Author's response to reviews

Title: Can Chitosan Chewing Gum Reduce the Serum Phosphate of Hemodialysis Patients? A Multi-Center Randomized Double-Blind Placebo-Controlled Trial

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Author's response to reviews: see over
Dear Dr. Gutierrez,

Thank you for your comments on our manuscript entitled "Can Chitosan Chewing Gum Reduce the Serum Phosphate of Hemodialysis Patients? A Multi-Center Randomized Double-Blind Placebo-Controlled Trial" by Akizawa et al.

The revised manuscript has been reviewed and approved by all of the authors of this manuscript. We have changed the title to “Effect of chitosan chewing gum on reducing serum phosphate in hemodialysis patients: a multi-center, randomized, double-blind, placebo-controlled trial”.

The following responses are our answers to the queries raised by the editors and reviewers. We trust that these amendments will make it easier for your readers to understand our manuscript.

1. Background section: "Increased level of serum phosphorus in HD patients is well recognized to cause cardiovascular calcification followed by cardiovascular disease." Please stay away from these sorts of statements. There are no studies that have definitively shown that higher phosphorus concentrations cause cardiovascular calcification or cardiovascular disease in hemodialysis patients. This is inferred from observational studies and animal studies. Please re-write this sentence to more accurately reflect the current state of the scientific literature on this topic.

We have replaced this sentence with the following: "Increased levels of serum phosphorus in HD patients are associated with an increased incidence and mortality of cardiovascular diseases [2]." (lines 77–79). We have also changed the reference.

2. Results: Please refer to Figure 1 under the patient characteristics and disposition section. You never actually indicate that there is a figure for this section in the text of the results.

We thank the reviewer for pointing out this omission. Figure 1 has been indicated in the text (line 224).

3. Results: Please indicate in Figure 1 how many patients needed to be screened to reach the 71 who were enrolled in the study. Please indicate the reason(s) that three individuals were excluded to get down to 68 who were randomized.

We did not record how many patients were screened because the screenings were conducted prior to informed consent. The reasons for exclusion from the study to obtain 68 out of 71 patients have been described on lines 210-212.
4. Results: please clarify was it meant when you say that 3 patients failed to meet the eligibility criteria in HD conditions-- please include these criteria in the Methods section. Please also clarify what is meant when you say that one patient was discontinued because of a change in HD conditions.

To clarify why three patients failed to meet the eligibility criteria, the conditions required for HD in our study have been added to the revised manuscript on lines 140–142 in the Methods section according to the reviewer’s request. The reason for withdrawal of one patient from the study because of a change in HD conditions has been added on lines 221-222 in the Results section.

5. Table 3 is confusing to read. What is being shown under the column for "n". Does this refer to the total number of participants in each category? If so, could you include the two-digit number on one line instead of stacked as single digits on top of each other? Please also change the configuration of this Table to be the same as Table 2 and Table 4... it is distracting to have different layouts for these three tables.

We apologize for the confusion in Table 3. We have re-arranged this table as suggested.

6. Please spend more time discussing the other "negative" clinical trials of chitosan use and how the current study adds to this literature.

We thank the reviewer for these suggestions. Our study was the first randomized, placebo-controlled, double-blind clinical study on the effect of chitosan in HD patients, and is shown in the ClinicalTrial.gov database: http://www.clinicaltrials.gov/ct2/show/NCT01039428?term=HS219&rank=1, although Dr. Block et al reported their negative results of chitosan chewing gum on serum phosphorous in HD patients in Nephron Clin Pract 2013: 123:93.

We have re-written the discussion to clarify what we expected with chitosan-loaded chewing gum in HD patients and the actual results. Readers of the Journal will understand that the recent comments on bias of the study by Savica et al., as reported by Oh and Uribarri in the Clin J Am Soc Nephrol (2014), were taken into consideration prior to our study.

7. There are numerous grammatical errors in English throughout the manuscript. If possible, please have a native English speaking individual or closest equivalent review the manuscript prior to re-submission.

We apologize for the numerous grammatical errors in our manuscript. The text has been revised by a native English speaker from a professional editing company according to the reviewer’s recommendation and the following editorial request.

Editorial Request 1:
Copyediting - We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific
expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

We thank the editor for the recommendation. Our manuscript has been revised by the proposed company (Edanz Editing).

Editorial Request 2:

Tables as additional files - We notice that you have included tables as additional files. If you want the tables to be visible within the final published manuscript please include them in the manuscript in a tables section following the references. Alternatively, please cite the files as Additional file 1 etc., and include an additional files section in the manuscript.

The tables have been included in the text following the References section.

We hope that you will now consider this study acceptable for publication in BMC Nephrology.

We look forward to hearing from you soon.

Yours sincerely,

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