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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Dear Dr. Gutierrez,


Thank you consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to your editor's and reviewer's comments.

EDITORIAL COMMENTS (Dr. Gutierrez)

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 the sentence pointed out with "Increased level of serum phosphorus in HD patients is well associated with increased incidence and mortality of cardiovascular diseases [2]." (page 5) and 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.

Figure 1 has been indicated in the text "The demographic and clinical
characteristics of the patient population were well balanced between the HS219 arm and placebo arm, as shown in Figure and Table 1." (page 10).

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, since the investigators selected a participant candidate based on his/her medical records prior to the informed consent.

The reasons excluded to get down 68 from 71 patients were described in the text " Written informed consents were obtained in 71 patients, but 2 withdraw their consent and 1 failed to meet the salivary flow rate > 1 g/2 min by the Saxon test before the release of the randomization code." at page 10.

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.

HD conditions required in our study have been added in the text " HD conditions including the dialysis time within 10% variation, blood flow rate within 10% variation, dialyzer, and dialysate were required to be maintained during the study." in Methods section (page 7) according to your request.

The reason of withdrawal by change of HD conditions has been shown in the text " Two patients were not included because of withdrawal of consent and one was not included for failure to comply with the study protocol because of a change in dialyzer during the treatment phase." in Results section (page 10).

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 have re-edited Table 3.

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

Our study was the first randomized placebo-controlled double-blind clinical study as you can see at NCT01039428 at ClinicalTrials; http://www.clinicaltrials.gov/ct2/show/NCT01039428?term=HS219&rank=1, although preparation of this manuscript have been delayed.

We have re-written the discussion in order to clarify what we expected in the chitosan (40 mg)-loaded chewing gum. In our revised discussion, the recent comments by Drs. Oh and Uribarri in the Clin J Am Soc Nephrol 2014 have been included, since we discussed this when designing the protocol (page 11-15).

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.

The text has been revised according to your recommendation at 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.

The manuscript has been revised by Edanz. We revised the title according to their recommendation as "Effect of chitosan chewing gum on reducing serum phosphate in hemodialysis patients: a multi-center, randomized, double-blind, placebo-controlled trial"

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 Reference section.

Reviewer #1 (Dr. Uribarri)

MAJOR COMPULSORY REVISION

1) The authors should read and incorporate within their discussion a recent review dealing on why we should not have expected any effect of the amounts of chewing gum used and serum phosphate in their hemodialysis patients (Oh MS, Uribarri J. What can we learn from the saga of chitosan gums in hyperphosphatemia therapy? Clin J Am Soc Nephrol. 2014 Jan 9. [Epub ahead of print]. Essentially, the amount of chitosan contained in the gum that were used is not large enough to expect any meaningful effect on reducing phosphate. The results of the current study confirm American studies previously published (reference 23).

These trials should have never been done because they were expected to fail, but since they were done I guess they should be published so that other workers in the field will not make similar mistakes.

Discussion section has been re-written to make clear what we had discussed the rationale how chitosan chewing gum works and what you knew as a result (page 11-15). We introduced Dr. Uribarri’s comment reported in the Clin J Am Soc
Nephrol 2014.

2) The idea in the conclusions that more scientific data are needed for any further development of chitosan... should be changed. The quantitative data to develop or not this therapy already exists in the literature (see above reference in CJASN 2014).

We revised our conclusion as depicted on page 15:

"HS219, chitosan-loaded chewing gum designed as a supplemental phosphate binder targeted salivary phosphate, did not present any add-on effect on salivary and serum phosphorous levels in HD patients with hyperphosphatemia treated with either sevelamer hydrochloride or calcium carbonate by randomized placebo-controlled double blind study."

Reviewer #2 (Dr. Uda)
Major compulsory revisions and Minor essential revision
Reviewer # has no suggested changes for the manuscript.

Reviewer #2 (Dr. Watanabe)
DISCRETIONARY REVISION

I suggest that authors should explain why authors enrolled patients with over 1g/2 min saliva flow rate by Saxon test. In general, 2g/2 min is borderline for xerostomia. Postorino et.al. (AJKD 2003) reported that mean salivary secretion was 3.3 g/2 min in HD patients (after dialysis session). There is a possibility that patients with xerostomia was enrolled, so saliva flow rate may have a wide range in this study.

In addition, authors need to shown further patients' details about drugs which affected to saliva, i.e. antihistamines or proton pump inhibitors, and about disease, i.e. Sjogren's syndrome or lupus, about habits i.e. alcohol or smoking.

We revised our Method section regarding the Saxon test as depicted on page 7:

"The inclusion criteria of salivary flow rate was set based on a feasibility study conducted in Japanese HD patients (data not shown in this article) that indicated the number of the patients whose salivary flow rate > 2 g/2 min by the Saxon test were limited, and the patients between 1 and 2 g/2 min were found to be able to chew the gum for 30 min."

We thought of the measured salivary flow rate and salivary phosphate as our target parameters. Although collected the data of the concomitant drugs, but we did not analyze the correlation between drugs affecting saliva and salivary flow rate.

Reviewer #2 (Dr. Shishido)
MINOR ESSENTIAL REVISION

1. In this paper, the authors use two similar terms, “phosphorus” and “phosphate”. Please confirm to use the two words suitably and properly in the
context.

"Phosphate" might be a proper term. We changed "phosphorous" with "phosphate", except describing the serum and salivary concentration/levels, since "P" levels (mg/dL) in clinical lab is indicated by the weight of phosphorous.

2. According to the protocol of this study, serum levels of phosphate, calcium, and albumin were measured in each treatment arms every week (week 0, 1, 2, 3, 4, 5 and 6). The authors provide those levels at only two points, baseline and week 3. However, the changes in serum P and corrected Ca levels provide important information to understand this study. I think that the authors should illustrate serum P levels throughout the 6-week study period.

If there is any biological responses were observed, the chart of change of phosphorous levels throughout the study would be very informative. However, our results were negative in all outcomes. Thus, we decided not to present the chart.