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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84675

Title: Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04122784
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Doctor, Research Assistant Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Russia

Manuscript submission date: 2023-03-24
Reviewer chosen by: Geng-Long Liu
Reviewer accepted review: 2023-04-20 11:26
Reviewer performed review: 2023-04-23 03:23
Review time: 2 Days and 15 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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. 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, disorders of the metabolic function of the liver, decreased appetite, increased muscle autophagy, increased serum myostatin (a protein that blocks muscle growth), catabolic effects of systemic inflammation induced by bacterial translocation from the gut, and low testosterone levels were found. This study aims to review the prospects for therapy targeted to gut microbiota for the sarcopenia in cirrhosis. Overall, this is an interesting

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study that may be helpful for the clinical management of sarcopenia in cirrhosis subjects. I have several concerns as follow: 1. Gut dysbiosis in patients with cirrhosis, and Small intestinal bacterial overgrowth in cirrhosis. More direct evidence/introduction were needed in these two sections. These two sections only introduce the gut bacterial issue in cirrhosis. How to transform to sarcopenia? Please address it. 2. A table is also needed for section "Treating gut microbiota in patients with cirrhosis: prebiotic disaccharides lactulose and lactitol" 3. The title "Treating gut microbiota in patients with cirrhosis: rifaximin" may not be suitable. The included studies were related to some other disorders, eg, Alzheimer's disease, Irritable bowel syndrome, Symptomatic uncomplicated diverticular disease, Chronic Kidney Disease, Gut diseases, Ulcerative colitis, Crohn's disease. The same issue in the next several sections. 4. In fact, the data on the fecal transplantation is rather limited, whereas the knowledge on rifaximin, prebiotic disaccharides and probiotics is rather informative. Therefore, the conclusion regarding these treatments needs reconstructed. Probably, rifaximin, prebiotic disaccharides and probiotics should also be mentioned in detailed, and fecal transplantation is a promising future direction instead. 5. A schematic diagram regarding the treatments (rifaximin, prebiotic disaccharides, probiotics and fecal transplantation) is helpful for the readers to better understanding the concept of this review.

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Manuscript NO: 84675

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03538235
Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Russia

Manuscript submission date: 2023-03-24

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-20 09:29

Reviewer performed review: 2023-04-26 14:46

Review time: 6 Days and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study analyzed the relationship between intestinal flora and sarcopenia in cirrhosis from several aspects, including imbalance of gut microbiota, excessive growth of gut bacteria, relationship between gut microbiota and gut muscle axis, and therapeutic prospects of gut microbiota regulating gut muscle axis. This study summarizes current relevant animal studies and mechanisms, and the summary is comprehensive. This problem is of great significance in clinical practice. However, there are still some issues to be addressed in this article: 1. It is suggested to supplement the clinical research related to intestinal microbial imbalance and cirrhosis of sarcopenia; 2. It is recommended to supplement the studies on the dominant intestinal flora and sarcopenia of cirrhosis in patients with cirrhosis; 3. It is suggested to refer to the literatures for clinical studies on the treatment of patients with cirrhosis with intestinal dominant flora, and supplement if necessary.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84675

Title: Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03075520
Position: Peer Reviewer
Academic degree: MD, MSc
Professional title: Chief Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Russia

Manuscript submission date: 2023-03-24

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-20 10:31

Reviewer performed review: 2023-04-28 11:44

Review time: 8 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No creativity or innovation

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Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Reviewers' comments Manuscript ID: 84675 Title:Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota Comments: 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

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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. It is a topic of interest to the researchers in the related areas ， but the paper needs large improvements before acceptance for publication.My detailed comments are as follows: 1.In this review, GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS are discussed along with Treating gut microbiota in cirrhosis: fecal transplantation. 2. The authors aimed to review the advances in GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS . But the parts of GUT-MUSCLE AXIS IN CIRRHOSIS is long ,should be abbreviated to 800 words in total ,the parts of PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS Are verbose ,it should be shorten to 1500 words totally. 3. There are too many references,they should be shorten to 80 references at most.In addition.The some of references are not up-to-date，references of the last 10 years should be cited,please cite last 10 years references ,especially references for the last 5 years. 4.The conclusion should be concise and only summarize the most important contribution of the research. Pelase make large revisions of the parts of GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS, references， and conclusion.After making large revisions,the paper may be considered for publication.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84675

Title: Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03075520
Position: Peer Reviewer
Academic degree: MD, MSc

Professional title: Chief Doctor, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Russia

Manuscript submission date: 2023-03-24

Reviewer chosen by: Li Li

Reviewer accepted review: 2023-05-26 06:40

Reviewer performed review: 2023-05-27 23:37

Review time: 1 Day and 16 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Reviewers' comments Manuscript ID: 84675

Title:Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota Comments：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. It is a topic of interest to the researchers in the related areas ， but the paper needsome improvements before acceptance for publication.My detailed comments are as follows: 1. There are still too many references,they should be shorten to 80 references at most.In addition.The some of references are not up-to-date，references of the last 10 years should be cited,please cite last 10 years references ,especially references for the last 5 years. 2.The conclusion should be concise and only summarize the most important contribution of the research. Pelase make some revisions of the parts of references，and

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conclusion again.After making some revisions,the paper may be considered for publication.