very suitable conditions for intestinal *Bacteroides* growth.<sup>87,88</sup> Intestinal probiotics can reduce inflammation, prevent diarrhea, and intestinal infections, all of which are favorable for the development of sarcopenia.<sup>89</sup>

## Mechanism: Nutritional Supplements

Protein supplementation is commonly used for the prevention and treatment of sarcopenia.<sup>70,72,73</sup> Meat is one of the main sources of protein<sup>90</sup> that can be classified into red meat (pork and beef), white meat (chicken and fish), and non-meat protein (soy and cereal). Zhu et al<sup>91</sup> compared the composition of gut bacteria in the caecum obtained from rats fed with proteins from white meat (chicken and fish), red meat (beef and pork), and other sources (casein and soy). They found a higher amount of *Lactobacillus* in the white meat than in the red meat or non-meat protein groups. However, Ma et al<sup>92</sup> found that *Lactobacilli*, *Bifidobacteria*, and butyrate-producing bacteria were reduced after protein supplementation in mice. This may be related to the difference in experimental methods.

Gut microbiota can affect the body's antioxidant effect, skeletal muscle health, and athletic ability.<sup>93</sup> Moreno-Pérez et al<sup>94</sup> found no increase in microbiota fermentation products (ammonia and SCFA concentrations) but an increase in the number of microbiota in athletes that received 10 weeks of protein supplementation (a mixture of whey and beef). This bacteria can fully decompose protein, increase intestinal protein's utilization rate,<sup>94</sup> and use urea as a nitrogen source.<sup>95</sup> In addition, the number of *Blautia*, *Roseburia*, and *Bifidobacterium longum* decreased; *Blautia* and *Roseburia* are associated with the production of SCFA, which has been proved to have health benefits.<sup>96</sup> In addition, Blanton et al found immature gut microbiota in malnourished, which indicated that bacteria in the gut might be related to the growth and development of children. In contrast, the gut imbalance microbiota may cause difficulty in nutrient absorption.<sup>97</sup>

Newsome et al used isotopic and genetic methods to explore gut microbiota that can provide an essential source for the synthesis of host tissue structure: essential amino acids, of which valine is most absorbed.<sup>98</sup> Valine and other branched-chain amino acids are the raw materials for protein synthesis and important energy sources in the body during hunger, lactation, exercise, and disease: the energy conversion of liver gluconeogenesis is accelerated, and the serum concentration of alanine and glutamic acid is reduced. At this time, supplementing branched-chain amino acids can save muscle glycogen, make the energy source of skeletal muscle to last, and increase muscle endurance.<sup>99,100</sup>

Many studies have established that intestinal microbiota can produce short-chain fatty acids (SCFAs).<sup>94,96</sup> In mice treated with antibiotics, the gut microbiota, the number of SCFAs, and the exercise endurance are reduced. After adding SCFAs, the exercise endurance of mice significantly increases. Therefore, the gut microbiota may affect muscle energy metabolism through SCFAs.<sup>101</sup> The gut microbiota can ferment indigestible carbohydrates to produce short-chain fatty acids. SCFS is mainly composed of three substances: acetate, propionate, and butyrate, absorbed from the intestinal cavity to regulate the metabolism of the whole body and affect muscle and fat metabolism.<sup>102</sup> SCFS can also regulate energy metabolism and immunity, prevent and treat the occurrence of sarcopenia and muscle atrophy.<sup>103,104</sup> The degree of fatty acid saturation is also highly correlated. In mice treated with saturated (HFD-sat), n-6 (HFD-n6), or n-3 (HFD-n3) fatty acids for 8 weeks, the saturated fatty acid group increased insulin resistance, colon permeability, and mesentery fat inflammation.<sup>105</sup> Zou et al implemented a calorie-restricted diet for non-obese patients (40% less than the recommended daily intake) and found limited changes in gut microbiota were limited; the changes in the concentration of gut microbiota-dependent plasma amino acids: 3-Increased methylhistidine, this substance is related to skeletal muscle protein.<sup>106</sup> However, there is no research directly on the connection between sarcopenia and nutrition through the gut microbiota, although there have been speculations that indirectly confirm this.

Some studies found that alcohol, dietary fiber can play a role in the gut-muscle axis. A cross-sectional study discovered that a high fiber diet could lead to a better physical function (short physical performance battery (SPPB) score and grip strength) compared with a diet with low fibers.<sup>107</sup> Bjørkhaug et al found a lower muscle

mass and different gut microbiota (more proteobacteria and fewer *Enterococcus faecalis* bacteria) in people with a long history of heavy alcohol consumption compared to a control group.<sup>108</sup> However, this study only clarified this phenomenon but did not prove the causality.

At the same time, another study found that eating time (day or night) has a certain impact on gut microbiota and muscle function. In comparison, eating at night should be avoided. Hormonal changes may play a role in this.<sup>109</sup>

Previous studies<sup>110</sup> have found that metronidazole can upregulate the expression of factors related to skeletal muscle neurogenic atrophy, such as Hdac4, myogenin, MuRF1, and atrogin1, decreasing the muscle mass of their hind limbs and the muscle fiber volume of the anterior tibial muscle in mice. It can also cause changes in the gut microbiota, which in turn affect the expression of genes related to muscle metabolism, including Cry2, Ror- $\beta$ , E4BP4, PPAR $\gamma$ , Bmal1, Per2, FoxO1, and Pdk4, and the expression of adiponectin increased. Adiponectin (ApN) is considered to be significantly associated with the occurrence of sarcopenia. A prospective cohort study by Huang et al indicated that an increased plasma ApN level in 434 elderly people is significantly associated with decreased physical activity.<sup>111</sup> Therefore, it is reasonable to guess that antibiotics use may cause gut microbiota imbalance and thus reduce muscle mass.

## Endocrine Part of Gut Microbiota

Skeletal muscle and adipose tissue are endocrine organs that secrete myokines and adipokines, impacting skeletal muscle. Suriano et al found that the gut microbiota can affect the skeletal muscle using myokines and adipokines metabolism.<sup>112</sup> Transplanting gut microbiota can increase fat mass and leptin in germ-free mice.<sup>103</sup> Leptin promotes fatty acid oxidation and triglyceride breakdown in skeletal muscle cells. Some studies believe that leptin can increase the risk of sarcopenia. It can also reflect inflammation related to lipodystrophy, thereby promoting sarcopenia through chronic inflammation.<sup>17,18</sup> Higher serum content of adiponectin, which has anti-inflammatory, antioxidant, and insulin-sensitizing effects, has been found in mice treated with antibiotics.<sup>33</sup> Furthermore, Huang et al found that the increase in plasma adiponectin levels in 434 elderly people was significantly associated with decreased physical activity and was associated with the occurrence of sarcopenia.<sup>34</sup> This data indicate that the gut microbiota has an essential role in regulating different adipokines. Moreover, androgens have the effect of

promoting muscle synthesis, and supplementing the gut microbiota can reduce muscle loss in individuals lacking androgens.<sup>113</sup> Therefore, the gut microbiota can interact with the endocrine system related to muscle mass and sarcopenia.

In obese mice, certain gut microbiota and its metabolites can regulate insulin clearance, while in mice treated with antibiotics, insulin clearance is impaired. *Clostridiaceae* is related to insulin levels, *Enterococcaceae* correlated with impaired insulin clearance, and *Peptostreptococcaceae* is related to insulin secretion damage. Hyperinsulinemia is the cause and result of obesity or insulin resistance. Hyperinsulinemia comes from insufficient insulin clearance or excessive insulin production. Insulin resistance makes muscle cells unable to use glucose but can only use glycogen or fat, which may cause muscle mass loss and cause sarcopenia.<sup>36</sup>

## Conclusions: Gut Microbiota: The Neglected Actor in Sarcopenia?

The gut microbiota can interact with muscle mass and its function through inflammation, immunity, energy metabolism, and insulin sensitivity, thus affecting the body's physiological function. The diagnostic criteria for sarcopenia and the detection methods of intestinal flora are rapidly developing, thus making the research process more convenient and efficient. Future research is warranted to further confirm the correlation, mechanism, and other details of the gut-muscle axis. Moreover, further studies on nutrition and exercise, and gut-muscle axis are also needed. Scholars should also focus on the effects of probiotics, prebiotics, synbiotics, and certain drugs on muscle mass and muscle function, as the gut-muscle axis is a very promising research direction in sarcopenia.

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## Disclosure

The authors report no conflicts of interest in this work.

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