Author’s response to reviews

Title: Zinc supplementation in patients with cirrhosis and hepatic encephalopathy: A systematic review and meta-analysis

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Author’s response to reviews:

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Professor Clare Collins and Professor Sharon Kirkpatrick
Editors-in-Chief
Nutrition Journal

Dear Editor:

Thank you for considering our resubmitted manuscript “Zinc supplementation in patients with cirrhosis and hepatic encephalopathy: A systematic review and meta-analysis” (Manuscript NUTJ-D-19-00009.R1) for publication in Nutrition Journal as an original article.

We greatly appreciate the constructive comments from the editor and reviewers. We are also very grateful for your effort to polish up our manuscript. On the following pages, we provide point-by-point responses to the comments made by the reviewers and the editor. Moreover, the supporting literature and a copy of comparison between original edition and revision edition were enclosed. We hope that our revised version will be received favourably.

Thank you for your consideration. I look forward to hearing from you.
Sincerely,

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REVIEWERS’ COMMENTS TO AUTHOR:

Reviewer #1:

This study primarily focuses on the effects of zinc supplementation in patients with cirrhosis and hepatic encephalopathy. There were some interesting results in this study. However, the experimental design in the study was inappropriate. The conclusion was wrong in this issue. I regret to say that this issue denied for publication.

Major

1. References #15 and #16 should be removed for meta-analysis. The treatment duration in both references was too short.

Response:

Thanks for your solid recommendation. It was not explicit enough to point out the inclusion of eligible study in final meta-analysis. Overall, Riggio et al. study (reference #16) was only presented in the qualitative synthesis, not in meta-analysis owing to lack of original data. We revised the description in the section of “Search results” as follows: “three studies [15, 26, 27] among those were excluded from the quantitative synthesis because the results were provided as figures only and primary data could not be obtained” (see Page 9, Line 178). In addition, Reding et al. study (reference #15) was also excluded in the final quantitative synthesis for using different intervention and comparison. Furthermore, we have emphasized the included studies of final meta-analysis by rewriting as follows: “Three studies [13, 17, 28] with a total of 227
patients comparing zinc supplementation plus lactulose versus lactulose alone were included in the meta-analysis (Fig 2)” (see Page 13, Line 217).

We also agreed that the treatment duration of both trials was too short to evaluation the effect of zinc supplements, so we rewrote the description in the section of “Synthesis of results” as follows: “In addition, there were two trials [14, 15] comparing short-term oral zinc supplementation to placebo in the NCT results. Reding et al. [14] showed that zinc supplementation administered orally for one week improved cirrhotic patients with HE grade I assessed by the NCT; while Riggio et al. [15], who presented the contradictory results as figures only without original data obtained, found that no significant differences of NCT either during zinc or placebo administration. The treatment duration in both of studies was too short to assess the efficacy of zinc supplementation, which was not appropriate to be pooled in our meta-analysis as well.” (see Page 14, Line 228).


2. Reference #27 should be removed for meta-analysis. Serum Zn levels in Zn supplemental group were not the same as those in control group.

Response: Thanks for your critical comments. We have removed Somi et al. study (reference #27) from included studies for not reporting relevant outcomes meeting our criteria. We rewrote the description in the section of “Search results” as follows: “Ultimately, seven studies were identified for the qualitative synthesis [13-15, 17, 26-28]” (see Page 9, Line 177). We also appreciate that you noticed the importance of basal levels of serum zinc in paired groups. As far as we understood, in Somi et al study, the mean serum zinc concentration at baseline were 63.97 ± 4.2 ug/dL in Zn supplemental group and 67.42 ± 3.02 in control group, which was not statistically significant difference (p = 0.57). We have emphasized the baseline characteristic of zinc levels as follows: “Furthermore, all patients were found to have baseline zinc deficiency, but there was no statistically significant difference between the zinc and control groups in each trial” (see Page 10, Line 191).

3. The effect of Zn supplementation was confirmed by only number connection test. However, no significant differences in digital symbol test and serum ammonia level were found between Zn and control groups. Therefore, the conclusion that "Zn
supplementation may improve the neuro-cognitive function in patients with cirrhosis and hepatic encephalopathy" seems to be inappropriate.

Response: Thanks for your solid recommendation and we agreed with your opinion. For more clarifying, we revised our paragraph in the section of “Discussion” as follows: “Finally, our study assessed the effect of zinc supplementation on cognitive functions only by two tests (NCT and DST), which mainly involved in psychomotor speed and attention. We could not determine whether Zn supplementation may improve different cognitive domains, including visuospatial perception, memory, executive function, language and praxis. Therefore, future high-quality RCTs with a large sample size encompassing all degrees of HE with the evaluation of other psychometric or neuro-physiologic testing are warranted to further elucidate our findings” (Page 21, Line 327). We also re-wrote the descriptions in the abstract and the section of “Conclusion” as follows: “In conclusion, a combination of zinc supplementation and lactulose over 3 to 6 months may improve the number connection test in cirrhotic patients with low grade HE, compared with lactulose only” (Page 21, Line 336).

Reviewer #2:

1. This is generally a well-written article. There are minor grammatical errors that need correcting.

Response: Thank you for your time and we appreciate the acknowledgment very much. We had already used a professional language editing service to improve our article. If needed, we can provided the certification of the English editing service at any time.

2. I did not see any figure legends. Figure legends are needed to make the figures more clear.

Response: Thanks for the reviewers’ solid recommendation. We rewrote the figure legends for clarity and put them together at the bottom of the manuscript. (see Page 29, Line 505)

3. Lastly, I have a concern about zinc supplementation recommendations. Some investigators in older articles were utilizing relatively high doses of zinc. It should be emphasized that this is zinc salt, and not elemental zinc. For example, 220mg of zinc sulphate is only 50mg of elemental zinc. It is generally recommended that most patients receive no more than 50mg of elemental zinc per day. I think the authors should add a cautionary note concerning this.
Response: Thanks for your excellent recommendation and we agreed with your concern. To add a cautionary note, we re-wrote the descriptions in the section of “Discussion” as follows “It is worth noted that the all included articles used zinc compounds as supplements, not elemental zinc. The maximum adult dose of elemental zinc is 40 mg a day [50]. Since different type of supplements contain various percentage of elemental zinc, it is warned that patients should follow the instructions of healthcare professionals when receiving zinc supplements for medical treatment (Page 19, Line 305)”.

Reviewer #3:

I read the interesting manuscript entitled "Zinc supplementation in patients with cirrhosis and hepatic encephalopathy: A systematic review and meta-analysis" an interesting work in which the authors claims some benefits about the use of oral zinc treating hepatic encephalopathy. Unfortunately the manuscript don't provide additional advances to a previous meta-analysis. Also neither additional clinical outcomes are provided.

Response: Thanks for your critical comments. We are very grateful for your kind reminder in sharpening our manuscript. Compared with previous meta-analysis in 2013, our study only included trials using a combination of zinc supplementation and lactulose as the intervention group and lactulose therapy alone as the control group in patients with low grade HE (≤ grade II). We also revised our description in the section of “Discussion” as follows to further elucidate our findings: “We reported a larger significant effect (SMD = -0.97%) in favor of additional zinc supplementation on the NCT results compared with lactulose alone than the previous meta-analysis (SMD = -0.62%). Moreover, apart from the NST, we investigated different endpoints including DST, which primarily used for assessing psychomotor speed and attention in cognitive function, as well as serum ammonia levels. Furthermore, we used the GRADE methodology to evaluate our confidence in the estimates of the treatment effect” (Page 20, Line 311).

#Ass Editor:

This paper updates an earlier review/meta-analysis on the same topic published in 2013. It is of interest to review the newer findings and to include studies published since then in the meta-analysis. However, as indicated by one reviewer, it may be advisable to exclude short-term supplementation studies and ref #27 in which baseline status differs between groups.

Please amend the abstract and paper to report differences more clearly only when statistically significant - as the other findings are not conclusive. For example (p16) 'Compared with lactulose therapy alone, the pooled effect for zinc supplementation plus lactulose therapy showed a small but non-significant effect'.
Response:

Thanks for the editor’s crucial recommendation and we appreciate your time to give us a chance to refine our paper. In this rewriting manuscript, we included 4 studies (reference #13, #14, #17, #28) in our quantitative synthesis eventually. We have removed Somi et al. trial (Reference #27) from included studies because it did not report relevant outcomes meeting our criteria. In addition, Riggio et al. study (Reference #16) was only presented in the qualitative synthesis, not in meta-analysis due to lack of original data. Reding et al. study (Reference #15) was also excluded in the final quantitative synthesis for using different intervention and comparison. Both of studies were only presented in quality analysis. We revised the paragraph in the section of “Synthesis of results” as follows: “In addition, there were two trials [14, 15] comparing short-term oral zinc supplementation to placebo in the NCT results. Reding et al. [14] showed that zinc supplementation administered orally for one week improved cirrhotic patients with HE grade I assessed by the NCT; while Riggio et al. [15], who presented the contradictory results as figures only without original data obtained, found that no significant differences of NCT either during zinc or placebo administration. The treatment duration in both of studies was too short to assess the efficacy of zinc supplementation, which was not appropriate to be pooled in our meta-analysis as well.” (see Page 14, Line 228).

We also re-wrote the description in the abstract and paper as follows to make inconclusive findings more concise: “However, compared with lactulose therapy alone, additional zinc supplementation demonstrated no significant difference in the digit symbol test (SMD: 0.44; 95% CI: -0.12 to 1.00; P = 0.12; very low certainty) or serum ammonia levels (MD: -10.86; 95% CI: -25.73 to 4.01; P = 0.15; very low certainty), reported in two trials (n = 137)” (Page 4 Line 67).