Zheng *et al. Cell Communication and Signaling* (2024) 22:558
https://doi.org/10.1186/s12964-024-01922-1

Cell Communication and Signaling

REVIEW Open Access

The gut microbiome, chronic kidney disease, and sarcopenia

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Abstract
Sarcopenia is a prevalent condition in patients with chronic kidney disease (CKD), intricately linked to adverse prognoses, heightened cardiovascular risks, and increased mortality rates. Extensive studies have found a close and complex association between gut microbiota, kidney and muscle. On one front, patients with CKD manifest disturbances in gut microbiota and alterations in serum metabolites. These abnormal microbiota composition and metabolites in turn participate in the development of CKD. On another front, altered gut microbiota and its metabolites may lead to significant changes in metabolic homeostasis and inflammation, ultimately contributing to the onset of sarcopenia. The disturbance of gut microbial homeostasis, coupled with the accumulation of toxic metabolites, exerts deleterious effects on skeletal muscles in CKD patients with sarcopenia. This review meticulously describes the alterations observed in gut microbiota and its serum metabolites in CKD and sarcopenia patients, providing a comprehensive overview of pertinent studies. By delving into the intricate interplay of gut microbiota and serum metabolites in CKD-associated sarcopenia, we aim to unveil novel treatment strategies for ameliorating their symptoms and prognosis.

Keywords Chronic kidney disease, Sarcopenia, Gut microbiota, Metabolomics

Introduction

Chronic kidney disease (CKD) is a condition associated with various metabolic disorders that can affect energy, protein, and muscle metabolism, and is considered a major risk factor for sarcopenia [1]. Meanwhile, with the increasing global prevalence of CKD, sarcopenia, as a prevalent condition in CKD, is also receiving increasing attention. According to the diagnostic criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) 2018, sarcopenia is characterized by low muscle mass, diminished muscle strength, and poor physical function [2]. A relevant study has indicated that the prevalence of sarcopenia in CKD patients ranges from 5–62.5% [3]. This variability of prevalence is mainly related to various factors such as the differences in study population (age, gender, race, stage of CKD), diagnostic criteria (such as those from EWGSOP and Asian Working Group for Sarcopenia), and methods used to assess

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muscle mass (such as dual energy X-ray absorptiometry, bioimpedance analysis and so on). In individuals with CKD, sarcopenia is frequently associated with poor physical activity performance, elevated risk of disability, increased incidence of cardiovascular events, and higher mortality [4–6]. Our previous research has found that low skeletal muscle density at the first lumbar vertebral level assessed by computed tomography, as an independent risk factor for both cardiac and all-cause death in CKD patients undergoing initial-dialysis [7]. Additionally, diaphragm dysfunction assessed by ultrasound has been shown to predict clinical outcomes in CKD patients receiving hemodialysis (HD) [8, 9]. Therefore, it is essential to investigate the factors contributing to the high prevalence of sarcopenia in CKD patients and to explore effective interventions.

Currently, our research along with findings from other teams suggest that the presence of hormonal imbalances, chronic inflammation, uremic toxin accumulation, metabolic acidosis, and related mechanical factors in CKD patients collectively contribute to a decrease in muscle synthesis and an increase in catabolism. This results in an unfavorable protein homeostasis balance, ultimately leading to the development of sarcopenia in patients [1, 10–12]. Notably, recent studies have also identified the significant role of gut microbiota disturbances in the development and progression of CKD with sarcopenia [13–15].

Altered gut microbiota has been observed in CKD patients experiencing sarcopenia [14]. Furthermore, there is evidence of the accumulation of gut microbiota-associated uremic toxins in the mice model of CKD with sarcopenia [16]. We hypothesized that gut microbiota could significantly contribute to the pathogenesis of sarcopenia in CKD. This contribution may occur through the destruction of gut barrier, accumulation of toxic metabolites, reduction of short-chain fatty acid (SCFA) and the induction of systemic low-grade inflammation [15, 17]. However, the underlying molecular mechanisms and signaling pathways remain inadequately understood. Therefore, further in-depth search and exploration of the changes and related mechanisms of gut microbiota and its serum metabolites in CKD patients with sarcopenia are needed, which in turn will provide new interventions for the prevention or amelioration of sarcopenia in CKD within a clinical setting.

In this review, we provide an overview of the current status of research landscape regarding gut microbiota disturbances in CKD patients, as well as a thorough examination of the alterations in gut microbiota and its metabolites associated with sarcopenia. Subsequently, we analyse the potential correlations among the gut microbiota, its serum metabolites and CKD with sarcopenia, proposing that the regulation of gut microbiota and its metabolites could emerge as a promising novel strategy for preventing or ameliorating sarcopenia in CKD.

Interaction between CKD and gut microbiota disturbances

It has long been observed that there is a complex interaction between the gut microbiota and the kidney, termed the gut-renal axis (Fig. 1). As CKD progresses, there are discernible changes in both the quantity and quality of gut microbiota changes, which are accompanied by alterations to the gut barrier, and an increase in gut permeability [18–20]. Primarily, shifts in the internal environment of CKD patients contribute to alterations in the gut microbiota. Increased levels of circulating urea in patients with progressive renal failure promotes the colonization and proliferation of urea-utilizing microbiota. Concurrently, the expansion of uricase-containing microbiota may result from increased colonic secretion of uric acid and oxalic acid, leading to gut microbiota disturbances [18, 21]. In addition to the above, reduced dietary fiber intake, increased constipation, diminished protein absorption, and frequent use of antibiotics and iron therapy are also involved in the development of gut microbiota disturbances in CKD patients [22]. Subsequently, changes in the gut microbiota give rise to heightened ammonia production in the intestinal lumen, and cause changes in intestinal pH [18, 22], thereby increasing gut permeability by modifying the tight junctions of intestinal epithelial cells [19]. Histological studies of the colon in CKD patients have revealed significant reductions in mucosal tight junction proteins, infiltration of inflammatory cells such as monocytes in the lamina propria, and thickening of the colon wall [20].

Gut microbiome dysbiosis

Gut microbiota

In the gut microbiota of patients with CKD, there is an increase in the levels of *Proteobacteria*, *Bacteroidetes*, *Clostridium*, *Enterobacteriaceae*, *Citrobacter* and *Coprobacillus*, while the abundance of *Lactobacillaceae*, *Lachnospiraceae*, *Ruminococcus*, *Faecalibacterium* and *Prevotella spp* are lower [18, 23–31], as illustrated in Table 1. Concurrently, there is a shift towards production of gut-derived uremic metabolites which is associated with the changes to the gut microbiota [32–34].

Gut-derived metabolites

Uremic metabolites have been categorized into small water-soluble molecules, protein-bound uremic toxins (PBUTs) and middle molecules based on their solubility and molecular weight. Small water-soluble molecules produced by gut microbiota, include asymmetric dimethylarginine (ADMA), which is associated with *Streptomyces coelicolor*, *Mycobacterium tuberculosis*

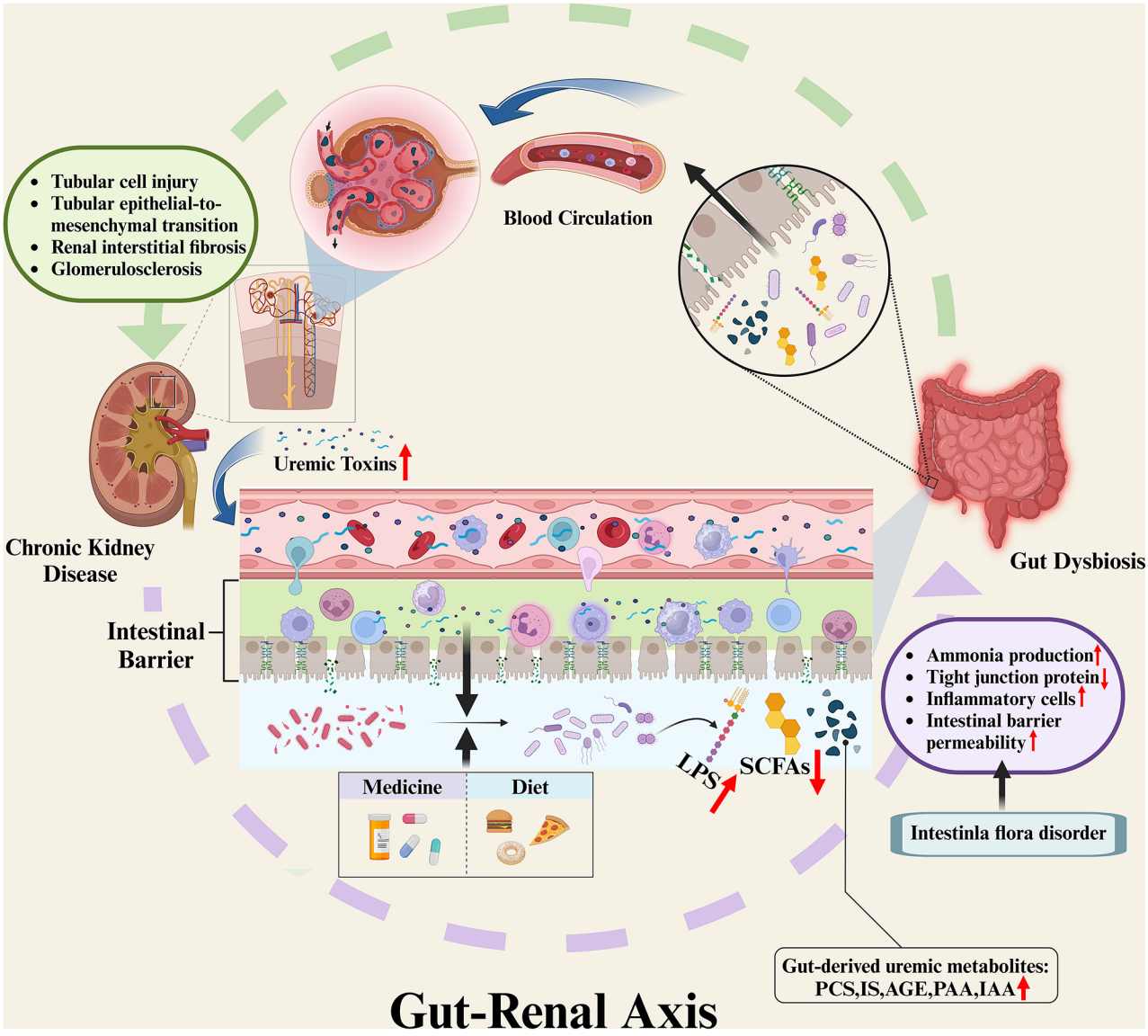

Fig. 1 Interaction between CKD and gut microbiota disturbance (Gut-Renal Axis). Increased levels of uremic toxins in the circulation of CKD patients lead to dysbiosis of the gut microbiota, while dietary intake and medication use of CKD patients are also involved in the process of dysbiosis. This leads to increased ammonia production in the intestinal lumen, which in turn leads to a decrease in tight junction proteins in the intestinal mucosa, infiltration of inflammatory cells in the lamina propria, and ultimately an increase in the permeability of the intestinal barrier. In turn, intestinal flora disorders also lead to accumulation of bacterial products including LPS and reduction in SCFAs levels, which are also involved in the process of impairment of intestinal mucosal barrier function. This makes it easier for gut-derived uremic metabolites, such as PCS, IS, AGEs, PAA, IAA, which accumulate in the intestinal lumen, to enter the systemic circulation. These uremic toxins reach the kidneys through the bloodstream, activate the corresponding pathways, and induce an inflammatory response that further causes tubular cell injury, tubular epithelial-to-mesenchymal transition, and renal interstitial fibrosis and glomerulosclerosis, thereby promoting the progression of CKD. LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; PCS, p-cresyl sulfate; IS, indoxyl sulfate; AGEs, advanced glycation end products; PAA, phenylacetic acid; IAA, indole-3-acetic acid. Image drawn with BioRender.com

and *Pseudomonas aeruginosa*, trimethylamine-N-oxide (TMAO), via *Firmicutes* and *Proteobacteria*, and urea, which is associated with *E. coli* are elevated in the blood of patients with CKD [35–38]. PBUTs such as p-cresyl sulfate (PCS), indoxyl sulfate (IS), indole acetic acid, kynurenines and phenylacetic acid are difficult to remove by dialysis and accumulate in CKD patients, thereby leading to systemic oxidative stress and inflammation [39–43]. In addition, advanced glycation end products (AGEs) accumulate in CKD patients and play a crucial role in CKD-associated complications (e.g. atherosclerotic cardiovascular disease, left ventricular hypertrophy, heart failure and anemia) [44]. AGEs contribute to insulin resistance and endothelial dysfunction in patients with diabetes or CKD by promoting inflammation and oxidative stress [45]. However, it is unclear whether

Table 1 Clinical studies of changes in gut microbiota in CKD patients

Study	Age	Sample size	Research object	Changes of microbes in CKD population
Vaziri ND et al. 2013 [18]	39–71 y	36	HD	Lower level of *Lactobacillaceae* and *Prevotellaceae*
Ye et al. 2018 [24]	30–75 y	153	HD	Lower level of *Firmicutes*, *Lachnospiraceae*, *Ruminococcaceae* and *Faecalibacterium* ; Higher level of *Bacteroidetes*, *Proteobacteria*, *Clostridiales*, and *Enterobacteriaceae*
Wang et al. 2020 [25]	>18 y	292	HD	Lower level of *Prevotella spp* (mainly *P. copri*), *Clostridium spp* and several butyrate producers (*Roseburia spp*, *Faecalibacterium prausnitzii* and *Eubacterium rectale*); Higher level of *Eggerthella lenta*, *Flavonifractor spp* (mainly *F. plautii*), *Alistipes spp* (mainly *A. finegoldii* and *A. shahii*) and *Fusobacterium spp*
Zhang et al. 2023 [31]	37–67 y	668	HD	Lower level of *Prevotella* and *Roseburia* ; Higher level of Blautia spp., *Dorea spp.*, and *Eggerthellaceae*
Wang et al. 2019 [28]	30–66 y	191	CKD 1–5	Lower level of *Prevotella*; Higher level of *Bacteroides*
Margiotta et al. 2020 [26]	≥65 y	79	CKD 3b-4	Lower level of *saccharolytic* and butyrate-producing bacteria (*Prevotella spp.*, *Faecalibacterium prausnitzii*, *Roseburia spp.*); Higher level of *Citrobacter*, *Coprobacillus*
Sato et al. 2021 [30]	20–90 y	111	CKD 1-3a	Lower level of butyrate-producing species *Roseburia inulinivorans*, *Ruminococcus torques* and *Ruminococcus lactaris* ; Higher level of *Bacteroides caccae* and *Bacteroides coprocora*
Wang et al. 2023 [27]	>18 y	88	CKD 1–5	Lower level of SCFA-producing bacteria (*R. bromii*, *R. callidus*, *R. hominis*, *E. rectale*, *F. prausnitzii*, *C. comes*, C. eutactus, C. sporogenes, *S. variabile*, *D. succinatiphilus*, *B. adolescentis*, *L. crispatus*, *A. indistinctus*, and *A. inops*); Higher level of *C. freundii*, *C. werkmanii*, *F. plautii*, and *A. caccae*.
Peters et al. 2023 [29]	44–71 y	2438	CKD 1–5	Lower level of eight species from genus *Prevotella*, and many species from class *Clostridia* within genera *Eubacterium*, *Clostridium*, *Roseburia*, and *Ruminococcus* ; Higher level of *Erysipelotrichia*, *Clostridia*, *Coriobacteriia*, and *Fusobacteriia*

AGEs-associated gut microbiota is altered in patients with CKD [44]. Currently, there is no evidence to support a direct link between the production or metabolism of middle molecules (including β2-microglobulin, ghrelin and parathyroid hormone, and so on) by gut microbiota. The available studies currently suggest that gut microbiota involvement is partially required for the physiological effects of most middle molecules [46].

Along with changes in gut-derived uremic metabolites, alterations in the gut microbiota of CKD patients also lead to a reduced secretion of other metabolites, such as short-chain fatty acids (SCFAs). Relevant studies have identified a reduction in SCFA-producing gut microbiota, including *Faecalibacterium*, *Eubacterium*, *Roseburia*, and *Anaerostipes* from the phylum *Firmicutes* and *Lactobacillus* in CKD patients, with a consequent reduction in serum SCFA levels [28, 46, 47]. As SCFA levels decrease and the pH in the intestinal lumen rises, pathogenic bacteria such as *Enterobacteriaceae* further grows [48], leading to an increase in related uremic toxin levels.

CKD progression

The relationship between gut microbiota disturbances and CKD is bidirectional. In CKD patients, the reduction in beneficial gut commensal microbiota and the proliferation of harmful gut microbiota leads to elevated levels of uremic toxins, the release of pro-inflammatory factors, a disruption of intestinal barrier, and abnormalities in the immune system [49]. These factors collectively exacerbate the progression of CKD.

Uremic toxins accumulation

The most studied gut microbiota-derived uremic toxins are PCS and IS. p-Cresol is a metabolite of tyrosine, and indole is produced by the metabolism of tryptophan. Both are absorbed through the gut and enter the liver for further metabolism to form PCS and IS, respectively, which are generally cleared and excreted by the kidneys [50]. Elevated levels of PCS and IS in the serum of CKD patients contributes to increased expression of deoxyribonucleic acid (DNA) methyltransferase [51], enhanced NADPH oxidase activity and reactive oxygen species (ROS) production [52]. Furthermore, they upregulate the expression of macrophage chemotactic protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1) in the kidney [53, 54], activate the renin-angiotensin-aldosterone system/transforming growth factor-β (TGF-β) pathway [55], and induce inflammatory responses. These responses subsequently lead to tubular cell injury, tubular epithelial-to-mesenchymal transition, renal interstitial fibrosis and glomerulosclerosis, which collectively promote CKD progression [56]. Moreover, researche has demonstrated that in the state of impaired kidney function, gut-derived uremic metabolites such as AGEs, phenylacetic acid (PAA), and indole-3-acetic acid (IAA) systemically accumulate in the body, which further

contributes to inflammation and the development of CKD [57].

Disruption of intestinal barrier

Simultaneously, the impairment of gut barrier caused by gut dysbiosis is also implicated in the progression of CKD. The overgrowth of harmful gut microbiota leads to the accumulation of endotoxins, such as lipopolysaccharides (LPS). For example, LPS activates macrophages by binding to Toll-like receptor 4 (TLR4), which leads to the release of pro-inflammatory cytokines such as IL-6 and TNF-α from macrophages and promotes the expression of soluble TNF receptors, thereby contributing to altered membrane permeability [46]. Meanwhile, the levels of butyrate-producing gut microbiota decrease in CKD patients. Butyrate, a type of SCFAs, is known for its ability in promoting the production of mucoproteins and tight junction proteins, as well as its anti-inflammatory and antioxidant effects. The decrease in butyrate levels in CKD patients exacerbates inflammation, and disrupts the gut barrier, making it easier for gut-derived uremic metabolites to enter the circulation and worsen CKD [58, 59].

Gut microbiota disturbances not only accelerate the progression of CKD, but also significantly impact cardiovascular disease, cognitive abnormalities, skeletal mineral-metabolism abnormalities, and other complications [37, 38, 60–64]. In summary, current studies have identified the presence of disturbed gut microbiota in CKD patients, leading to corresponding changes in their related metabolites. Simultaneously, disturbed gut microbiota and its metabolites may also play an important role in the progression of CKD as well as in other comorbidities, underscoring the significance of the gut-kidney interaction.

Gut microbiota in patients with Sarcopenia: changes and influences

The gut microbiota may have detrimental effects on muscle mass and function by inducing anabolic imbalances, insulin resistance, promoting chronic systemic inflammation [65, 66]. This connection between gut microbiota and muscle has been termed the "gut-muscle axis", and this hypothesis has been well validated in non-CKD animal models. Interventions targeting the "gut-muscle axis" through modulation of gut microbiota can partially reverse skeletal muscle injury and enhance muscle mass and function [67, 68]. However, studies exploring the 'gut-muscle axis' in humans remain limited, with only a few studies having reported associations between altered gut microbiota with sarcopenia in non-CKD patients [65, 69–73](Table 2). There were two animal studies, four clinical studies, and one study that investigated both human populations and mice. Among the animal studies, two involved microbiota transplantation, and the changes in the gut microbiota of the sarcopenic mice model were characterized by an increase in the abundance of *Bacteroidaceae* and *Fusobacteriaceae* [16, 73]. Additionally, one animal study reported a decrease in the abundance of *Lactobacillus* in the sarcopenic model group [16]. These five clinical observational studies included a total of 1586 human subjects, all of these subjects were elderly and older than 53 years of age. In the sarcopenia population, similar to the findings in animal studies, an increase in the abundance of *Bacteroidaceae* and *Fusobacteriaceae* was observed [69–71]. One of the studies noted a decrease in the abundance of *Prevotellaceae* [72], indicating that the role of gut microbiota in the development of muscle loss is a crucial area of research. However, due to the limitations of observational studies, along with the differences in race, geographic factors, and dietary conditions among the populations included, no definitive

Table 2 Changes in the composition of gut microbiota associated with sarcopenia

Study	Research object	Age	Sample size	Changes of microbes in sarcopenia group
Wang et al. 2022 [70]	human	53–81 y	1417	Higher level of *Desulfovibrio piger*, *Clostridium symbiosum*, *Hungatella effluvii*, *Bacteroides fluxus*, *Absiella innocuum*, *Coprobacter secundus* and *Clostridium citroniae*
Han et al. 2022 [71]	human	65–78 y	88	Lower level of *Ruminococcacae*, *Prevotellaceae*, and *Akkermansiaceae* ; Higher level of *Bacteroidaceae* and *Fusobacteriaceae*
Ticinesi et al. 2020 [65]	human	70–86 y	17	Lower level of *Faecalibacterium* prausnitzii, *Roseburia inulinivorans* and *Alistipes shahii*
Picca et al. 2019 [69]	human	>70 y	35	Lower level of *Barnesiellaceae* and *Christensenellaceae* ; Higher level of *Oscillospira* and *Ruminococcus*
Fielding et al. 2019 [72]	human	70–82 y	29	Lower level of family-level *Prevotellaceae*, genus-level *Prevotella* and *Barnesiella*, and species-level *Barnesiella intestinihominis*
	microflora colonized mice	-	36	
Uchiyama et al. 2020 [16]	mice	13 week	20	Lower level of *Lactobacillus*, *Lactonifactor* and *Tannerrella* ; Higher level of *Allobaculum*, *Clostridium cluster IV* and *Alistipes*
Lee et al. 2023 [73]	mice	9 week	45	Higher level of *Alistipes*, *Lachnospiraceae*, and *Bacteroides*.

causal relationship between gut microbiota disturbances and sarcopenia has been established.

Since the composition of gut microbiota is strongly influenced by external factors such as diet, nutrition, medication and lifestyle, which are key contributors to the development of sarcopenia, it is hypothesized that the gut microbiota acts as a mediator of these external factors, thereby affecting muscle mass and function in individuals with sarcopenia [66, 74] (Fig. 2).

First, dysfunction in gut mucosal barrier may play a central role. Studies conducted on aged mice indicates that dysbiotic gut microbiota is associated with impaired gut barrier function [75]. This impairment facilitates entry of bacterial products into the systemic circulation, thereby activating inflammatory responses and inducing dysregulation of the immune system, ultimately affecting muscle mass and strength [76, 77].

Second, metabolites produced by gut microbiota are unequivocally associated with sarcopenia. A

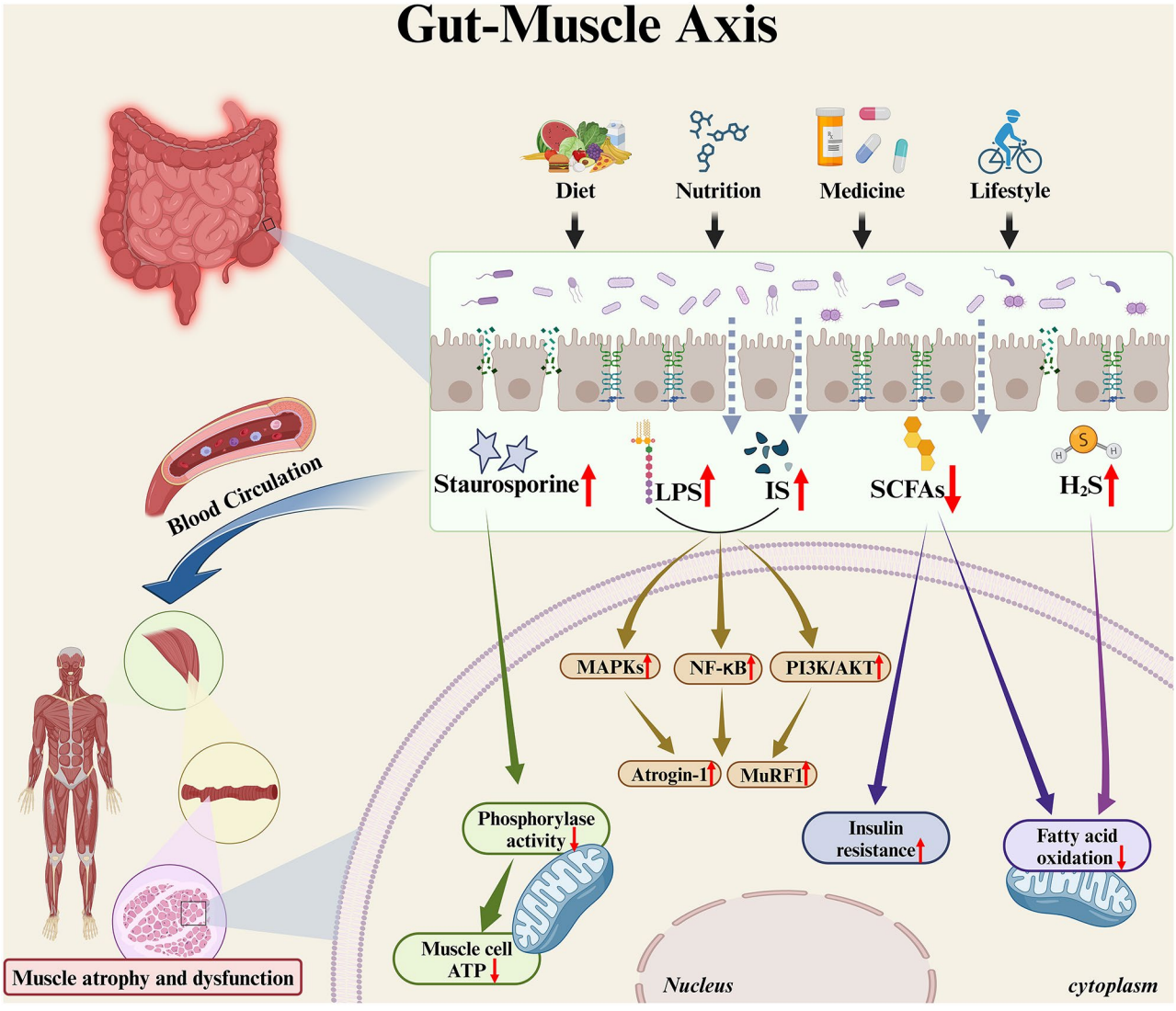

Fig. 2 Influence of gut microbiota and its metabolites on muscle mass and function. In patients with sarcopenia, diet, nutrition, medication and lifestyle profoundly affect the composition of the gut microbiota. Along with their disturbed gut microbiota and impaired intestinal barrier function, bacterial products from the intestinal lumen are more likely to enter the systemic circulation and affect the overall muscle mass and function through the bloodstream. Staurosporine is a broadly specific kinase inhibitor that reduces muscle cell mitochondrial phosphorylase activity and ATP production. While both IS and LPS can upregulate the expression of muscle atrophy-related genes such as Atrogin-1 and MuRF1 by activating the PI3K/AKT, NF-κB and MAPKs signaling pathways. Reduction of SCFAs may promote insulin resistance in muscle cells and, together with the accumulation of hydrogen sulfide, reduces mitochondrial fatty acid oxidation, which further contributes to the increase of intramuscular fatty acid deposition. The above changes in gut microbiota metabolites ultimately lead to a decline in muscle mass and function through various pathways. ATP, adenosine triphosphate; IS, indoxyl sulfate; LPS, lipopolysaccharides; PI3K/AKT, phosphoinositide 3-kinase /protein kinase B; NF-κB, nuclear factor-κB; MAPKs, mitogen-activated protein kinase; SCFAs, short-chain fatty acids; H_2S, hydrogen sulfide. Image drawn with BioRender.com

metagenomic study based on a rural Chinese population identified six gut microbiota species that were positively correlated with the severity of sarcopenia. Among them, *Desulfovibrio piger* is one of the most abundant and prevalent *Desulfovibrio* bacteria in the human digestive tract [70]. This sulphate-reducing bacterium has the capability to reduce dietary sulfites and sulfates, leading to the sulfation of mucopolysaccharides in mucins and the subsequent generation of hydrogen sulfide [78]. Hydrogen sulfide may be involved in the pathogenesis of sarcopenia by inhibiting fatty acid oxidation, thereby negatively impacting muscle energy utilization and decreased muscle endurance, and on the other hand, damaging the gut epithelium, causing systemic and chronic inflammation [79, 80]. Additionally, besides the production of hydrogen sulfide, *D. piger* is also associated with the biosynthesis of staurosporine [70], a broadly specific kinase inhibitor and a commonly-used stimulator of apoptosis that can reduce adenosine triphosphate (ATP) production in C2C12 mouse muscle myoblasts, thereby leading to muscle atrophy and dysfunction [81]. Furthermore, IS and LPS both trigger muscle atrophy and systemic inflammatory responses by upregulating the expression of muscle atrophy-related genes through activation of the phosphoinositide 3-kinase (PI3K) /Akt, nuclear factor kappa-B (NF-κB), and mitogen-activated protein kinases (MAPKs) signaling pathways in a CKD mouse model [82]. Alternatively, study has shown that in a mice model fed a high-fat diet, SCFAs can increase muscle fatty acid oxidation via adenosine monophosphate activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-δ (PPARδ) signaling pathways. In several in vitro studies using rodent and human intestinal cell lines, SCFAs may also improve muscle insulin sensitivity by increasing the levels of the gut-derived peptides tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) [83]. The reduction in SCFA production may promote insulin resistance, diminish mitochondrial fatty acid oxidation, increase intramuscular fatty acid deposition, ultimately leading to a decline in muscle mass and function [65, 66].

In general, alterations in gut microbiota and its metabolites can induce notable changes in the anabolic-catabolic balance and inflammation, which are involved in the pathogenesis of sarcopenia. However, since both gut microbiota and muscle metabolism are influenced by diet, exercise, age, and various other relevant factors, the hypothesis of "gut-muscle axis" cannot be fully confirmed in the broader population. Substantial advancements for mechanistic research and comprehensive clinical studies need to be performed.

Renal-gut-muscle axis in CKD patients with Sarcopenia

For individuals suffering from CKD and sarcopenia, the concept of "renal-gut-muscle axis" has been proposed, which means that kidney and gut microbiota play roles in the maintenance of skeletal muscle mass, composition, and body functions. Furthermore, it suggests that disruptions in gut microbiota-derived uremic metabolites negatively affect the skeletal muscles of CKD patients [15].

Relevant animal or clinical studies

Research revealed that adenine-induced CKD-mice exhibited significantly diminished grip strength, running distance, skeletal muscle and muscle fiber size, and a reduced number of mitochondrial-rich muscle fibers compared to control mice [16]. The gut microbiota of CKD mice had reduced *Lactobacillus* and increased *Clostridales* and *Erysipelotrichales*. Notably, transplantation of fecal bacteria from this group of mice into healthy, germ-free mice resulted in muscle depletion similar to symptoms observed in CKD mice. At the same time, a substantial accumulation of gut-derived uremic metabolites was noted in both CKD mice and those receiving the fecal transplant. In particular, the serum concentrations of IS, hippuric acid (HA), phenyl sulfate (PhS), and indoles and phenol in feces were significantly elevated in both types of mice. This study suggests that in CKD mice, gut microbiota disturbances lead to impaired gut barrier function and the onset of a systemic inflammatory state, as well as heightened levels of associated bacterial metabolites. These factors are partly involved in the progression of sarcopenia [16].

A clinical study involving elderly non-dialysis CKD patients (with an eGFR between 10 and 45 mL/min/1.73 m^2) demonstrated that individuals with sarcopenia exhibited a higher abundance of *Micrococcaceae* and *Verrucomicrobiaceae* families, and *Megasphaera*, *Rothia*, *Veillonella*, *Akkermansia* and *Coprobacillus* genera. Conversely, they had a lower abundance of the *Gemellaceae* and *Veillonellaceae* families, along with *Acidaminococcus* and *Gemella* genera. Although significant differences in the gut microbiota between sarcopenia and non-sarcopenia patients were identified, the study did not identify statistically significant differences for uremic toxins (indoxyl sulphate and p-cresyl sulphate) and inflammatory cytokines (tumor necrosis factor-α, interleukin-6, interleukin-17, interleukin-12 p70, monocyte chemoattractant protein-1 and fetuin-A), except for interleukin-10, which was found at higher levels in non-sarcopenia patients. However, further analysis failed to establish a specific association between interleukin-10 and the gut microbiota [14]. This cross-sectional study highlighted associations between CKD patients with sarcopenia and gut microbiota disturbances, but more pertinent clinical

trials are required to validate their correlation, especially given that this cohort only included elderly non-dialysis CKD patients.

Based on these findings, it is reasonable to assume that the existence of "renal-gut-muscle axis" in CKD patients with sarcopenia. However, further experimental and theoretical studies are imperative to substantiate this assumption.

Mechanism of renal-gut-muscle axis

Building upon the available insights, this article delves into the impact of gut microbiota and its derived serum metabolites on skeletal muscle in CKD patients (Fig. 3).

First, the altered composition and function of the gut microbiota in CKD patients leads to an increased level of urease-expressing *Enterobacteriaceae*, resulting in heightened permeability of intestinal epithelial cells [21, 84]. Second, alterations in gut microbiota-associated metabolites, including IS, PCS, and others, further contribute to the deterioration of skeletal muscle mass and function [56].

IS and PCS

Originating from the *Enterobacteriaceae* family, IS and PCS experience an upswing in the intestinal lumen of CKD patients and can enter the bloodstream due to the compromised intestinal barrier, thereby exerting a detrimental impact on skeletal muscle [56]. IS and PCS can accumulate in skeletal muscle, thereby triggering the expression of myostatin and atrogin-1, which are markers of muscle atrophy. This leads to a decrease in muscle mass, induces insulin resistance in muscle cells, and augments intramuscular lipid content [85–87]. In addition, comprehensive metabolomics revealed that IS is involved in the pathogenesis of sarcopenia by enhancing glycolysis via nuclear factor (erythroid-2-related factor)-2 on the one hand, and suppressing the tricarboxylic acid (TCA)

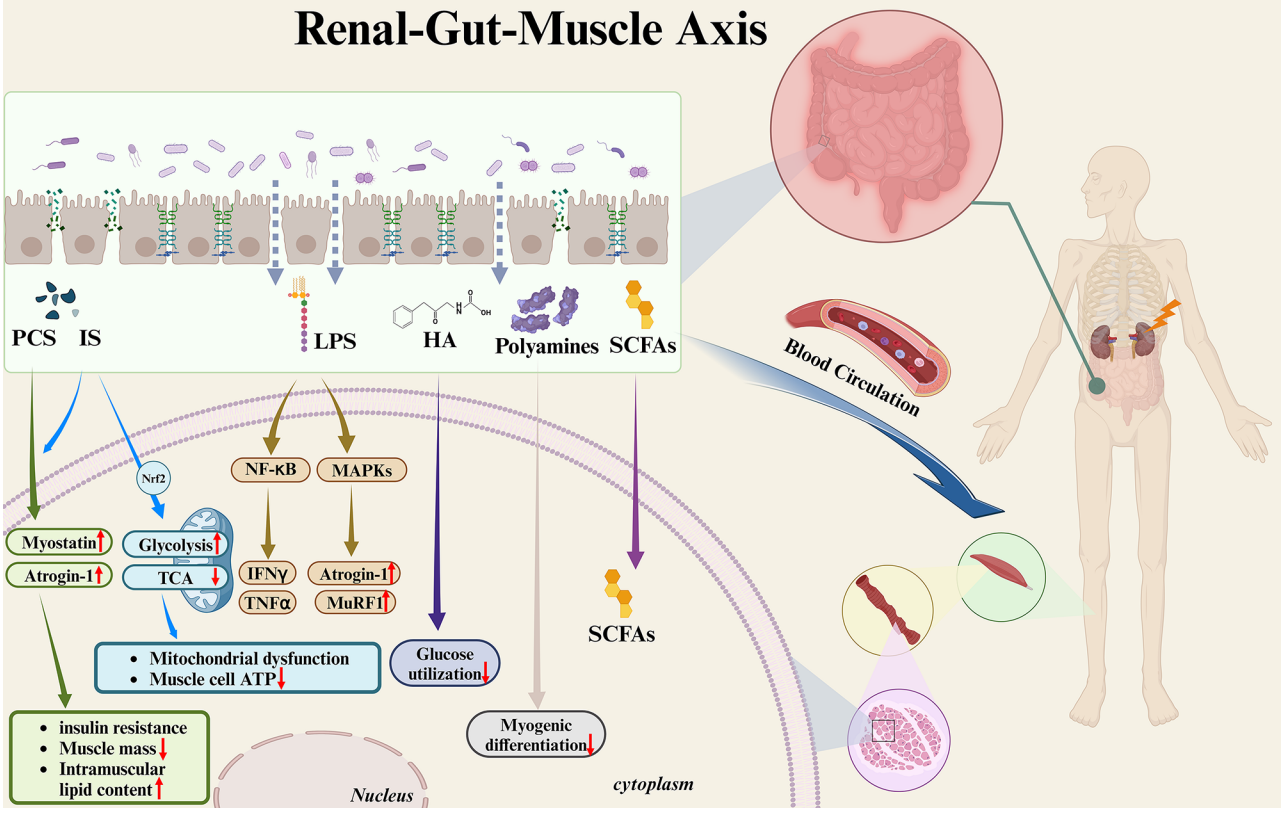

Fig. 3 Effects of gut microbiota-related metabolites on skeletal muscle in CKD patients. In patients with CKD, changes in the gut microbiota lead to heightened intestinal permeability. This allows gut-derived bacterial metabolites to enter the bloodstream, thereby inducing deterioration of skeletal muscle mass and function. IS and PCS accumulate in skeletal muscle, inducing the expression of the muscle atrophy markers myostatin and atrogin-1, thus leading to a reduction in muscle mass, insulin resistance, and increased intramuscular lipid content. In addition, IS can lead to increased glycolysis via Nrf2 on the one hand, and to downregulation of the TCA cycle on the other hand, thereby inducing mitochondrial dysfunction and ATP shortage in muscle cells. LPS can lead to muscle atrophy mediated by NF-κB through IFNγ/TNFα induction. LPS can also cause muscle atrophy by up-regulating atrogin-1 and MuRF1 via MAPKs. HA may contribute to the decline in muscle function by inhibiting glucose utilization in muscle cells. Metabolites of polyamines may inhibit myogenic differentiation and cause muscle atrophy. SCFAs may have a negative impact on muscle due to their reduced levels. IS, indoxyl sulfate; PCS, p-cresyl sulfate; Nrf2, nuclear factor (erythroid-2-related factor)-2; TCA, tricarboxylic acid; ATP, adenosine triphosphate; LPS, lipopolysaccharides; NF-κB, nuclear factor-κB; MAPKs, mitogen-activated protein kinase; HA, hippuric acid; SCFAs, short-chain fatty acids. Image drawn with BioRender.com

cycle on the other, which collectively causes mitochondrial dysfunction and ATP shortage [85].

Other gut-derived bacterial metabolites

Various gut microbiota metabolites that have been linked to muscle function and physical performance in adults, such as HA, polyamines, LPS, SCFA, and others. However, the relationship between these metabolites and skeletal muscle in CKD patients remains controversial and warrants confirmation in future studies. (a) HA, originating from the degradation of aromatic compounds by intestinal bacteria, has been identified as an inhibitor of glucose utilization in muscle cells. This inhibition may contribute to muscle weakness in CKD patients [88]. (b) Alterations in the balance of polyamines, metabolites of proteins, could also contribute to the dysregulation of muscle metabolism. In CKD patients, increased degradation of spermidine and spermine to acrolein has been observed, which inhibits myogenic differentiation and causes muscle atrophy in animal models [89, 90]. (c) LPS, a metabolite of gram-negative bacteria, follows a specific signaling pathway in muscle atrophy in CKD patients, which is known as the lipopolysaccharide/toll-like receptor/ NF-κB signaling pathway. Disturbances of the gut microbiota in CKD patients causes an increase in lipopolysaccharides, further activating this pathway, leading to muscle atrophy mediated by NF-κB through interferon (IFN)γ/tumor necrosis factor (TNF)-α induction [91]. LPS can also upregulate atrogin-1 and muscle RING-finger protein-1 (MuRF1) through p38 MAPK after activating toll-like receptors, causing muscle atrophy [92]. (d) Conversely, gut microbiota-derived SCFA (including acetate, propionate, and butyrate), known for their positive effects on the renal-gut-muscle axis, are reduced in CKD subjects [28]. While animal studies also have shown a positive effect of SCFAs on young animal muscles [67, 93], its impact on muscles in patients with end-stage renal disease (ESRD) have yet to be evaluated.

In summary, there is a potential connection among the renal, muscle, and gut microbiota in CKD patients. CKD patients exhibit alterations in gut microbiota composition and function, along with diminished gut barrier function. These changes, coupled with shifts in metabolites associated with gut microbiota, further exacerbate muscle damage, ultimately fostering the development of sarcopenia, which is collectively known as the "renal-gut-muscle axis". Consequently, research endeavors should delve into the intricate interactions among the gut, muscle and gut microbiome, as well as the associated molecular mechanisms, in order to develop innovative interventions.

Novel therapy for CKD patients with Sarcopenia: improving gut microbiota

Current therapies

Currently, clinical interventions predominantly revolve around nutritional adjustments, exercise, and medication for CKD patients with sarcopenia [1]. Nutritional intervention, constituting a fundamental therapeutic approach, emphasizes adequate energy intake. A meta-analysis revealed that oral nutritional supplements, encompassing a blend of protein, essential amino acids, and other macronutrients, can improve muscle mass in CKD patients on dialysis [94]. However, caution is advised against excessive protein intake, as it may elevate the risk of acidosis. Recommendations propose that CKD patients with a high risk of ESRD (CKD stage 4–5) should refrain from a daily protein intake exceeding 0.8 g protein/kg, while patients with a low risk of ESRD (CKD stage 3) can moderate their protein intake to 1.5 g/kg [95]. However, it's crucial to note that the above recommendations warrant further evaluation through rigorous clinical trials.

Exercise stands out as another non-pharmacological strategy to improve the quality of life and prognosis of CKD patients with sarcopenia. In a mouse model of CKD, both resistance exercise and endurance training decreased proteolysis in skeletal muscle, which was associated with increased phosphorylation of Akt and forkhead transcription factors 1 (FoxO1) and suppressed activation of caspase-3 and ubiquitin–proteasome proteolytic system (UPS) [96]. Furthermore, a randomized controlled trial revealed that 30–45 min of aerobic and resistance exercise (alternating between treadmill, elliptical crosstrainer, Nu-Step crosstrainer, and recumbent stationary bike) three times per week could enhance muscle function, while possibly reducing oxidative stress and markers of inflammation in CKD patients by inducing the expression of antioxidant enzymes and inducing mitochondrial biogenesis [97, 98].

Finally, regarding pharmacological interventions, researchers have evaluated the efficacy of drugs such as myostatin antagonism and omega-3 polyunsaturated fatty acids (PUFAs) in addressing muscle atrophy. However, further studies are warranted to validate their efficacy and safety. Myostatin antagonism demonstrated the reversal of muscle mass loss in a mice model of CKD [99]. Nonetheless, a clinical trial in the Duchenne muscular dystrophy population was prematurely terminated due to potential adverse effects of myostatin antagonism, including epistaxis and capillary dilatation, as well as a lack of evidence of therapeutic efficacy [100]. In another clinical trial involving maintenance hemodialysis CKD patients, PUFAs supplementation administered to the test group for 12 weeks reduced proteolysis in their forearm muscles [101], suggesting its feasibility for further

investigation in CKD patients with sarcopenia. Besides the aforementioned therapeutic approaches, regulating the gut microbiota and its metabolites emerges as a promising therapy for CKD patients with sarcopenia.

Emerging therapies

Current approaches to improving the disturbances of gut microbiota and its metabolites in CKD patients with sarcopenia primarily involve dietary intervention, prebiotic and probiotic therapy. These strategies aim to decrease uremic toxins, mitigate oxidative stress, and attenuate systemic inflammatory responses. In addition, fecal microbiota transplantation (FMT) and adsorption therapy have also demonstrated positive outcomes in both clinical and animal studies (Table 3) [68, 93, 102–109].

Dietary habits

The high variability of the gut microbiota is closely related to dietary habits, as long-term dietary patterns shape the gut microbiota [110]. Consuming foods rich in dietary fiber may alter the gut microbiota to a fermentation pattern favorable to SCFA production [15]. This is achieved by modifying the carbohydrate/protein ratio and reducing the duration of amino acid fermentation. Consequently, this shifts reduces the circulating levels of gut-derived uremic metabolites, maintaining the function and integrity of the intestinal mucosa, and improves muscle mass and physical functioning in young animals [102, 106, 111]. It has also been demonstrated that dietary fiber supplementation can improve grip strength in the elderly [103]. Therefore, increasing the intake of dietary fiber, particularly soluble fiber, in the diets of CKD patients may positively impact skeletal muscle, as soluble fiber is fermented by gut microbiota into SCFAs, which further inhibit the growth of pathogenic bacteria [112].

Probiotics and prebiotics

Probiotics and prebiotics play a pivotal role in fostering the growth of beneficial flora by selectively increasing

Table 3 Clinical and animal studies related to the improvement of gut microbiota and its metabolites

Study	Study design	Research object	Sample size	Intervention	Main result
Cancello et al. 2019 [102]	Longitudinal intervention study	Human, elderly obese women	20	Hypocaloric Mediterranean diet	*Akkermansia* and *Parabacteroides* as well as of SCFAs producers were improved; Lowered the abundance of *Collinsella*, typically associated with obesity.
Buigues et al. 2016 [103]	RCT	Human, people aged 65 and older	60	Prebiotic (composed of a mixture of inulin plus fructooligosaccharides)	The overall rate of frailty was not significantly modified, but exhaustion and handgrip strength were significantly improved.
Huang et al. 2019 [104]	RCT	Human, healthy people aged 20–30 y	54	Probiotics (*Lactobacillus plantarum TWK10*)	Body fat significantly decreased; Muscle mass and endurance performance significantly increased.
Yamamoto et al. 2015 [105]	Longitudinal observational study	Human, HD	20	AST-120	IS, PCS and phenyl sulfate continued to decrease.
Okamoto et al. 2019 [106]	-	Animal, young, healthy mice	-	High-fiber diet	Fecal SCFAs were increased; Muscle mass and treadmill endurance capacity were increased.
Yang et al. 2018 [107]	-	Animal, CKD mice	-	Prebiotic fiber xylooligosaccharide (XOS)	Six out of the nine bacterial genera enriched in CKD were significantly reduced; Cecal SCFA production increased and blood PCS were decreased.
Ni et al. 2019 [68]	-	Animal, C57BL/6 mice (10 months)	46	Probiotics (*Lacticaseibacillus casei LC122* or *Bifidobacterium longum BL986*)	Gut barrier function was improved; Muscle strength and function were enhanced.
Scheiman et al. 2019 [93]	-	Animal, C57BL/6 mice	32	Probiotics (*Veillonella atypica*)	Running time of extreme treadmill and the circulating SCFAs concentration were increased.
Liu et al. 2022 [108]	-	Animal, CKD rat	35	FMT	*Lactobacillus johnsonii* and *Lactobacillus intestinalis* were improved; PBUTs accumulation was reduced.
Nishikawa et al. 2015 [109]	-	Animal, CKD mice	48	AST-120	Plasma IS levels were significantly ameliorated; Exercise capacity and mitochondrial biogenesis of skeletal muscle were improved.

glycolytic bacteria (responsible for breaking down dietary fiber) and decreasing proteolytic bacteria in the colon, consequently reducing the production of uremic toxins [107]. Probiotics are defined by the World Health Organization as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [113]. Currently utilized probiotics include *Bifidobacterium*, *Lactobacillus* and *Streptococcus*. Prebiotics are non-digestible food components selectively utilized by the gut microbiota that may contribute to restoring the integrity of the colonic barrier and modulating the composition of the microbiota, with examples such as inulin, resistant starch, oligofructose, galactooligosaccharide, among others. Studies indicate that oligofructose can boost the number of *Bifidobacteria* in the gut, leading to an increase in muscle proportion and a decrease in fat proportion [114]. Probiotics may ameliorate muscle loss symptoms in CKD by regulating energy metabolism [68, 93, 104, 115]. However, both probiotic and prebiotic treatments have relatively limited research regarding their application in CKD patients with sarcopenia. There is substantial variability in the survival of these strains within the human body, as well as in the nature of the prebiotic species. Therefore, further research is necessary to comprehensively explore their therapeutic potential.

Fecal microbiota transplantation

FMT may play a role in improving intestinal barrier permeability and mitigating gut microbiota-associated uremic toxins by reconstituting the gut microbiota in CKD patients with sarcopenia. Analogous to organ transplantation, FMT involves the collection and processing feces from a healthy donor, subsequently transplanted into the recipient through procedures such as colonoscopy or enema. In recent years, oral methods of FMT mediated by enteric capsules have also emerged, which improves patient compliance [116]. Some investigators have transplanted fecal contents from sham-operated donors into the intestines of CKD rats disinfected with a mixture of antibiotics, and it was observed that FMT significantly reduced serum levels of uremic toxins, thereby reducing renal injury and inflammatory status [108]. However, there is currently insufficient evidence to advocate for the widespread implementation of FMT in CKD patients with sarcopenia, though FMT remains a promising therapeutic avenue.

Oral adsorbents

Oral adsorbents may exhibit efficacy in CKD patients with sarcopenia by binding to uremic toxins. The currently employed oral adsorbent, AST-120, consists of microspheres made from porous carbon material that reduce serum IS levels and the incidence of end-stage renal disease in a dose-dependent manner [117, 118]. In a CKD rat model, AST-120 improved intestinal barrier function and mitigated plasma endotoxin levels and oxidative stress [109, 119]. Furthermore, AST-120 also reduced serum levels of IS, PCS, phenyl sulfate levels and oxidative stress in CKD patients on hemodialysis [105]. Thus, applying this approach to decrease concentrations of gut microbiota-associated uremic toxins may partially ameliorate skeletal muscle atrophy in CKD patients. Further validation through pertinent animal experimental studies is required.

In conclusion, the improvement of gut microbiota and its derived serum metabolites could prove to be an effective strategy for improving symptoms and prognosis of CKD patients with sarcopenia in clinical practice. Nevertheless, interventions aimed at improving outcomes for CKD patients dealing with sarcopenia remain relatively understudied, with the involved mechanisms yet to be thoroughly elucidated.

Conclusions and perspectives

Sarcopenia is closely related to the unfavorable prognosis of CKD patients. Those with sarcopenia often face an elevated risk of death and adverse cardiovascular events. The gut microbiota is a crucial factor that influences physiological function. A complex interaction interplay exists between disturbances of gut microbiome and CKD patients with sarcopenia. The gut microbiota and its serum metabolites may significantly contribute to the pathogenesis of sarcopenia in CKD, including inducing muscle atrophy such as IS, PCS, etc., and exerting a positive effect on the renal-gut-muscle axis such as SCFA. Hence, improvement of the gut microbiota and its serum metabolites could emerge as a novel and broadly promising strategy for preventing or ameliorating sarcopenia in patients with CKD. This could involve supplementation with dietary fiber, probiotics and prebiotics, FMT, and oral adsorbents. However, the lack of large-scale clinical studies investigating changes in gut microbiota and its metabolites in CKD patients with sarcopenia, coupled with an incomplete understanding of the molecular mechanisms associated with the "renal-gut-muscle axis" and the injurious effects of certain gut-derived uremic metabolites to skeletal muscle, underscores the need for further research. In this context, additional studies are imperative to unveil the alterations and effects of gut microbiota and its serum metabolites in CKD patients with sarcopenia. These studies should aim to explore the potential benefits of interventions targeting gut microbiota and gut-derived metabolites in CKD patients with sarcopenia.

Abbreviations

CKD	Chronic kidney disease
HD	Hemodialysis
SCFA	Short-chain fatty acid

PBUTs	Protein-bound uremic toxins
ADMA	Asymmetric dimethylarginine
TMAO	Trimethylamine-N-oxide
PCS	P-cresyl sulfate
IS	Indoxyl sulfate
AGEs	Advanced glycation end products
DNA	Deoxyribonucleic acid
ROS	Reactive oxygen species
MCP-1	Macrophage chemotactic protein-1
ICAM-1	Intercellular adhesion molecule-1
TGF-β	Transforming growth factor-β
PAA	Phenylacetic acid
IAA	Indole-3-acetic acid
LPS	Lipopolysaccharides
ATP	Adenosine triphosphate
PI3K	Phosphoinositide 3-kinase
NF-κB	Nuclear factor kappa-B
MAPKs	Mitogen-activated protein kinases
AMPK	Adenosine monophosphate activated protein kinase
PPARδ	Peroxisome proliferator-activated receptor-δ
PYY	Peptide tyrosine tyrosine
GLP-1	Glucagon-like peptide-1
HA	Hippuric acid
PhS	Phenyl sulfate
TCA	Tricarboxylic acid
IFN	Interferon
TNF	Tumor necrosis factor
MuRF1	Muscle RING-finger protein-1
ESRD	End-stage renal disease
FoxO	Forkhead transcription factors
UPS	Ubiquitin–proteasome proteolytic system
PUFAs	Polyunsaturated fatty acids
FMT	Fecal microbiota transplantation

Author contributions
GZ and JC contributed to the conception of the work and drafted the manuscript. XW, WH and BW revised the manuscript. All authors contributed to the critical reading and approving the final version.

Funding
This study was funded by the Young Scholars of Yangtze River Scholar Professor Program (2024 WB); the National Natural Science Foundation of China (82100615 and 82100721); the China Postdoctoral Science Foundation (2022M710686); the Foundation of Jiangsu Commission of Health (M2021048); and the Project of Taizhou Clinical Medical School of Nanjing Medical University (TZKY20220209 and TZKY20230101).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 22 June 2024 / Accepted: 1 November 2024
Published online: 21 November 2024

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