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Human Gut Microbiome: the Hypothesis of a Gut-Muscle Axis in the Elderly

Menschliches Darm-Mikrobiom: Die Hypothese einer Darm-Muskel-Achse im Alter

REVIEW

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Summary

› **In the last decade,** scientists have accumulated increasing evidence showing that the human gut microbiota, i.e. the ensemble of bacteria symbiotically living in the intestinal lumen of every individual, is involved in many aspects of human physiology and, possibly, disease.

› **In fact,** specific alterations of the gut microbiota, generally referred with the term of "dysbiosis", have been detected in a large number of acute and chronic diseases, not involving only gastroenteric system. The microbiota may exert its influence on distant organs with multiple mechanisms, involving modulation of inflammation, anabolism, insulin sensitivity, bioavailability of nutrients, release of toxins, and metabolically active mediators.

› **In this short review,** we summarize the basis of the "gut-muscle axis" hypothesis, that is, the possible influence exerted by gut microbiota composition on skeletal muscle metabolism and function. This hypothesis is particularly focused on the pathophysiology of sarcopenia, the age-related loss of muscle mass and function associated with a large number of adverse outcomes in older people.

› **Although no human studies** support the possible involvement of gut microbiota in the onset of sarcopenia, some studies performed on mouse models seem to support the assumption that the age-related decline in muscle mass and function is associated with a distinct gut microbiota composition towards dysbiosis.

› **More studies** should thus investigate the possible connections between gut microbiota and muscle health.

KEY WORDS:
Microbiota, Sarcopenia, Mobility Limitations, Aging, Inflammation, Muscle Mass, Muscle Function

Zusammenfassung

› **In den letzten zehn Jahren** haben Wissenschaftler immer mehr Beweise dafür gesammelt, dass die menschliche Darm-Mikrobiota, d. h. das Ensemble von Bakterien, die symbiotisch im Darmlumen jedes Einzelnen leben, an vielen Aspekten der menschlichen Physiologie und möglicherweise an Krankheiten beteiligt ist.

› **Tatsächlich** wurden spezifische Veränderungen der Darm-Mikrobiota, die im Allgemeinen mit dem Begriff „Dysbiose" bezeichnet werden, bei einer Vielzahl von akuten und chronischen Erkrankungen nachgewiesen, die nicht nur das Magen-Darm-System betreffen. Die Mikrobiota kann ihren Einfluss auf entfernte Organe mit mehreren Mechanismen ausüben, zu denen die Modulation von Entzündungen, Anabolismus, Insulinempfindlichkeit, Bioverfügbarkeit von Nährstoffen, Freisetzung von Toxinen und metabolisch aktiven Mediatoren gehören.

› **In diesem kurzen Überblick** fassen wir die Grundlage der Hypothese „Darm-Muskel-Achse" zusammen, d. h. den möglichen Einfluss der Darm-Mikrobiota-Zusammensetzung auf den Stoffwechsel und die Funktion des Skelettmuskels. Diese Hypothese konzentriert sich insbesondere auf die Pathophysiologie der Sarkopenie, den altersbedingten Verlust von Muskelmasse und Funktion, der mit einer Vielzahl von negativen Folgen bei älteren Menschen verbunden ist.

› **Obwohl keine Humanstudien** die mögliche Beteiligung von Darm-Mikrobiota am Beginn der Sarkopenie unterstützen, scheinen einige Studien an Mausmodellen die Annahme zu unterstützen, dass der altersbedingte Rückgang der Muskelmasse und -funktion mit einer ausgeprägten Darm-Mikrobioten-Zusammensetzung in Richtung Dysbiose verbunden ist.

› **Weitere** Studien sollten daher die möglichen Zusammenhänge zwischen Darm-Mikrobiota und Muskelgesundheit untersuchen.

SCHLÜSSELWÖRTER:
Mikrobiota, Sarkopenie, Bewegungseinschränkungen, Altern, Entzündung, Muskelmasse, Muskelfunktion

Introduction: Gut Microbiota Physiology

Gut microbiota is defined as the community of bacteria, protozoa, archaea, viruses and fungi symbiotically living with the host in the gastrointestinal tract. The bacterial component of gut microbiota is the most numerous and studied in pre-clinical and clinical environments. It is estimated that every human being harbors as much as 10^{14} bacterial cells in the gut lumen, with a genome 150-times larger than that of the host and a weight estimated between 750 g and 1.5 kg. A healthy gut microbiota is composed of a large number of species, between 1100 and 2000, mostly concentrated in the distal part of the gastroenteric tract (caecum, colon, sigma) (27, 32, 37).

The best and simplest way to study gut microbiota composition is to analyze fecal samples. Since most species contained in the gut microbiota cannot be cultivated with traditional laboratory techniques, next-generation sequencing methods, i.e. metagenomics, are necessary to obtain a precise picture of the overall microbiota composition (46). ›

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These methods are based on the identification of polymorphisms of a single bacterial gene coding for 16S rRNA and comparison of obtained sequences with known sequences listed in taxonomic databases, in order to assign each polymorphism to a single taxon. This technique (16S rRNA microbial profiling) allows to determine the composition of gut microbiota from both a qualitative (i.e., which taxon is present) and quantitative (i.e., how much it is represented) point of view (46).

The gut microbiota composition of healthy adults is characterized by a relatively low number of species with high representation (including Bacteroides, Prevotella, Eubacterium, Alistipes) and a large number of species with low relative abundance but relevant metabolic activity (including Clostridium, Anaerotruncus, Butyrivibrio, Faecalibacterium, Akkermansia) (20). In adults, this composition is characterized by stability over time and resilience to perturbations (17).

A certain degree of inter-individual variability is also present. Several genetic, environmental and clinical factors influence this variability (35). These factors include geography, diet, lifestyle, ageing, diseases and drug treatments (50). The importance of diet as modulator of gut microbiota composition has been particularly emphasized in the scientific literature (29, 47). A large consumption of animal proteins has been linked with a shift towards expansion of microbial populations belonging to the phylum Bacteroidetes, while consumption of fruit and vegetables induces expansion of microbial populations belonging to Firmicutes (29, 47). Additionally, several studies performed on both animal models and human beings underline that physical activity and exercise may contribute substantially to increase gut microbiota diversity and limit the expansion of microbial taxa with a potentially harmful effect (7).

Moreover, during aging, gut microbiota composition is physiologically characterized by increased inter-individual variability, reduced resilience after stressful events and reduced overall number of taxa represented. These alterations are generally emphasized in those subjects with mobility-disability and residing in nursing homes (14, 19, 21).

The Systemic Influence of Gut Microbiota

From a medical point of view, alterations in gut microbiota composition have been associated with a large number of diseases, not involving only the gastroenteric system (for example, diabetes, obesity, asthma, Parkinson's disease, chronic kidney disease) (27). These alterations are generally defined with the term of "dysbiosis", indicating a reduced biodiversity (i.e., lower number of species represented), underexpression of taxa with purported beneficial metabolic activites and overexpression of pathobionts, including gram-negative opportunistic pathogens belonging to Enterobacteriaceae (13).

However, most of this evidence comes from cross-sectional studies, so that it is not possible to determine whether dysbiosis represents a cause, a co-factor, or simply a consequence of systemic diseases (37). Moreover, studies exploring the functional profiling of microbial communities and the effects of gut microbiota modulation with probiotics or functional foods are still lacking in several areas of microbiome research (37).

Nevertheless, the current state-of-art allows hypothesizing that gut microbiota may influence the physio-pathology of several organs outside the gastrointestinal system, including liver, brain, kidneys, lungs and bones (31). Several possible mechanisms may be involved (43), listed in Table 1. Among these mechanisms, the gut microbiota-induced modulation of systemic inflammation seems fundamental (25). A dysbiotic gut microbiota may in fact produce pro-inflammatory metabolites or toxins, like lipopolysaccharide (LPS), absorbed by intestinal epithelium, or promote reduction of gut mucosa permeability ("leaky gut"), allowing bacteria to enter circulation (25).

For example, several studies performed on animal models support a link between dysbiosis and many aspects of the physio-pathology of dementia ("gut-brain axis"), including the capacity to promote neuroinflammation (43). Although studies on human beings are scarce, the role of gut microbiota in modulation of brain function has already been demonstrated in hepatic encephalopathy (4). Dysbiosis may also influence kidney function ("gut-kidney axis") in chronic kidney disease progression (12), and even the formation of kidney stones, implying a reduced representation of bacteria degrading oxalate, which is the main component of stones (41). Recent evidence also supports the existence of a "gut-bone axis", since the administration of a probiotic containing Lactobacillus reuteri can be associated with a reduction of the age-related bone mineral density loss in older women (33).

The Gut-Muscle Axis In Muscle Wasting Disorders

In this scenario of increasing evidence that gut microbiota may influence the physio-pathology of distant organs, three research groups have independently hypothesized that a "gut-muscle axis" also exists, particularly in the onset and clinical course of age-related sarcopenia (18, 34, 39). In older people, sarcopenia has been defined as an age-related reduction of muscle strength and quantity or quality in the absence of any identifiable single underlying cause (15). It has a prevalence of 15-25% in community-dwellers over 70 years of age, with peaks of up to 50% in subjects over 85 years old admitted to hospital for acute diseases (28). It also represents a frequent complication of hospital stay in older people, and is frequently associated with frailty, multimorbidity and poor quality of life (8). The clinical relevance of sarcopenia mainly depends on its capacity to predict functional disability and mortality, justifying its label as a "geriatric giant" (6).

From a physio-pathological point of view, sarcopenia is a multi-factorial condition influenced by immobility, physical activity, malnutrition, malabsorption, age-related motor neuron losses, and endocrine factors physiologically occurring with aging, including insulin resistance, abnormal thyroid function, reduced growth hormone and reduced sexual hormone synthesis (23). However, a central role is played by chronic systemic inflammation. This mechanism alone is able to reduce insulin sensitivity, promote a shift towards muscle protein degradation at the expense of protein synthesis, reduce muscle mitochondrial biogenesis and function, and impair muscle capillarity, ultimately leading to reduced muscle mass and function (16). Sarcopenic patients in fact have increased levels of serum C-reactive protein (CRP), although studies on other inflammatory mediators, such as interleukin-6, have not given clear results (5). Moreover, an aged immune system and inadequate nutrition may play a central role in stimulating chronic inflammation activation, and thus support the maintenance of sarcopenia (40, 49).

All these physio-pathologic elements may be influenced by the gut microbiota. In older subjects, gut microbiota composition may represent a marker of health status and probably a predictor of health decline and mortality (42). The frailty index, a clinical measure of fitness, is associated with gut microbiota dysbiosis, characterized by reduced

Table 1

Summary of the main mechanisms by which gut microbiota is able to influence the physio-pathology of distant organs, with a specific focus on the putative "gut-muscle axis".

MECHANISM	POSSIBLE MEDIATORS	RELEVANCE FOR THE SKELETAL MUSCLE
Release of bacterial toxins into circulation	Lipopolysaccharide and other species-specific toxins	Stimulation of chronic inflammation and immune system activation
Reduced gut mucosa permeability	Bacteria or their components penetrating circulation	Stimulation of chronic inflammation and immune system activation
Production of metabolites with endocrine function	Short-chain fatty acids (acetate, propionate, butyrate)	Promotion of insulin sensitivity
		Promotion of muscle anabolism and adipose tissue catabolism
		Modulation of inflammation
		Stimulation of mitochondrial biogenesis
		Reduction of myocyte apoptosis
Modulation of dietary amino acid bioavailability	None	Availability of substrates for protein synthesis
Synthesis of substances with nutritive significance for the host	Folate, riboflavin, vitamin B12, glycine betaine	Stimulation of anabolism and insulin-growth factor-1 synthesis
		Prevention of oxidative stress and endothelial damage
		Improvement of redox reactions
		DNA synthesis, methylation and repair
Transformation of dietary nutrients into metabolically active mediators	Urolithins derived by ellagitannins (most known example)	Improved mitochondrial biogenesis and muscle strength
Modulation of autonomic nervous system function	Unknown	None known

representation of taxa with possible anti-inflammatory effects (such as Faecalibacterium prausnitzii) and blooming of pathobionts (21).

In this context, the gut microbiota may influence the skeletal muscle metabolism through multiple mechanisms, summarized in table 1.

First, gut microbiota has a well-demonstrated capacity of modulating the anabolic-catabolic balance. Germ-free mice exhibit a persistently lean phenotype even when fed a high-fat diet (3). Conversely, the transplantation of fecal microbiota from malnourished Malawian children to germ-free mice resulted in mouse failure-to-thrive, underlying that gut microbiota represents a fundamental transducer of pro-anabolic stimuli from diet to the host organs and tissues (9). Moreover, the administration of a probiotic blend containing Lactobacillus reuteri to transgenic mice genetically prone to muscle wasting and cachexia resulted in a significant improvement in muscle mass and size and in prevention of age-related decline of muscle mass (45).

Second, several metabolites produced by the gut microbiota can be absorbed by the gut mucosa and influence the skeletal muscle physiology (39). Some of these are used by the host as nutrients, and include folic acid, riboflavin, vitamin B12, glycine betaine and some amino acids. These nutrients have different effects on skeletal muscle physiology, ranging from promotion of DNA synthesis and repair to stimulation of anabolism and cell proliferation through the mediation of insulin growth-factor 1 (IGF-1) (39). A healthy gut microbiota can produce relevant amounts of these substances, and also promote amino acid bioavailability. Conversely, dysbiosis may be associated with reduced production of these nutrients and absorption of amino acids, negatively influencing the muscle protein turnover (26).

Other microbial metabolites, once absorbed into the circulation, may act as endocrine mediators with a significant influence on skeletal muscle metabolism and function. The main of these mediators are represented by short-chain fatty acids (SCFAs), i.e. acetate, propionate and butyrate (11). These substances are produced by specific microbial communities including Faecalibacterium, Butyricimonas, Succinivibrio, Pseudosuccinivibrio and even some non-pathogenic Clostridia. They have a well-documented effect of insulin-sensitivity promotion, modulation of inflammation, modulation of satiety and stimulation of adipose tissue catabolism, ultimately resulting in pro-anabolic stimuli for the skeletal muscle cells (11). In myocytes, acetate and propionate promote glucose uptake and activation of peroxisome-proliferator activated receptors δ (PPARδ), resulting in increased mitochondrial biogenesis (11). Propionate also improves lipid mobilization from adipose tissue, with improved fatty acid oxidation in muscular mitochondria (11). The administration of butyrate to aging mice determined significant improvements in skeletal muscle cross-sectional area and overall lean mass, through a specific action of inhibition of the muscular enzyme histone deacetylase (48). Gut microbiota dysbiosis is generally characterized by a selective depletion of SCFA producers, resulting in a possibly reduced pro-anabolic or anti-catabolic effect for the skeletal muscle (39).

A healthy gut microbiota may also transform some substances contained in foods into metabolically active mediators influencing muscle function. For example, a specific metabotype of human gut microbiota is able to transform the ellagitannins contained in pomegranates, nuts and raspberries into a compound called urolithin A, exhibiting the capacity of improving muscle strength and exercise resistance in rats (36).

On the other side, age-related gut dysbiosis is associated with increased gut mucosa permeability, resulting in the penetration of bacterial toxins and even bacterial cells into the host circulation. These elements favor the activation of inflammatory response and promote chronic inflammation, representing one of the main mechanisms leading to muscle wasting (10).

All these elements support the plausibility of the existence of a gut-muscle axis influencing the physiopathology of sarcopenia. However, no human studies have confirmed this hypothesis to date. A single investigation, performed on ›

mouse models of age-related sarcopenia, has shown that sarcopenic mice have distinct signatures in the fecal microbiota composition, with significant depletion of SCFA-producing taxa and reduced capacity of metabolizing amino acids (38). These findings partly confirm gut "gut-muscle axis" hypothesis, but more studies are needed to verify the impact of gut microbiota on skeletal muscle function. In fact, the gut microbiota alterations associated with sarcopenia may represent only a consequence of the condition, and not an active player involved in its physio-pathology (37).

However, the effects of gut microbiota manipulation through probiotics or functional foods on human skeletal muscle represent a promising area of research in the future. The interactive connections between physical function, cognitive function, and microbiota should also be explored, since in aging physical function is strongly linked with cognition (24, 44).

Diet represents another fundamental player in these complex mechanisms. The studies performed on undernourished African children show that malnutrition is associated with profound alterations of gut microbiota towards dysbiosis (9). Age-related sarcopenia is often associated with malnutrition, especially in nursing home residents with mobility limitations or reduced access to physical activities (1). In this context, the microbiome could represent a fundamental transducer of pro-anabolic stimuli from diet to skeletal muscle. In nursing home residents, low-quality diets and low nutrient intake could influence muscle mass wasting through mediation of intestinal microbiome (39).

Moreover, recent evidence supports the beneficial role of exercise on the diversity and functionality of human intestinal microbiota (7), suggesting that the putative gut-muscle axis may function in both senses (39). In animal models, the exercise-induced beneficial effects on gut microbiota allow to attenuate the pathological response to stressors, such as chemically-induced colitis (2). These findings may imply that some of the benefits induced by physical exercise programs in cancer patients undergoing active radio- or chemotherapeutical treatment (30) are mediated by the gut microbiota, opening new, unexpected scenarios in the relationship between exercise, skeletal muscle and microbiota.

Conclusions and Perspectives

The existence of a gut-muscle axis in human physio-pathology is highly plausible, especially in aging and age-related skeletal muscle wasting conditions. Diet and microbial metabolism of nutrients play a central role on this putative gut-muscle axis. However, no human studies support this hypothesis at the current literature state-of-art.

Future studies should assess the composition and functionality of intestinal microbiota in muscle wasting disorders, and of course more research is needed before gut microbiota can represent a reasonable and valid therapeutical target in muscle diseases.

Futhermore, the interactive connections between diet, exercise and microbiome will also need careful investigation in the future. A healthy intestinal microbiota, as that associated with physical exercise, may act as a significant modifier of several physio-pathological processes, involving the whole body and not limited to the gastrointestinal system. Conversely, the hypothesis that at least some of the harmful effects of inactivity are mediated by the gut microbiota composition and functionality should be also tested for its important practical implications.

Conflict of Interest
The authors have no conflict of interest.

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