



March 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8744-edited.doc).

Title: Nutrition and exercise in the management of liver cirrhosis

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of the reviewers:

1 The format has been updated.

2 Revisions have been made according to the suggestions of the reviewers.

(1) Comments made by Reviewer 02861042: 1. Referring to the problem of obesity and sarcopenia in LC patients, the increasing problem of NAFLD and NASH in the industrial countries should be discussed.

→ We appreciate your great advice. According to your suggestion, we added the following sentences in the “**2.2. Sarcopenic obesity**” section.

Added sentences (page 9, lines 4 – 8): Furthermore, obesity is frequently accompanied by nonalcoholic fatty liver disease (NAFLD), and the prevalence of this liver disease is increasing in industrialized countries^[55-57]. NAFLD can progress to nonalcoholic steatohepatitis and LC. Given this global trend, sarcopenic obesity will likely be a major condition in LC patients in the future.

(2) Comments made by Reviewer 02861042: It would be nice to have figures or tables to quickly summarize the information. I.e. I suggest a table with strength and weakness of different methods to access sarcopenia. In addition a figure illustrating a practical approach to sarcopenic LC patients would be great including assessment and a stepwise management.

→ Thank you very much for your helpful suggestion. In accordance with your suggestion, we have created a table that displays the strengths and weaknesses of the different methods used to evaluate PEM and sarcopenia.

Table 1 Methods to assess PEM and sarcopenia in LC patients

Added sentence (page 10, line 5): Table 1 lists the methods used to assess PEM and sarcopenia.

Furthermore, the following relevant sentences were added to "**Handgrip strength**" in section "**3.4. Methods for sarcopenia assessment**".

Added sentence (page 14, lines 4 – 6): The European Working Group on Sarcopenia in Older People (EWGSOP) recommends handgrip strength as a practical measure of muscle strength^[14].

Added sentence (page 14, lines 9 – 10): However, it should be noted that considerable variation in the measurement methods has the potential to introduce measurement errors^[90].

→ Following your advice, we also created a figure illustrating a practical approach to LC patients with sarcopenia or sarcopenic obesity.

Added sentence (page 22, lines 7 – 9): Figure 1 shows a tentative practical approach for managing LC patients with sarcopenia or sarcopenic obesity.

Figure 1 A practical approach for managing LC patients with sarcopenia or sarcopenic obesity. LC: Liver cirrhosis; PEM: Protein-energy malnutrition; CT: Computed tomography; MRI: Magnetic resonance imaging; DXA: dual energy X-ray absorptiometry; BCAA: Branched chain amino acid.

(3) Comments made by Reviewer 02861208: In the introduction the authors mention obesity in Liver cirrhosis patients and make reference to a study that found excess caloric intake and high BMI in hepatitis C virus-related cirrhosis. Excess caloric intake and high BMI do not reflect obesity in patients with liver cirrhosis; not every patient with excess caloric intake has or will develop obesity and high BMI only reflects increased weight in relation to the patient's size and this weight can be due to water retention and not necessarily obesity.

→ Thank you very much for your comments. We are aware that in the case of decompensated LC patients, BMI does not necessarily correlate with the amount of muscle and fat mass because such patients frequently have edema and ascites. None of the patients described in the cited references (19, 20) had any clinical evidence of hepatic decompensation. To enhance the accuracy of the following sentence, we inserted the word "compensated" in its latter part. Furthermore, although excess caloric intake does not necessarily cause obesity, it seems evident that a significant percentage of compensated LC patients who consume excess calories will be overweight or obese.

Original sentence (page 4, lines 15 – 18): For example, 72.4% of patients had excess caloric intake in a study of compensated hepatitis C virus (HCV)-related LC ^[19], and 61% of HCV-related LC patients have a body mass index (BMI) ≥ 25 kg/m²^[20].

Revised sentence (page 4, line 17): For example, 72.4% of patients had excess caloric intake in a study of compensated hepatitis C virus (HCV)-related LC ^[19], and 61% of compensated HCV-related LC patients have a body mass index (BMI) ≥ 25 kg/m²^[20].

(4) Comments made by Reviewer 02861208: The content from the heading "Assessment method for

PEM in LC patients” requires the most changes in the manuscript. The title should read “Assessment methods for PEM in LC patients” or “Nutritional assessment in LC patients”.

→ Thank you very much for pointing out this mistake. According to your suggestion, we changed the heading of Chapter 3.

“Assessment methods for PEM in LC patients”.

(5) Comments made by Reviewer 02861208: The authors state that Harris-Benedict equations can be used as an assessment method for malnutrition, but it is only useful to assess resting energy expenditure and based on this, calculate the specific nutritional requirements for the patient's diet and they have been shown to underestimate caloric requirements in patients with chronic diseases. Harris-Benedict equations should be removed from the manuscript.

→ We appreciate your great advice. According to your suggestion, we removed the section “3.1. **Harris-Benedict equations**” and deleted the relevant references. Accordingly, the section numbers of Chapter 3 were changed.

(6) Comments made by Reviewer 02861208: The authors mention fat free acids levels in this section. Fat free acids levels are not a method for nutritional assessment but a marker and they have not been validated in patients with liver cirrhosis; this should be removed from the manuscript.

→ Thank you very much for your comment. Following your suggestion, we removed the section “3.4. **FFA**” and deleted the relevant references. Accordingly, the section numbers of Chapter 3 were changed.

(7) Comments made by Reviewer 02861208: Imaging methods for sarcopenia assessment are successfully addressed; but the authors also include bioimpedance analysis. First the authors state that bioimpedance analysis (BIA) has been recently used, but it has been widely used since the 90's and since then several studies in patients with liver cirrhosis have shown that the conventional analysis is biased by fluid retention even in compensated patients because body composition data is obtained from prediction equations based on healthy subjects. Phase angle derived from BIA is a nutritional marker and since is a direct measurement it is not biased by prediction equations; phase angle needs to be addressed. And BIA should be moved to PEM assessment and not sarcopenia assessment.

→ We appreciate this helpful comment. According to your advice, “**Bioimpedance analysis (BIA)**” was moved to section 3.3. of Chapter 3 “**Assessment methods for PEM in LC patients**” and was revised.

Original sentences (page 13, lines 13 – 20): Recently, bioimpedance analysis (BIA) has been used to assess body composition. This method is based on the measurement of tissue conductivity. Skeletal muscle is a major body component with low resistance and therefore is a dominant conductor^[72]. Several studies have revealed that the estimated values of skeletal muscle mass obtained from BIA are not significantly different from those obtained from MRI^[72] or DXA^[77]. Because of its convenience and low cost, BIA is a potential alternative candidate for the above methods^[14]. BIA has been reported to be

limited in the assessment of LC patients with ascites^[78].

Revised sentences (page 12, lines 1 – 17): Bioimpedance analysis (BIA) is another measure to assess PEM. This method is based on the measurement of tissue conductivity^[72]. Skeletal muscle is a major body component with low resistance and is therefore a dominant conductor^[73]. A study with LC patients has demonstrated that BIA is a reliable bedside tool for the estimation of body cell mass, although it is limited in the case of LC with ascites^[74]. The phase angle (PA) is a derived measure calculated from two parameters of BIA: $PA = \text{arc-tangent reactance/resistance} \times 180^\circ / \pi$ ^[75]. Several studies have demonstrated that PA is useful in the assessment of the nutritional status in hemodialysis^[76] or preoperative^[77] patients. Another study has suggested that PA can serve as a prognostic indicator in cancer patients^[78]. With regard to LC, a recent study indicated that PA is a promising parameter for the assessment of patient nutritional status^[79]. Furthermore, a study suggested that PA is more predictive of survival than commonly used body composition information: a low PA is associated with shorter survival time^[80]. Several studies have revealed that the estimated values of skeletal muscle mass obtained by BIA are not significantly different from those obtained by magnetic resonance imaging (MRI)^[73] or dual energy X-ray absorptiometry (DXA)^[81] (see below). Because of its convenience and low cost, BIA is a potential alternative to these imaging methods^[14].

(8) Comments made by Reviewer 02861208: The authors use “muscle strength” term but the proper term is “handgrip strength” and this heading lacks information.

→ Thank you very much for your suggestion. Following your advice, we changed the heading from “Muscle strength” to “Handgrip strength”.

(9) Comments made by Reviewer 02861208: In the heading of “Nutritional management for LC patients” the authors mention the consequences of decreased dietary intake but they do not mention the recommended caloric and protein intake, this should be added based on international guidelines.

→ Thank you very much for this important comment. As guidelines for the nutritional management of LC patients, we described the recommendations from the ESPEN guidelines.

Added sentence (page 15, lines 8 – 11): The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend that energy and protein intake should be 35 – 40 kcal/kg of body weight per day and 1.2 – 1.5 g/kg of body weight per day, respectively^[93].

(10) Comments made by Reviewer 02861208: Branched chain amino acids are broadly addressed and even though the authors make a very interesting review of this issue this heading looks like the main topic of the article and it takes focus from the exercise topic. It should be somewhat shortened.

→ Thank you very much for your suggestion. Following your advice, we deleted the following two paragraphs because the usefulness of BCAA in the treatment and prevention of HCC but not the treatment of LC is discussed in those paragraphs.

Original sentences (page 16, lines 19 – 21 and page 17, lines 1 – 17):

BCAA supplementation can also be helpful in maintaining nutritional status and liver function in LC patients with HCC who undergo various treatments for HCC such as surgical resection^[103], radiofrequency ablation^[104], and transcatheter arterial chemoembolization^[105-107]. A long-term follow-up study of patients who received transcatheter arterial chemoembolization for HCC suggested that BCAA and carbohydrate mixtures were both beneficial in increasing serum albumin levels, reducing morbidity, and improving quality of life in HCC patients^[105]. Furthermore, recent studies of liver transplantation have suggested that postoperative BCAA supplementation may restore impaired energy metabolism^[108] and reduce the incidence of bacteremia^[109].

Improved nutritional status with BCAA treatment may present a protective effect against hepatocarcinogenesis in LC patients. In a randomized controlled trial investigating BCAA effects on hepatocarcinogenesis in HCV-related LC patients, BCAAs were shown to be potential inhibitors of hepatocarcinogenesis in patients with compensated LC and a serum albumin level < 4.0 g/dl^[110]. Some retrospective analyses have also indicated that BCAA supplementation may decrease the incidence of hepatocarcinogenesis in LC patients^[111,112]. More recently, a prospective study of LC patients found that BCAAs reduced the risk of HCC (relative risk, 0.45; 95% confidence interval, 0.24 - 0.88) and mortality (relative risk, 0.009; 95% confidence interval, 0.0002 - 0.365)^[113]. This evidence suggests that BCAA supplementation is a promising strategy for the prevention of hepatocarcinogenesis in LC patients.

(11) Comments made by Reviewer 02861208: In the heading "Exercise management for LC patients" the authors mention the benefits obtained from exercise but recommendations of specific types of exercise and duration are not mentioned. This needs to be addressed deeply since is one of the two topics mentioned in the title.

→ We appreciate your helpful comments. There are many studies on the exercise management of sarcopenia or obesity but few on exercise management for LC patients. However, we found some studies in which exercise programs were effective for LC patients. We added the following sentences with reference to the study results.

Added sentence (page 20, lines 12 - 13): However, there are some preliminary data with regard to efficacious exercise management for LC patients.

Added sentences (page 20, lines 17 - 21 and page 21, lines 1 - 8): Most recently, a randomized pilot study with LC patients, in which most participants had Child-Pugh grade A LC, examined whether an exercise program combined with leucine supplementation (10 g/day) can improve patient outcome. The program included three sessions per week of a 1-h treadmill and cycle ergometry exercise at an intensity of 60 - 70% of the maximum heart rate, over a period of 12 weeks. The intervention group had improved exercise capacity, as shown by the 6-min walk test (from median 365 m to median 445 m) and the 2-min step test (from median 100 steps to median 150 steps), increased lower thigh circumference, and improved health-related quality of life; the control group had no significant changes^[143]. During the study, no adverse events due to the implementation of the exercise program were observed. These studies suggest the possibility that moderate exercise combined with LC-specific nutritional support can increase skeletal muscle volume and improve the outcomes of LC patients.

Furthermore, we cited several references in section "5.2. Assessment of nutritional status and

complications for exercise management”.

Original sentence (page 20, lines 14 – 16): With regard to LC, inappropriate exercise may cause undesirable outcomes due to the impaired energy metabolism and/or complications associated with LC, including ascites, hepatic encephalopathy, portal hypertension, and hepatopulmonary syndrome.

Revised sentence (page 20, 2 – 4): With regard to LC, inappropriate exercise may cause undesirable outcomes due to the impaired energy metabolism and/or complications associated with LC, including ascites^[137], hepatic encephalopathy^[138], portal hypertension^[139], and hepatopulmonary syndrome^[140].

3 References and typesetting were corrected.

Finally, our manuscript has been improved by the use of an English language editing service, American Journal Experts.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading "Nobuyuki Toshihuni". The signature is written in a cursive, flowing style.

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