



Sarcopenia in cirrhosis: Prospects for therapy targeted to gut microbiota

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Abstract

Decreased muscle mass and function, also known as sarcopenia, is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Decreased barrier function of the gut and liver, gut dysbiosis, and small intestinal bacterial overgrowth (SIBO) can lead to increased blood levels of ammonia, lipopolysaccharides, pro-inflammatory mediators, and myostatin. These factors have complex negative effects on muscle mass and function. Drug interventions that target the gut microbiota (long-term use of rifaximin, lactulose, lactitol, or probiotics) positively affect most links of the compromised gut-muscle axis in patients with cirrhosis by decreasing the levels of hyperammonemia, bacterial translocation, and systemic inflammation and correcting gut dysbiosis and SIBO. However, although these drugs are promising, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis. No data exist on the effects of fecal transplantation on most links of gut-muscle axis in cirrhosis; however, the results of animal experimental studies are promising.

Key Words: Cirrhosis; Muscle; Fragility; Liver; Microbiota; Microbiome

Core Tip: Sarcopenia is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Drugs that target the gut microbiota positively affect most links of the compromised gut-muscle axis in patients with cirrhosis. However, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis.

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INTRODUCTION

Sarcopenia is defined as the loss of muscle mass, strength, and physical function[1]. Sarcopenia has been detected in 14%-55% of patients with cirrhosis[2-6] and attracts the attention of researchers increasingly[7-10]. Sarcopenia was found in 68.5% of patients with cirrhosis who were admitted to the intensive care unit[11]. Recent studies have shown that sarcopenia in patients with cirrhosis is associated with poor short- and long-term prognoses[3,6,11,12]. The decrease in muscle mass in patients with cirrhosis over a year also has an unfavorable prognostic value[13]. A recent meta-analysis of 22 studies confirmed that sarcopenia is an independent predictor of increased mortality in patients with cirrhosis[14].

Sarcopenia in patients with cirrhosis is associated with a decrease in the quality of life[15], increased hepatic venous pressure gradient[12], portal hypertension-related complications (ascites and upper gastrointestinal varices), infections (urinary tract infection and spontaneous peritonitis), hepatic encephalopathy, increased risk of hepatocellular carcinoma, longer hospital stay, higher 30-d readmission rate, lower body mass index and serum albumin levels, longer prothrombin time, higher total bilirubin concentrations, and higher Child-Pugh score[16-20]. In addition, patients with cirrhosis have an increased amount of fat in the muscles (myosteatorsis), which is also an unfavorable prognostic factor[21].

The exact mechanisms underlying the development of sarcopenia in patients with cirrhosis have not yet been established. Among the factors contributing to the development of sarcopenia in cirrhosis, are disorders of the metabolic function of the liver, decreased appetite[22], increased muscle autophagy[2], increased serum myostatin (a protein that blocks muscle growth)[6], catabolic effects of systemic inflammation induced by bacterial translocation from the gut[23-24], and low testosterone levels[25] were found.

GUT-MUSCLE AXIS IN CIRRHOSIS

Gut dysbiosis in patients with cirrhosis

Cirrhosis is associated with a disturbed composition of the gut microbiota, or dysbiosis[26-29]. Despite some inconsistencies, most studies have shown that in patients with cirrhosis, there was an abundance of harmful bacteria of taxa Bacilli, Streptococcaceae, Enterococcaceae, Proteobacteria, and Enterobacteriaceae, and there was a decrease in beneficial gram-positive bacteria of families Ruminococcaceae and Lachnospiraceae[30-42]. The harmful bacteria are facultative anaerobes; therefore, they can survive in oxygenated tissues, penetrate them, and spread throughout the body. This process was termed bacterial translocation and is believed to be an important contributor to the progression of cirrhosis, including the development of a systemic inflammatory response[26-29]. In addition, harmful Enterobacteriaceae of the phylum Proteobacteria, which are abundant in the gut microbiota of patients with cirrhosis, have an active endotoxin [lipopolysaccharide (LPS)]. Since cirrhosis increases the permeability of the intestinal barrier[43-46], LPS can penetrate the body (molecular bacterial translocation), leading to a systemic inflammatory response. The production of short-chain fatty acids (SCFA) by beneficial bacteria also decreases in patients with cirrhosis[30]. These SCFAs are used as a source of energy by intestinal epithelial cells, strengthen the intestinal barrier, and act on specific receptors to regulate human body functions[47]. The metabolism of bile acids, which also affect many human metabolic pathways through their special receptors[48], depends on the gut bacteria and disturbs in cirrhosis[42].

The values of the MELD scale that used to assess the risk of death in patients with cirrhosis are directly correlated with the abundance of harmful gut bacteria from the families Staphylococcaceae, Enterococcaceae, and Enterobacteriaceae, and inversely correlated with the abundance of beneficial bacteria from the families Lachnospiraceae and Ruminococcaceae [36]. Patients with acute-on-chronic liver failure have a lower abundance of beneficial gram-positive bacteria[36]. The Child-Turcotte-Pugh score, used to assess cirrhosis severity, correlates positively with the abundance of Streptococcaceae and negatively with the abundance of Lachnospiraceae[41]. Severe dysbiosis is associated with higher C-reactive protein (CRP) levels, lower serum albumin and cholinesterase levels, and poorer long-term prognosis[40]. The abundance of Lachnospiraceae is negatively correlated with the risk of hospitalization of cirrhosis patients in the intensive care unit

[49]. Abundant Enterobacteriaceae, Enterococcaceae, and Streptococcaceae are associated with hepatic encephalopathy, circulatory failure, and respiratory failure within 30 d of hospitalization of these patients, respectively[49].

Serum LPS levels are positively correlated with the abundance of Enterobacteriaceae and negatively correlated with the abundance of Lachnospiraceae and Ruminococcaceae[36]. Most of the bacterial genetic material found in the blood and ascitic fluid of patients with cirrhosis is from harmful Proteobacteria and Bacilli instead of the beneficial Lachnospiraceae and Ruminococcaceae that are dominant in the gut[50,51]. The serum level of pro-inflammatory cytokine tumor necrosis factor- α (TNF- α) is positively correlated with the serum LPS level and the risk of cirrhosis decompensation, spontaneous bacterial peritonitis, and acute-on-chronic liver failure[52].

Therefore, gut dysbiosis in patients with cirrhosis is associated with bacterial translocation, systemic inflammation, decompensation of liver function, and poor short- and long-term prognoses.

Small intestinal bacterial overgrowth in cirrhosis

Small intestinal bacterial overgrowth (SIBO) is an increase in the content of bacteria in the small intestine[53] and has been detected in almost half of patients with cirrhosis[54]. The prevalence of SIBO increases with increasing severity of cirrhosis[54]. Patients with cirrhosis and SIBO have ascites, minimal and overt hepatic encephalopathy, and spontaneous bacterial peritonitis more often than those without SIBO[54-55]. No relationship has been found between SIBO on the one hand and hypocoagulation, alanine aminotransferase, glutamyl transpeptidase activity, white blood cell, platelet counts, hemoglobin, ascitic fluid albumin levels, and esophageal varices on the other hand in cirrhosis[54]. In patients with cirrhosis, SIBO is associated with the presence of bacterial DNA in peripheral blood[56], higher serum LPS[57] and CRP [58] levels, splanchnic vasodilation, and hyperdynamic circulation[58]. Gut microbiota changes in patients with both cirrhosis and SIBO do not correspond to cirrhosis-associated gut dysbiosis. Therefore, gut dysbiosis and SIBO are most likely separate disorders[59] and SIBO is an independent factor associated with bacterial translocation, systemic inflammation, and the development of several complications in cirrhosis.

Gut-muscle axis in cirrhosis

The pathology of the gut microbiota (gut dysbiosis and SIBO) influences the development of sarcopenia (gut-muscle axis) in patients with cirrhosis.

Bacterial translocation-induced systemic inflammation causes protein catabolism and decreases muscle mass. This is evidenced by the association of sarcopenia with biomarkers of bacterial translocation (LPS) and systemic inflammation (TNF- α) in cirrhosis[23-24]. TNF- α reduced the formation of proteins in muscles[60]. The injection of LPS into the bodies of experimental animals had a similar effect[61].

The second mechanism of harmful effect of the gut microbiota disorders on the muscle tissue in cirrhosis is based on the fact that an excess amount of bacteria in SIBO competes with the human body for nutrients that enter the intestine with food. In support of this mechanism, an association was found between SIBO and malnutrition in cirrhosis[62].

A third mechanism linking the pathology of the gut microbiota with sarcopenia in cirrhosis is associated with an increase in the formation of myostatin, a protein that enhances protein catabolism in muscles, and inhibits their growth [63-65]. Serum myostatin levels are elevated in patients with cirrhosis and are correlated with the severity of sarcopenia [6]. Increased myostatin formation in patients with cirrhosis is likely associated with hyperammonemia that led to an increase in the myostatin level as well as a decrease in muscle mass and strength by an NF- κ B-mediated mechanism in experimental animals[66]. However, such effects were not observed in mice with knockout of the myostatin gene[66]. The muscles are normally one of the main sources of ammonia in the body. Therefore, through negative feedback, hyperammonemia may reduce muscle mass to reduce the formation of ammonia by muscles. However, in patients with cirrhosis, the main source of ammonia for systemic circulation is the gut microbiota, which catabolize dietary and mucous proteins. Normally, gut microbiota-derived ammonia is neutralized by the liver; however, in patients with cirrhosis, the detoxifying function of the liver is reduced and portocaval shunts work around it, which leads to a dysfunction of this mechanism for regulating the volume of muscle mass[67-70]. In addition, hyperammonemia may lead to the development of sarcopenia in other ways[69], including increased autophagy[71] and inhibition of muscle protein anabolism[72].

The increased serum TNF- α levels are associated with the increased myostatin gene expression and the decreased muscle mass in experimental cirrhosis, suggesting that systemic inflammation can lead to sarcopenia increasing myostatin production among other mechanisms[24].

Several recent studies have reported changes in the composition of the gut microbiota associated with sarcopenia[73-76]. The abundances of Bacteroidaceae, *Eggerthella*, *Escherichia coli*, *Fusobacterium*, Micrococcaceae, *Rothia*, *Veillonella*, *Weissella*, and other bacteria are associated with a decrease in muscle mass, while the abundances of *Acidaminococcus*, *Akkermansia*, *Anaerotruncus*, *Anaerostipes*, *Barnesiellaceae*, *Bifidobacterium catenulatum*, *Catenibacterium*, *Collinsella*, *Coprococcus*, *Coriobacteriaceae*, *Desulfovibrio*, *Dialister*, *Dorea*, *Erysipelatoclostridiaceae*, *Granulicella*, *Intestinimonas*, *Lachnospiraceae*, *Megasphaera*, *Methanobrevibacter*, *Oscillospira*, *Prevotella*, *Ruminococcus flavefaciens*, *Senegalimassilia*, and other bacteria showed an association with normal muscle mass in patients with cirrhosis. The pronounced heterogeneity of these results were obtained that may be caused by different methods used to assess the muscle mass of patients. Patients with sarcopenia had higher serum levels of CRP, TNF- α , interleukin 1-beta, 2 and 6, granulocyte-macrophage-colony-stimulating factor, fibroblast growth factor, and C-X-C motif chemokine ligand 10 than patients without it[73]. Although serum LPS and myostatin levels in this study were higher in patients with sarcopenia than in those without, this increase did not reach the limit of significance[73]. There was no significant difference in zonilin and other cytokines levels and reported manifestations of cirrhosis between patients with and without sarcopenia[73]. Patients with sarcopenia were more likely to have ascites, higher Child-Pugh scores[76], and lower albumin levels[75] than patients with normal muscle mass. No other significant associations were reported in these studies on associations between gut microbiota and muscle mass in cirrhosis.

Disorders of the gut-muscle axis in cirrhosis are shown simplified in [Figure 1](#).

Therefore, it is assumed that the condition of the gut microbiota plays an important role in the development of sarcopenia in patients with cirrhosis and therapy aimed at the gut microbiota (antibiotics, prebiotics, probiotics, and fecal transplantation) may be useful in the treatment and prevention of sarcopenia.

PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS

Treating gut microbiota in patients with cirrhosis: rifaximin

Rifaximin is a poorly-absorbed antibiotic used against harmful intestinal bacteria. Recent meta-analyses have shown that rifaximin effectively eliminates SIBO[77,78] in patients with irritable bowel syndrome[79-82], cystic fibrosis[83], Crohn's disease[84], diabetes[85], celiac disease[86], acromegaly[87], uncomplicated diverticular disease[88,89], systemic sclerosis[90], rosacea[91], and ulcerative colitis[92]. However, rifaximin was ineffective against SIBO in patients after gastrectomy[93]. The meta-analyses also noted that rifaximin is generally well-tolerated and has a low incidence of side effects[77,78]. Other antibiotics, such as chlortetracycline[94], neomycin, doxycycline, amoxicillin/clavulanate, ciprofloxacin[95], and metronidazole[96] were less effective than rifaximin in eradicating SIBO.

Rifaximin also improved intestinal barrier function (reduced blood levels of diamine oxidase and D-lactic acid), mitigated systemic inflammation (decreased serum CRP level and erythrocyte sedimentation rate)[92], and accelerated orocecal transit[85].

Rifaximin increases the abundance of beneficial bacteria (*Akkermansia*, *Bifidobacterium*, *Faecalibacterium prausnitzii*, and *Ruminococcaceae*) and decreases the number of harmful ones (*Alphaproteobacteria*, *Eggerthella*, *Enterococcus*, and *Streptococcaceae*) in several studies ([Table 1](#))[79,97-106].

Meta-analyses have shown that rifaximin is effective in the primary and secondary prevention of spontaneous bacterial peritonitis, a clinical manifestation of bacterial translocation in patients with cirrhosis; rifaximin was superior to norfloxacin and other antibiotics in this respect[107-110]. Rifaximin also reduces the risk of mortality and need for liver transplantation in patients with cirrhosis[111]. In addition, it is effective in the management of hepatic encephalopathy, which is associated with hyperammonemic conditions such as sarcopenia, and significantly reduces blood ammonium levels in patients with cirrhosis[111-113]. One study reported that rifaximin eradicated SIBO in 76% of patients with cirrhosis-associated minimal hepatic encephalopathy, and this was associated with a more prominent decrease in blood ammonium levels than in patients with cirrhosis without SIBO that were also treated with rifaximin[114].

Rifaximin decreased the blood LPS levels in cirrhosis[115-121], and this was associated with a decrease in serum ammonia levels[118]. Rifaximin also reduces circulating neutrophil expression of TLR-4, which is the main endotoxin receptor[122]. However, the effects of rifaximin on various biomarkers of systemic inflammation in cirrhosis have been inconsistent across studies.

Importantly, rifaximin does not alter the overall resistome[123]; *i.e.*, their intake does not lead to the development of antibacterial resistance. Rifaximin also reduces the rate of all bacterial infections[124] and variceal bleeding in patients with cirrhosis[125-126], prevents the development of hepatorenal syndrome[127-128] and refractory ascites[129-130]. The use of rifaximin in patients with cirrhosis led to a decrease in the abundance of harmful *Streptococcus*, *Eggerthella*, and *Veillonella* ([Table 2](#))[42,117-120,122,130,131].

Overall, the literature suggests that rifaximin does positive affect the main pathogenetic links of the disordered gut-muscle axis in cirrhosis, in particular SIBO, hyperammonemia, and bacterial translocation. Rifaximin also modulates the composition of the gut microbiota reducing the number of bacterial taxa has been associated with muscle loss in patients with cirrhosis. This drug has shown excellent safety and tolerability for long-term use in patients with cirrhosis[127,132,133]. It is very important, since the prevention and treatment of sarcopenia require long-term therapy. This suggests that rifaximin may be effective and safe for these purposes in cirrhosis.

Although other antibiotics have also had positive effects on the prevention of spontaneous bacterial peritonitis, hepatic encephalopathy, and the reduction of bacterial translocation and hyperammonemia in patients with cirrhosis[111,134-136], most of them have poorer safety profiles and fewer number of studies. Thereby, recommendations to investigate their long-term effects on the prevention and treatment of sarcopenia in patients with cirrhosis seem premature. However, this does not exclude their potential use when new data on the efficacy and safety of their long-term use become available.

Rifaximin prevents skeletal muscle atrophy and weakness by decreasing intramuscular myostatin and pro-inflammatory cytokine levels in experimental cirrhosis[24,137]. An uncontrolled study showed that the long-term use of rifaximin in patients with cirrhosis improved nutritional status and allowed patients to maintain a constant amount of muscle mass[138]. Randomized placebo-controlled studies on the effects of long-term rifaximin use on muscle mass, serum myostatin, and other biomarkers of gut-muscle axis disorders in cirrhosis are required to verify this data.

Treating gut microbiota in patients with cirrhosis: prebiotic disaccharides lactulose and lactitol

Lactulose and lactitol are artificial disaccharides that are not broken down by human digestive enzymes and are utilized by the intestinal microbiota. These drugs are primarily used as osmotic laxatives for conditions that involve constipation (including irritable bowel syndrome)[139-141]. They also used for the prevention and treatment of hepatic encephalopathy[142,143], because the abundance of these carbohydrates switches the metabolism of gut bacteria from proteolytic to saccharolytic. This leads to a decrease in the formation of ammonium and other neurotropic metabolites of amino acids[144], and their laxative effects accelerate the removal of these harmful products from the intestine.

Table 1 The effect of rifaximin on the composition of the gut microbiota in various diseases

Disease	Taxa that increase in the abundance after rifaximin	Taxa that decrease in the abundance after rifaximin
Alzheimer's disease [97]	Anaerostipes, Blautia, Erysipelotrichaceae, Erysipelatoclostridium, Faecalitalea, Lactobacillus, and Ruminiclostridium	
Irritable bowel syndrome [79,98-100]	Acidimicrobiales, Acidobacteria, Alteromonas, Arthrobacter, Bacillus, Bacteroidaceae, Butyricimonas, Chloroflexi, Cytophagia, Coprobacillus, Bifidobacterium, Deinococcales, Devosia, Dyella, Faecalibacterium prausnitzii, Frankiales, Gordonibacter, Holdemania, Kocuria, Methylophilales, Micrococcales, Micromonosporales, Nitriliruptorales, Parabacteroides, Prevotellaceae, Propionibacteriales, Rhizobiales, Rhodobacterales, Sphingomonadales, and Streptomycetales	Alphaproteobacteria, Anaerotruncus, Blautia luti, Butyricimonas, Cronobacter, Escherichia, Eubacterium ventriosum, Rhodospirillales, Romboutsia, Roseburia inulinivorans, Streptococcaceae, and Tyzzerella
Symptomatic uncomplicated diverticular disease [101-102]	Akkermansia, Bacteroidaceae, Citrobacter, Coprococcus, Dialister Ruminococcaceae, and Veillonellaceae	Anaerotruncus, Anaerostipes, Blautia, Christensenellaceae, Dehalobacteriaceae, Eggerthella lenta, Haemophilus parainfluenzae, Mogibacteriaceae, and Pasteurellaceae
Chronic Kidney Disease [103]	-	Anaerotruncus, Clostridium, and Turicibacter
Gut diseases [104]	Faecalibacterium	Ruminococcus and Roseburia
Ulcerative colitis [105]	Bacteroides and Bifidobacterium	Enterococcus and Lactobacillus
Crohn's disease [106]	Bifidobacterium, Atopobium, and Faecalibacterium prausnitzii	

Table 2 The effect of rifaximin on the composition of the gut microbiota in patients with cirrhosis

Ref.	Taxa that increase in the abundance after rifaximin	Taxa that decrease in the abundance after rifaximin
Bajaj <i>et al</i> [120]	Eubacteriaceae	Veillonellaceae
Kaji <i>et al</i> [117]		Streptococcus, Veillonella
Kaji <i>et al</i> [118]		Streptococcus, Veillonella
Kakiyama <i>et al</i> [42]		Veillonellaceae
Kawaguchi <i>et al</i> [131]		Lactobacillus, Streptococcus, Veillonella
Lv <i>et al</i> [130]	Bacteroides vulgatus	Bacteroides uniformis, Eggerthella lenta, Haemophilus, Prevotella, Roseburia
Patel <i>et al</i> [122]		Akkermansia, Hungatella, Streptococcus, Veillonella
Zeng <i>et al</i> [119]	Bacteroidaceae	Veillonellaceae

Meta-analyses have shown that lactulose and lactitol are effective against hepatic encephalopathy and that they reduce blood ammonia levels. They also decrease the risk of other serious liver-related adverse events, such as liver failure, variceal bleeding, hepatorenal syndrome, spontaneous bacterial peritonitis and other serious infections. These drugs also have excellent safety profiles and have been shown to reduce mortality [111,145-148].

Lactulose and lactitol can be safely taken for six months or more [149-151]. However, they may cause steatorrhea, which can worsen the nutritional status of patients [152].

We were unable to find any data on the effects of these disaccharides on SIBO. Two factors should be considered in this case. First, since these drugs are growth factors for bacteria, they can provoke the development of SIBO. However, SIBO can be eliminated by accelerating intestinal motility caused by these drugs. Further research is required to determine which effect outweighs the other.

The intake of lactitol was accompanied by an increase in the abundance of *Bifidobacterium*, *Lactobacillus*, *Veillonella*, *Enterobacter*, *Sutterella*, *Haemophilus*, and *Aggregatibacter*, and a decrease in the abundance of *Bacteroides*, *Clostridium*, *Eubacterium*, *Klebsiella*, *Pseudoflavonifractor*, and coliform bacteria (Table 3) [153-157]. In addition, there was a decrease in the LPS concentration in the blood of patients with chronic viral hepatitis [158].

The use of lactulose is associated with an increase in the levels of *Bifidobacterium* and *Lactobacillus* and a decrease in the abundance of *Clostridium*, *Eubacterium*, *Enterococcus*, and *Enterobacteriaceae* in patients with cirrhosis (Table 3) [153,154,159,160]. However, other studies have not shown an effect of lactulose on the composition of gut microbiota [161,162]. Several studies demonstrated that the use of lactulose in patients with minimal hepatic encephalopathy led to a decrease in the blood levels of LPS, bacterial DNA, and pro-inflammatory cytokines (TNF- α , IL-6 and IL-18) [160,163,164].

Table 3 The effect of lactitol and lactulose on the composition of the gut microbiota

Ref.	Disease	Taxa that increase in the abundance after disaccharide	Taxa that decrease in the abundance after disaccharide
Lactitol			
Riggio <i>et al</i> [153]	Cirrhosis	Lactobacilli	Enterobacteria and Enterocicci
Ballongue <i>et al</i> [154]	Healthy persons	Bifidobacterium, <i>Lactobacillus</i> and <i>Streptococcus</i>	Bacteroides, Clostridium, coliforms, and <i>Eubacterium</i>
Li <i>et al</i> [155]	Chronic constipation	Actinobacteria, Bifidobacteriales, Bifidobacteriaceae, <i>Anaerostipes</i> , and <i>Bifidobacterium</i>	-
Tarao <i>et al</i> [156]	Cirrhosis	Bifidobacterium and <i>Lactobacillus</i>	Bacteroides and <i>Clostridium</i>
Lu <i>et al</i> [157]	Cirrhosis	Bifidobacterium, Veillonella, Enterobacter, Sutterella, Haemophilus, <i>Aggregatibacter</i> , <i>Lactobacillus salivarius</i> , <i>L. fermentum</i> , and <i>L. oris</i>	Klebsiella <i>Pseudoflavonifractor</i> , and others
Chen <i>et al</i> [158]	Chronic viral hepatitis	Bifidobacterium and <i>Lactobacillus</i>	Clostridium perfringens
Lactulose			
Riggio <i>et al</i> [153]	Cirrhosis	Lactobacilli	-
Ballongue <i>et al</i> [154]	Healthy persons	Bifidobacterium, <i>Lactobacillus</i> and <i>Streptococcus</i>	Bacteroides, <i>Clostridium</i> , coliforms and <i>Eubacterium</i>
Ziada <i>et al</i> [159]	Minimal hepatic encephalopathy	Bifidobacterium, <i>Lactobacillus</i> , and Bacteroidaceae	Enterobacteriaceae and <i>Enterococcus</i>

The use of lactulose and lactitol has also been associated with a decrease in the amount of bacterial proteolysis products such as cresol, skatol, phenol, and indole in the feces, as well as an increase in the amount of lactate in the feces. Lactate can acidify the feces [154] and convert neutral ammonia to ammonium ions which, unlike ammonia, do not pass through the intestinal barrier because of the presence of an electric charge. Thus, these drugs not only decrease the bacterial catabolism of amino acids with the formation of ammonia, but also decrease ammonia absorption from the intestine. These drugs significantly reduce hyperammonemia after an amino acid load [143].

Thereby, these prebiotic disaccharides reduce the severity of the following adverse factors of the disordered gut-muscle axis in cirrhosis: hyperammonemia, bacterial translocation, and systemic inflammation. Most studies have shown positive effects of these drugs on the composition of the gut microbiota. However, their impact on SIBO is yet to be explored. These drugs are considered safe for long-term use. However, their effects on myostatin levels and muscle mass in patients with cirrhosis and other diseases have not been studied.

Treating gut microbiota in patients with cirrhosis: probiotics

Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts [165]. They can be used to treat liver diseases [165-166].

Meta-analyses have shown that probiotics are effective in the prevention and treatment of hepatic encephalopathy and that they decrease the blood levels of LPS and ammonia. However, they do not have a significant effect on mortality or the incidence of spontaneous bacterial peritonitis in patients with cirrhosis [111,167-170]. A meta-analysis did not show that probiotics have a significant effect on the serum level of pro-inflammatory cytokines (TNA-alpha and IL-6) [169]. Another meta-analysis revealed that probiotics do not significantly affect CRP levels, but they lead to a decrease in TNF- α levels [171]. Among the studies not included in these meta-analyses, the following described the effect of probiotics on inflammatory biomarkers in cirrhosis. The probiotic fungus *Saccharomyces boulardii* decreases serum CRP levels and ameliorates hyperdynamic circulation in patients with decompensated cirrhosis [172]. *Escherichia coli* Nissle 1917 reduced the serum levels of IL-6, IL-8, and interferon- γ in patients with hepatic encephalopathy [160]. The probiotics that included *Clostridium butyricum* and *Bifidobacterium infantis* strengthen the intestinal barrier [173].

Probiotics have been shown to be safe when used for six months in patients with cirrhosis [174].

The use of probiotics in cirrhosis leads to an increase in the numbers of *Bifidobacterium*, *Lactobacillus*, Lachnospiraceae, Bacteroidaceae, Clostridiales incertae sedis XIV, *Faecalibacterium prausnitzii*, *Syntrophococcus sucromutans*, *Bacteroides vulgatus*, *Prevotella*, *Alistipes shahii*, *Clostridium* cluster I, *Clostridium coccoides*, and *Eubacterium cylindroides* and a decrease in the numbers of Enterobacteriaceae, *Enterococcus*, *Proteus hauseri*, *Citrobacter* sp., and *Morganella* (Table 4) [159,160,175-178].

Meta-analyses have also shown that probiotics effectively eliminate SIBO [179-180]. This has been observed in patients with cirrhosis [181], chronic liver disease [182], secondary lactase deficiency [183], diarrhea-predominant irritable bowel syndrome [184-186], gastric and colorectal cancer [187], systemic sclerosis [188], and bariatric surgery [189].

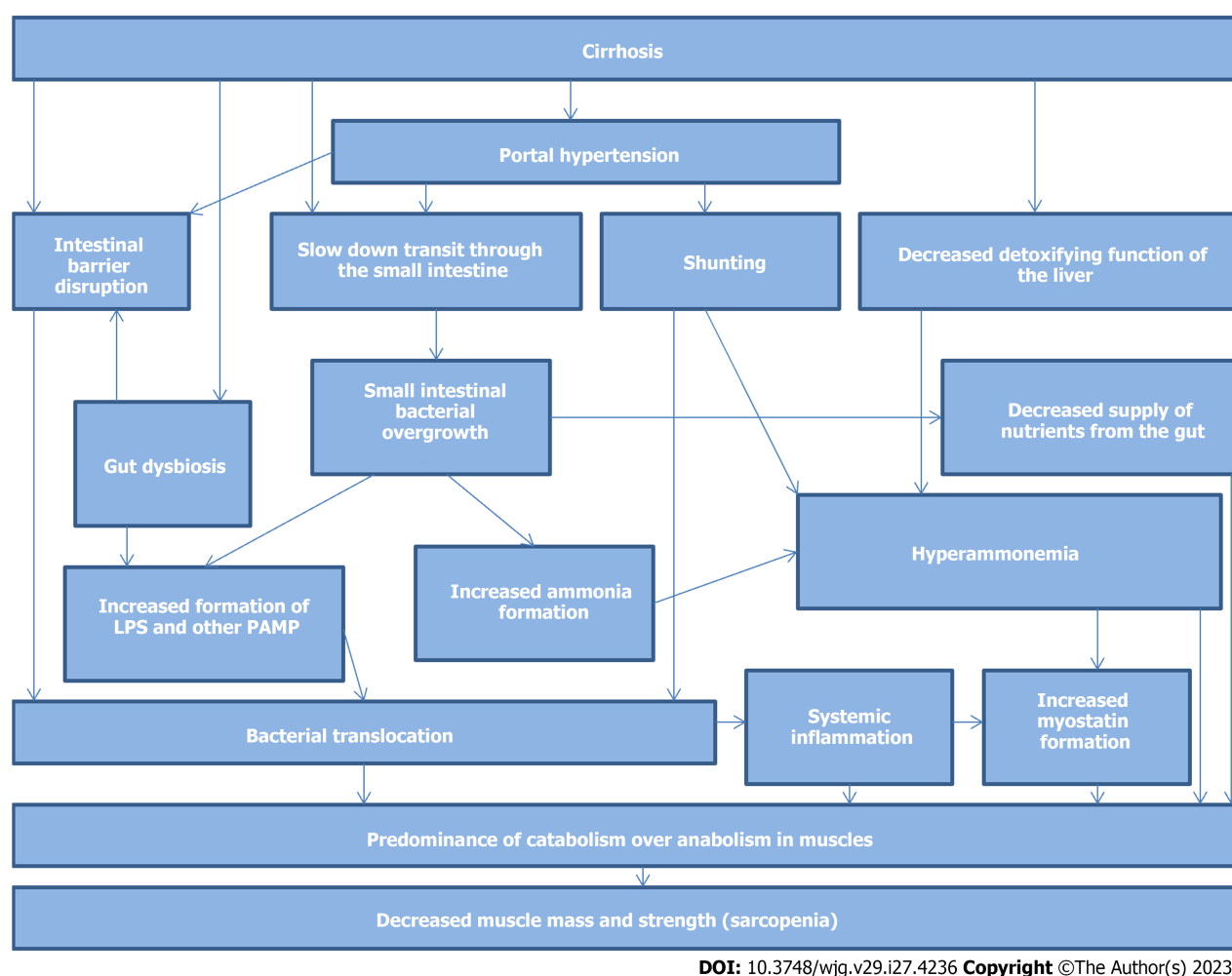


Figure 1 Simplified diagram of gut-muscle axis disorders in patients with cirrhosis. LPS: Lipopolysaccharide; PAMP: Pathogen-associated molecular patterns.

The meta-analysis showed that probiotics enhance both muscle mass and muscle strength in patients with sarcopenia that was not associated with cirrhosis[190]. The probiotic that included *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* decreased myostatin levels in a mouse model of muscular atrophy[191].

Although probiotics have been shown to be effective against several pathological links of the disturbed gut-muscle axis in patients with cirrhosis (SIBO, gut dysbiosis, hyperammonemia, and bacterial translocation), improve muscle function, and increase muscle mass in sarcopenia of another origin, no study has evaluated the effect of probiotics on muscle mass and function in cirrhosis.

Treating gut microbiota in cirrhosis: fecal transplantation

Fecal transplantation involves the transfer of intestinal microbiota from the donor to the intestine of a recipient. This procedure is effective in hepatic encephalopathy[192-194] and leads to an increase in the abundance of Ruminococcaceae and Bifidobacteriaceae and a decrease in the abundance of Streptococcaceae and Veillonellaceae in patients with cirrhosis [193].

No data exist on the effects of this procedure on the severity of hyperammonemia, bacterial translocation, systemic inflammation, myostatin levels, muscle mass and strength, or SIBO in patients with cirrhosis. No human studies have been conducted on the effect of fecal transplantation on muscle mass and strength in patients with sarcopenia of any origin; however, the results of animal experimental studies are promising[195].

CONCLUSION

Drug interventions targeting the gut microbiota positively affect most links of the compromised gut-muscle axis in cirrhosis (Table 5, Figure 2). Therefore, they are promising for the treatment and prevention of sarcopenia in cirrhosis, but have not yet been investigated in randomized controlled trials for these purposes. There are no data on the effect of fecal transplantation on most links of the gut-muscle axis and sarcopenia in cirrhosis, but the results of animal experimental studies are promising.

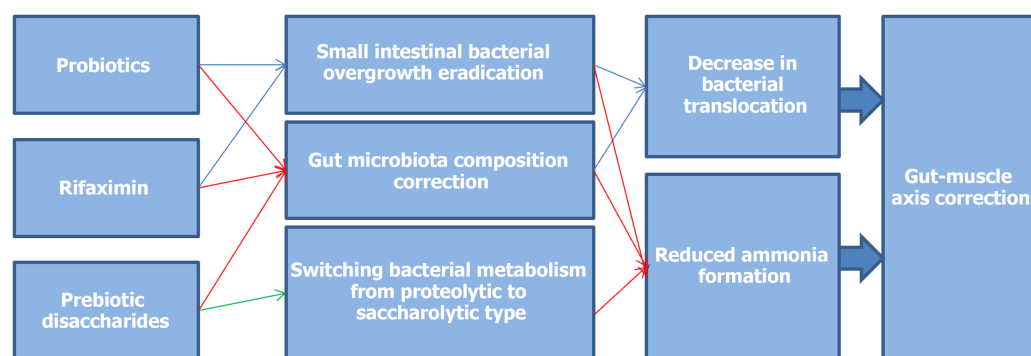
Table 4 The effect of probiotics on the composition of the gut microbiota in cirrhosis

Probiotic	Taxa that increase in the abundance after the probiotic	Taxa that decrease in the abundance after the probiotic
Lactobacillus acidophilus[159]	Bifidobacterium, Lactobacillus, and Bacteroidaceae	Enterobacteriaceae and <i>Enterococcus</i>
Escherichia coli Nissle 1917[160]	Bifidobacterium and <i>Lactobacillus</i>	Pathogenic enterobacteria
Escherichia coli Nissle 1917[175]	Bifidobacterium and <i>Lactobacillus</i>	<i>Proteus hauseri</i> , <i>Citrobacter</i> , and <i>Morganella</i>
Yakult 400[176]	<i>Clostridium coccoides</i> and <i>Eubacterium cylindroides</i>	Enterobacteriaceae
Lactobacillus GG[177]	Clostridiales Incertae Sedis XIV and Lachnospiraceae	Enterobacteriaceae
Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58[178]	Faecalibacterium prausnitzii, Syntrophococcus sucromutans, Bacteroides vulgatus, Alistipes shahii, and <i>Prevotella</i>	

Table 5 Effects of interventions targeting the gut microbiota on pathogenic factors in the gut-muscle axis in cirrhosis

Intervention	SIBO	Gut dysbiosis	Hyperammonemia	Bacterial translocation	Systemic inflammation
Rifaximin	+	+	+	+	CR
Prebiotic disaccharides	ND	+	+	+	+
Probiotics	+	+	+	+	CR
Fecal transplantation	ND	+	ND	ND	ND

+: A positive effect of this drug on this disorder has been reported; SIBO: Small intestinal bacterial overgrowth; CR: Conflicting results, ND: No data.



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Figure 2 Proposed mechanisms of action of drugs targeting the gut-muscle axis in cirrhosis.

FOOTNOTES

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