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Gut Microbiota Contribute to Age-Related Changes in Skeletal Muscle Size, Composition, and Function: Biological Basis for a Gut-Muscle Axis

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Abstract

Skeletal muscle is a highly plastic tissue that plays a central role in human health and disease. Aging is associated with a decrease in muscle mass and function (sarcopenia) that is associated with a loss of independence and reduced quality of life. Gut microbiota, the bacteria, archaea, viruses, and eukaryotic microbes residing in the gastrointestinal tract are emerging as a potential contributor to age-associated muscle decline. Specifically, advancing age is characterized by a dysbiosis of gut microbiota that is associated with increased intestinal permeability, facilitating the passage of endotoxin and other microbial products (e.g., indoxyl sulfate) into the circulation. Upon entering the circulation, LPS and other microbial factors promote inflammatory signaling and skeletal muscle changes that are hallmarks of the aging muscle phenotype. This review will summarize existing literature suggesting cross-talk between gut microbiota and skeletal muscle health, with emphasis on the significance of this axis for mediating changes in aging skeletal muscle size, composition, and function.

Keywords

Skeletal muscle; Gut microbiota; Aging; Inflammation; Sarcopenia

Introduction

Skeletal muscle is the largest organ in the human body, comprising ~ 40% of total body mass [1]. The musculoskeletal system is best known for its role in locomotion and postural stabilization, but also serves as a large macronutrient reservoir, protects internal organs, maintains core temperature, and communicates with other bodily through the release of growth factors and cytokines [2]. For the past decade, the endocrine nature of skeletal muscle has been extensively examined, facilitating the characterization of a muscle secretome and providing unique insights into inter-organ communication networks [3, 4]. Equally as important as the effects of skeletal muscle secreted products on peripheral tissues are the ways in which external factors may act to modify skeletal muscle. One system with

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tremendous potential to impact host physiology is that of gut microbiota, the bacteria, archaea, viruses, and eukaryotic microbes that reside in the gastrointestinal tract [5]. The transformative power of gut microbiota on human physiology was emphasized in a groundbreaking study by Ridaura and colleagues [6], who demonstrated that fecal microbiota transplant from obese humans into lean animals precipitated body composition shifts consistent with the phenotype of their donor, highlighting the transmissible effects of metabolic phenotype via microbial exchange.

The human body is composed of an estimated 30 trillion cells living in symbiosis with diverse microbial communities [7]. In an effort to better understand our nature as human superorganisms, a decade ago the National Institute of Health launched the human microbiome project (HMP), an international public health initiative aimed at characterizing microorganisms associated with human health and disease [8]. Making use of advances in the field of metagenomics, HMP-associated studies employ high-throughput 16 s rRNA gene sequencing to streamline the analysis of gut microbial communities [8]. Human gut microbiota are mainly composed of Bacteroidetes and Firmicutes [9], which together account for more than 90% of all phylogenetic types, and are further subdivided to consist of more than 100 distinct bacterial species [10]. The composition of gut microbiota is shown to be dynamic throughout the lifespan, undergoing rapid changes from birth until ~ 3 years of age, after which greater stability is established [11, 12]. In later years (> 65 years), however, the proclivity for aberrant changes in microbial composition appears to accelerate [13–15]. Although the underlying cause(s) (host vs environment) of this apparent age-related microbial imbalance have yet to be defined, its relevance is underscored by the growing number of studies showing associations between gut ecology and cancer [16], cardiovascular disease [17], obesity [6], diabetes [18], and muscle wasting [19], some of the most prevalent conditions afflicting older members of society today.

Gut microbiota are emerging as a salient contributor to human health and disease [5], and their effects are particularly pronounced in older years [20]. As such, the interaction between gut microbiota and other organ systems (e.g., liver and brain) has been a recent focus of scientific inquiry [21, 22]. Furthermore, the existence of a gut-muscle communication pathway has been posited [23]. The purpose of this review will be to discuss existing literature suggesting communication between gut microbiota and skeletal muscle, with emphasis on the potential significance of this axis for mediating changes in aging muscle health. We will begin by reviewing the more well-recognized impact of gut microbiota on skeletal muscle metabolism before transitioning to the lesser acknowledged role of gut microbiota on the regulation of skeletal muscle size, composition, and function. To conclude, we will integrate these findings and propose a “gut-muscle axis” that we believe plays a role in the age-related loss of muscle mass and function (sarcopenia) [24].

Gut Microbiota and Skeletal Muscle Metabolism

Gut microbiota are intricately involved in helping to perform a number of necessary functions for their host. Given their gastrointestinal habitation, perhaps the more ostensible of these roles is their influence on metabolic function (e.g., nutrient absorption and amino acid synthesis) [25]. The importance of gut microbial health in energy metabolism is

exemplified by cases of Kwashiorkor, a form of severe acute malnutrition accompanied by perturbations in amino acid and carbohydrate metabolism that can be transiently ameliorated by dietary therapeutics that promote microbial reconfiguration (increased *Bifidobacterium*, and *Lactobacillus reuteri and gasseri*) [26]. Meanwhile, excess nutrient uptake and storage (i.e., obesity) is associated with low microbial diversity and changes in the relative abundance of the major bacterial phyla (Bacteroidetes and Firmicutes) [27–29]. While these findings provide support for microbial regulation of local metabolic function, evidence also suggests that gut microbiota may impact distal metabolic activity in skeletal muscle tissues [23, 30].

In a pioneering study conducted in 2004, Backhed et al. infused germ-free (GF) mice, animals born and raised in sterile conditions and lacking a microbiome, with the cecal contents of conventionally raised animals, and demonstrated a 60% increase in body fat with reciprocal reductions in insulin sensitivity and glucose tolerance [31]. As skeletal muscle is an integral component of glucose disposal, these findings suggest microbial-mediated regulation of muscle metabolic function. In support of this sentiment, bacterial colonization of GF mice appears to decrease skeletal muscle metabolic efficiency, as evidenced by an increase in tricarboxylic acid cycle intermediates without an appreciable increase in high-energy phosphate stores [31]. To understand the seemingly superior metabolic phenotype in microbiome-deficient mice, the same research group compared skeletal muscle protein activity and gene expression in GF and conventionally raised animals [23]. Compared to mice with gut microbiota, skeletal muscle from GF mice was characterized by markedly greater activity of AMP-activated protein kinase (AMPK) and carnitine palmitoyl transferase-1 (CPT-1), indicative of an elevated oxidative capacity. Taken together, these early studies suggest that gut microbiota can influence body composition by means of regulating skeletal muscle bioenergetic pathways.

To identify a mechanistic link between microbial dysbiosis and metabolic derangement (i.e., skeletal muscle insulin resistance), Cani et al. [18] subjected young mice to a high-fat diet, which is known to induce chronic low-grade chronic inflammation (e.g., IL-1, IL-6, and TNF-α elevation), a reported contributor to insulin resistance [32, 33]. As expected, high-fat fed mice exhibited an increase in body weight and inflammatory markers as well as a decrease in glucose tolerance. In addition, circulating levels of lipopolysaccharide (LPS), a component of the outer membrane of gram negative bacteria, were 2- to-3-fold elevated in high-fat fed mice when compared with control fed animals. Pertinently, high-fat feeding is shown to compromise epithelial tight junctions and increase intestinal permeability [34, 35], evidence that suggests a role for high-fat induced leak of LPS from the intestine into the circulation.

To examine the contribution of circulating LPS (i.e., metabolic endotoxemia) to insulin insensitivity, the same research team subjected wild-type and CD-14 mutant mice, which lack an endotoxin receptor, to LPS infusion [18]. In support of LPS-mediated dysregulation of insulin signaling, pro-inflammatory cytokine induction and impairments in glucose tolerance were observed exclusively in the wild-type animals. Endotoxin-mediated reductions in glucose tolerance have been similarly shown in humans inoculated with LPS, as evidenced by significant increases in skeletal muscle NF-κβ binding activity and JNK

phosphorylation, which synergistically inhibit insulin signaling [36]. These studies and others [30, 37], show that circulating LPS, a prominent component of gut microbiota, induces skeletal muscle inflammation and insulin resistance thereby contributing to the development of metabolic syndrome. While these findings implicate LPS and inflammation as causative agents in the process, inflammation-independent alterations in skeletal muscle metabolism have also been observed. For example, in response to the gut microbiota-specific metabolite indoxyl sulfate [38], C2C12 myoblasts exhibit an up-regulation of glycolysis and an increase in the activity of the pentose phosphate pathway [39]. Similarly, exposure of myotubes to gut microbial-derived extracellular vesicles induces insulin resistance [30], highlighting the multitude of ways in which gut microbiota may influence the metabolic function of skeletal muscle.

Insulin-resistant type 2 diabetes may occur at any age, but its prevalence is greater in older years (> 25% in persons ≥ 65 years) [40]. Older adults with diabetes are at an increased risk for cardiovascular complications, reduced functional status, loss of independence, and mortality [41]. With the relationship between inflammation and insulin resistance in mind, Ghosh et al. sought to assess the contribution of circulating endotoxin to this age-related inflammatory/insulin-resistant phenotype [42]. As hypothesized, in older individuals circulating LPS and skeletal muscle TLR4 (a receptor for LPS [43]) gene expression and protein content were higher, and insulin sensitivity (quantified by HOMA-IR) was lower than their younger counterparts. These findings suggest that an age-related increase in LPS levels might contribute to the greater occurrence of diabetes in older persons.

Gut Microbiota and Skeletal Muscle Size, Composition, and Function

Muscle Size

Age-related inflammation is associated with reductions in skeletal muscle size and function (sarcopenia) [44]. Furthermore, obesity appears to exacerbate the progression of sarcopenia by compounding inflammatory burden [45], resulting in a state of sarcopenic obesity, defined as inadequate muscle mass relative to total body size [24]. A variety of phenomena have been proposed to contribute to this age-related heightened inflammatory state including redox stress [46], immuno- and endocrine senescence [47, 48], DNA damage [49], epigenetic modification [50], and a distortion of gut microbial homeostasis [51] that is associated with increased levels of circulating endotoxin [42]. An extreme model of LPS-induced inflammation is the clinical condition sepsis, a life-threatening illness characterized by severe muscle wasting due to both increases in proteolytic degradation and reductions in protein synthesis [52]. Ubiquitously discussed in the context of skeletal muscle inflammation, TNF-α and IL-6 are strongly induced by circulating LPS [53] and elevated in aging individuals [54, 55]. Macrophage production of TNF-α is shown to occur early in the stress response, and has been demonstrated to stimulate protein degradation and apoptosis in cultured cells [56, 57]. Meanwhile, secreted by both macrophages and T-cells, studies in both animals and humans implicate IL-6 involvement in the repression of protein synthesis [58, 59]. Interpreted in unison, these findings demonstrate the ability of LPS-associated cytokines to determinately affect protein equilibrium (i.e., synthesis and breakdown), and suggest that elevated endotoxin levels with age may contribute to reductions in muscle mass.

It is interesting to note that the tryptophan derivative indoxyl sulfate, which is similarly shown to increase with age [60], is reported to induce inflammatory cytokine expression (IL-6 and TNF-α) and markers of muscle atrophy (myostatin and atrogin-1) similar to that of LPS in cultured myocytes [61]. Furthermore, in vivo administration of indoxyl sulfate is shown to increase atrogene expression in conjunction with decreased muscle mass in mice [61]. These findings highlight the importance of comprehensively examining microbial metabolites for triggers of myocellular adaptation [62], rather than focusing on a single microbial byproduct.

From a feasibility standpoint, the ability to influence skeletal muscle size by altering the composition of gut microbiota is attractive, particularly in circumstances where muscle loading may be challenging (e.g., immobilization, hospitalization, spaceflight). One of the first studies to target gut microbiota as a means to affect lean tissue mass was conducted by Bindels et al. using a leukemic mouse model [19]. Microbial profiling in these cachectic mice revealed gut dysbiosis characterized by selective modulation of *Lactobacillus* spp. To restore lactobacilli levels, the leukemic mice were given an oral probiotic containing *Lactobacillus reuteri and L. gasseri* that appeared to decrease serum levels of inflammatory cytokines (IL-6 and MCP-1) and atrogene expression (MuRF1 and Atrogin-1) in conjunction with an increase in mass of the tibialis anterior. Interestingly, these effects appear to be bacterial species specific, as *L. acidophilus* supplementation did not appear to affect inflammatory or atrophy markers [19]. However, *L. plantarum* supplementation has demonstrated to increase lean mass and function (grip strength and swim time) in healthy young mice [63]. Taken together, these studies suggest a link between *Lactobacillus* species and skeletal muscle size that is worthy of further investigation in humans.

Prebiotics are fermented non-digestible compounds that support the proliferation of health-promoting bacteria [64] and thus may influence skeletal muscle health. The efficacy of prebiotic supplementation to support beneficial skeletal muscle changes was demonstrated in a study by Cani et al., who showed a decrease in circulating LPS and inflammation and an increase in muscle mass in obese mice fed the prebiotic fiber oligofructose [65]. Follow-up analyses confirmed the favorable effect of prebiotic feeding on gut microbiota, as was evidenced by a shift in the ratio of Bacteroidetes/Firmicutes in addition to increases in the levels of *Lactobacillus* and *Bifidobacterium* spp. [66]. In further support of a link between prebiotics with skeletal muscle, administration of a synbiotic containing inulin-type fructans and *Lactobacillus reuteri* was shown to reverse increases in *Escherichia* and promoted proliferation of *Lactobacillus and Bifidobacterium* in leukaemic mice [67]. Coupling of these microbial alterations with restoration of intestinal homeostasis (e.g., increase tight junction proteins) and a reduction in muscle wasting suggests that *Lactobacillus* and *Bifidobacterium* may influence gut-muscle communication and regulate muscle size. Interestingly, *Bifidobacterium* are shown to decrease with age [68], and are associated with lower intestinal [69] and circulating LPS levels [70]. Thus, an age-related decrease in gut *Bifidobacterium* content may underlie increases in circulating endotoxin that are shown to induce skeletal muscle atrophy [71]. While we were not able to identify any studies showing *Bifidobacterium* supplementation to increase muscle mass, data showing butyrate (associated with *Bifidobacterium* [72]) treatment to protect against age-related muscle atrophy [73] supports the idea that pre- and/or probiotic supplementation, which is shown to

increase the abundance of *Bifidobacterium* and butyrate producers in older individuals [74, 75], may prophylactically moderate aging muscle loss.

Muscle Composition

While the age-associated loss of muscle mass is purported to play a role in the loss of strength and function [76, 77], strength declines far exceed reductions in muscle mass [78], suggesting a change in intrinsic muscle function (i.e., muscle quality). Although a number of factors have been implicated in aging muscle quality deficits [79, 80], adipose tissue infiltration in skeletal muscle (i.e., change in muscle composition) has been shown to increase with age [81] and is associated with mobility impairment [82]. To assess the relationship between gut microbiota, inflammation, and muscle composition, Collins et al. subjected young rats to a high-fat high-sucrose diet and found an increase in *Enterobacteriaceae* (gram-negative member of the Proteobacteria phylum) and a decrease in the abundance of *Lactobacillus spp.*, changes that have been similarly reported with aging [83, 84]. Concomitant with these changes, the authors reported an increase in circulating inflammatory cytokines (IL-6, TNF-α, and MCP-1) and intramuscular fat after just 3 days [85], suggesting rapid dysregulation of these seemingly inter-connected systems. Regulation of muscle composition by gut microbiota is supported by associations between gut bacteria involved in energy metabolism and porcine intramuscular fat content [86]. Furthermore, age-related changes in gut microbiota have also been proposed to evoke fat infiltration into bone [87, 88], culminating in a triad of aberrant muscle, bone, and adipose tissue dysregulation (osteosarcopenic obesity). A limitation of these analyses is an inability to distinguish if changes in microbiota are a driver or a product of this compromise to bone and muscle integrity. However, probiotic rescue (*Lactobacillus reuteri and gasseri*) of inflammation and muscle/bone loss in mice proposes that gut microbiota initiate this relationship [19, 67, 89].

Also contributing to changes in muscle composition, aging has been associated with alterations in myosin heavy chain (MHC) distribution [90]. Specifically, aging muscle appears to undergo a fast-to-slow fiber-type shift [91], that is hypothesized to reduce whole muscle power and increase fall risk [92, 93]. Although a topic of intense scrutiny, studies have yet to elucidate a definitive mechanism underlying this phenomenon. It is thus interesting to note that over the course of the past year, two independent studies have observed changes in skeletal muscle MHC composition following interventions aimed at manipulating gut microbiota [63, 94]. Pertinently, in one of these studies by Yan and colleagues [94], transfer of gut microbiota from an obese pig to a GF mouse replicated the host myocellular phenotype, which mirrored that of aging skeletal muscle (i.e., fast fiber atrophy concomitant with a fast-to-slow fiber type shift). These findings highlight the possibility that gut microbiota can transfer muscle fiber characteristics, and open the door for studies investigating the transplant of microbiota from young to old as a means to improve skeletal muscle size and composition.

Muscle Function

Age-related changes in skeletal muscle size and composition summate to yield reductions in skeletal muscle function (strength and power) [77] that ultimately affect physical performance and the ability to live independently [95]. One of the first studies to link

changes in gut microbiota with functional capacity was conducted by van Tongeren et al. [84], who studied fecal microbes in a relatively small cohort of advanced agers (n = 23; ~ 86 years). Upon stratifying subjects by frailty score, a unique bacterial signature characterized by marked reductions in *Lactobacillus* (~ 8-fold less) and commensurate increases in the quantity of *Enterobacteriaceae* (~ 6-fold more) in frail agers emerged. Moreover, higher functioning subjects may have been protected from dysbiotic shifts in gut microbiota by a greater abundance of butyrate-producing bacteria such as *Faecalibacterium prausnitzii*. Indeed, butyrate is shown to enhance intestinal barrier function by reinforcing tight junction assembly [96], which, in theory, should prevent endotoxin translocation and reduce circulating inflammation [97]. The association between butyrate-generating bacteria and functional capacity is supported by metagenomics findings in a larger sample of older adults (n = 178; ~ 78 years) [98] demonstrating that community-dwelling elders had more butyrate-producing microbes than those in long-stay residence. Additionally, institutionalized elderly had a greater abundance of *Enterobacteriaceae* and *Escherichia/Shigella*, and less gut microbial diversity when compared with the community dwellers. Given the corresponding change in diet (i.e., low in plant-based nutrients and fiber and high in sucrose and saturated fat) and microbial composition when individuals enter long-term care facilities [99], geriatric clinicians are encouraged to work with older individuals undergoing residence relocation to pursue nutritional strategies that aim to prevent the loss of healthy microbes (e.g., butyrate-producing bacteria). Relevantly, prebiotic supplementation (inulin plus fructooligosaccharides) has been shown to increase muscle strength (handgrip) and endurance (exhaustion) in frail older adults [100], thereby highlighting the utility of prebiotic supplementation as a treatment for age-associated deficits in muscle function.

Studies investigating gut microbiota of athletes provide unique insight into microbial characteristics associated with high levels of physical function. Comparison of these bacterial traits to those of populations with reduced functional capacity (e.g., mobility-limited older adults) can provide data-driven targets for therapeutic intervention. One of the first investigations to assess gut microbiota in athletes was conducted by Clarke et al. who studied elite rugby players, individuals with large quantities of lean muscle tissue [101]. Comparison of microbial diversity among these athletes and both healthy normal weight (BMI ≤ 25) and overweight (BMI ≥ 28) age-matched controls elicited a hierarchical pattern (athletes > healthy > overweight), suggesting an association between microbial diversity, body composition, and physical function. While these findings implicate exercise training as a possible therapy for favorably altering the gut microbiota, greater total energy and protein intake in the athlete group may have affected these results. However, correlations between microbial diversity and cardiorespiratory fitness [102] in concert with the exercise training mediated rescue of high-fat diet-induced microbial disturbance [103] support the idea that exercise training may impart beneficial effects on gut health. In particular, regular physical activity may help to combat reductions in butyrate-producing microbiota (*Clostridiales, Roseburia, Lachnospiraceae, and Erysipelotrichaceae*) [102] and *Lactobacillus* levels [103] that are commonly seen with aging [15, 84, 98]. The beneficial changes in gut health seen with exercise training implicate skeletal muscle contraction as a regulator of microbial composition, and provide evidence for bi-directional gut-muscle effects. As a result, the superior microbial milieu in exercise trained persons may explain lower levels of plasma

endotoxin and inflammatory markers (plasminogen activator inhibitor type-1) in active vs sedentary individuals [104]. Interpreted as a whole, these findings advocate that exercise training is an effective means to promote beneficial changes in gut microbial health that seem to reduce circulating inflammation and support the maintenance of muscle mass and function.

Establishing an Aging Gut-Muscle Communication Axis

Inspection of the existing literature suggests that gut microbiota may play an important role in influencing aging skeletal muscle health (Fig. 1). We propose regulation of skeletal muscle by gut microbiota to occur in an endocrine manner, beginning with a disturbance in gut homeostasis and culminating with alterations in skeletal muscle characteristics. While changes in gut microbiota can be attributed to either host (genetics, age) or environmental (activity, diet) factors, we have focused on microbial dynamics with organismal aging. Although limited in number, investigations of age-related changes in gut microbiota describe a bacterial community that is both less diverse and lacking in microorganisms responsible for the production of butyrate (indicative of gastrointestinal health) [15, 84, 98, 99], and more abundant in pathogens belonging to the Proteobacteria phylum (e.g., *Enterobacteriaceae*) [15, 68, 83]. Associated with these changes is a decrease in the integrity of epithelial tight junctions and increased intestinal permeability [14], facilitating the translocation of microbial byproducts into circulation. Perhaps the most widely studied of these bacterial derivatives is LPS, the major component of the outer membrane of gram-negative bacteria that is found to be elevated in the circulation with aging [42]. Once in the blood, circulating endotoxin promotes systemic inflammation that appears to trigger maladaptation of skeletal muscle. As described throughout this review, these changes may manifest in older adults as decreases in muscle size and integrity that compromise physical function and ultimately detract from quality of life.

Perspectives and Steps Forward

In 2008, the NIH launched the Human Microbiome Project as a public health initiative to characterize the microorganisms contributing to human health and disease. In just a decade’s time, high-throughput 16 s rRNA gene sequencing techniques have identified robust associations between gut microbial ecology and many of the leading causes of death worldwide (e.g., heart disease, cancer, and diabetes) [16–18]. Although this field is still in its infancy, the data presented here provide evidence to suggest a bidirectional communication network between gut microbiota and skeletal muscle. This relationship is exemplified by commensurate changes in gut health and skeletal muscle with aging. Research in murine models has begun to identify microbial targets with likely skeletal muscle ramifications. These findings lay the framework for strategic human interventions aiming to manipulate microbial ecology as a means to benefit skeletal muscle health and extend healthy life years in a rapidly expanding aging population.

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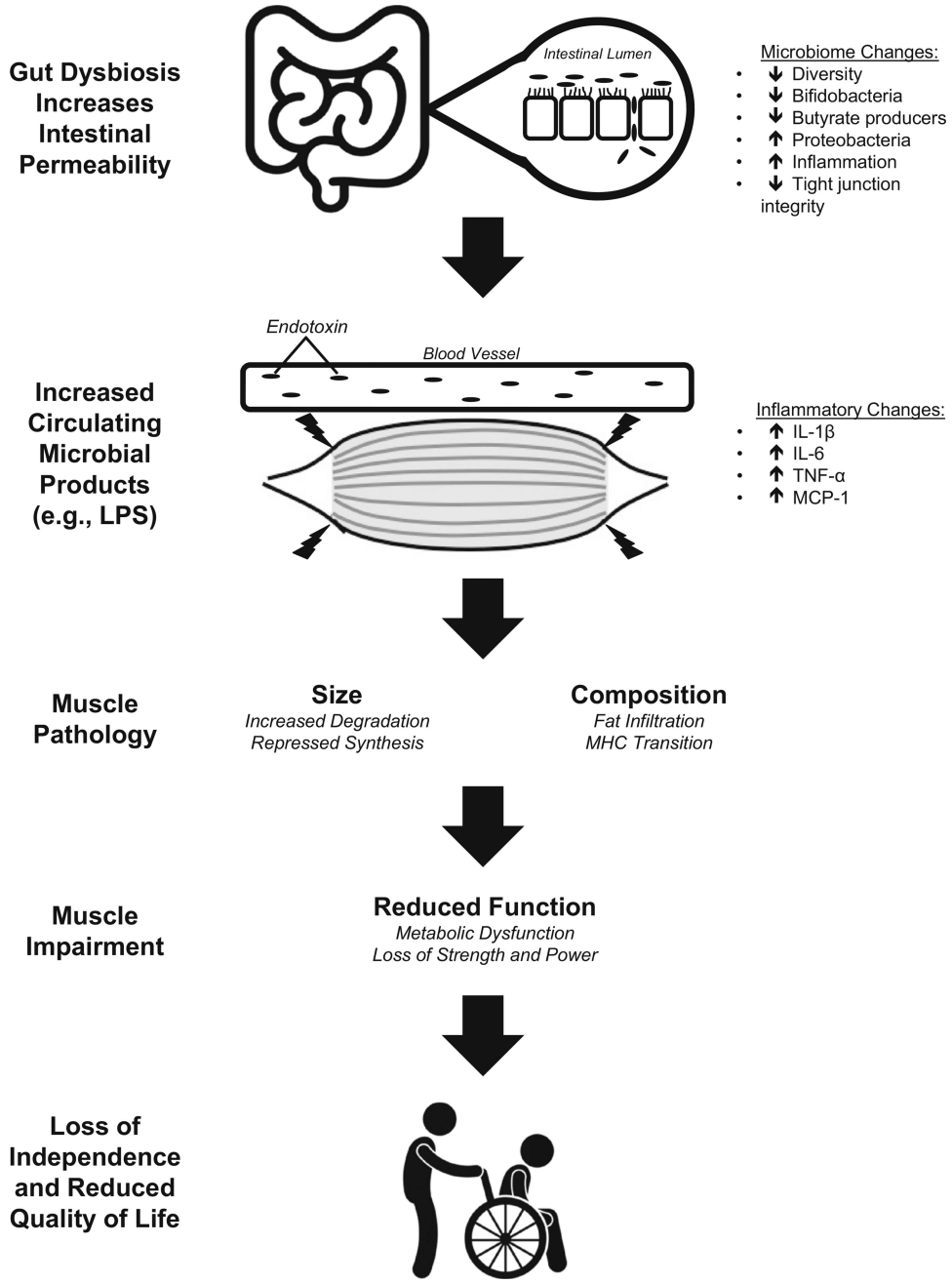

Fig. 1.

A gut-muscle axis that contributes to age-related changes in skeletal muscle size, composition, and function. Microbial shifts in the aging gut reduce tight junction integrity and increasing intestinal permeability allowing for the passage of microbial products (e.g., LPS, indoxyl sulfate, butyrate) into the blood. Once in the circulation, endotoxin and other microbial factors trigger pro-inflammatory signaling that is hypothesized to promote skeletal muscle atrophy concomitant with deleterious composition shifts. These changes lead to impairments in both the metabolic and contractile characteristics of skeletal muscle that

reduce functional capacity and ultimately compromise functional independence and quality of life in older adults