Author's response to reviews

Title: The relationship between proton pump inhibitor use and serum magnesium concentration among hemodialysis patients: a cross-sectional study

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Author's response to reviews: see over
May 31, 2015

Re: The relationship between proton pump inhibitor use and serum magnesium concentration among hemodialysis patients: a cross-sectional study

Dear Editorial Board,

We are pleased to submit a revised version of our manuscript titled "The relationship between proton pump inhibitor use and serum magnesium concentration among hemodialysis patients: a cross-sectional study" to BMC Nephrology for consideration of publication as an original article.

We have addressed the reviewers’ comments, with each point outlined in our ‘Response to Reviewers’ below. We have also modified the text accordingly.

We hope the manuscript will now be suitable for publication in BMC Nephrology.

Sincerely,

Paraish Misra, Ahsan Alam, Mark Lipman and Sharon Nessim
Response to Reviewers

Reviewer: David Leehey

Reviewer's report: The authors have submitted a paper that confirms the findings of Alhosaini et al. (Am J Nephrol 2014) that PPIs are associated with lower mean serum Mg levels in HD patients. The paper is clear and well written. However, the way the paper is written it might appear to a reader that theirs is a novel rather than a confirmatory observation. In particular, the statement on P. 8 lines 19-21 is not referenced (it refers to Alhosaini et al., ref 10). The reference number needs to be added. There is validity to their subsequent statement (lines 21-23) that their study adds to the literature by validating this association in a larger and more diverse cohort of HD patients.

We thank the reviewer for the feedback. We had mistakenly omitted the reference for the above statement. It has now been added.

Major Compulsory Revisions:

Introduction. P. 4, line 19. Do the authors know that all of the patients had little or no urine output, i.e., did they exclude non-oliguric patients or patients with residual renal function. This may be important as diuretics are a risk factor for PPI-induced hypomagnesemia, and this risk appears to still be present in HD patients still taking diuretics. Were any of the authors’ patients taking diuretics?

We did not exclude non-oliguric patients, nor did we quantitate patients’ residual renal function (RRF) at the time of Mg measurement as this was a retrospective study. However, we excluded patients who had initiated dialysis within the prior 3 months, and this would be the time when patients’ RRF would be highest. The vast majority of patients in the study were already on dialysis for at least 1 year by the time the Mg measurements were recorded (the median time on dialysis overall was 32 months, with an interquartile range of 20-63 months in the PPI users, and 16-43 months in the non-users). There is evidence to suggest that HD patients tend to lose their RRF relatively quickly - for example, in a study by Moist et al (JASN 2000) looking at predictors of loss of RRF, 69% of patients on HD has urine volume <200cc/24 hours at 1 year. Therefore, it is very unlikely that the patients in our study had significant renal Mg losses (even among those on diuretics).

Methods. Were there any other exclusions (see above)?

All exclusion criteria are outlined in the text: if they were receiving dialysis for < 3 months, if they were hospitalized at any time over the 3-month period during
which the blood tests were drawn, or if they had a history of chronic diarrhea, or an ileostomy or colostomy).

Results. The authors should add a few more factors to their multivariate analyses. Specifically, they should adjust for diuretic use, Kt/V, nPCR, and possibly serum albumin.

We thank the reviewer for this suggestion. Data on diuretic use was not collected, but as mentioned above, diuretics would be unlikely to have had a significant influence on renal Mg wasting in a prevalent HD population with little or no urine output. Similarly, due to the retrospective nature of the study, we did not collect data on nutritional parameters. We have now acknowledged this as a limitation in the discussion.
Reviewer: COSTAS FOURTOUNAS

Reviewer's report: This is a single center cross sectional study regarding hypomagnesemia and the use of PPIs in hemodialysis (HD) patients. The authors studied a total of 155 HD patients divided into a PPIs group (n=86) and a non PPIs group (n=69). The main finding is that the PPIs group presented statistically significant lower levels of serum Mg. The findings seem interesting but there are some points that need to be clarified. The authors implicate that HD patients have not significant residual renal function. They should add data regarding urine volume in both groups. What about high dose diuretics (furosemide) in some/any patients? Hypomagnesemia in HD may also be a marker of chronic inflammation or a marker of poor nutritional status (Dousdampanis et al HEMO INT 2014;18: 730-9). So, the authors should investigate if markers of inflammation (CRP, etc) or poor nutrition (serum albumin, etc) may present differences between the 2 groups and be added in the multivariate regression model.

We thank the reviewer for these comments. As mentioned in our response to the first reviewer, unfortunately we did not have data on urine volume in the 2 groups because it was a retrospective study and urine volume is not routinely measured in HD patients. However, we excluded patients who had initiated dialysis within the prior 3 months, and this would be the time when patients' RRF would be highest. The vast majority of patients in the study were already on dialysis for at least 1 year by the time the Mg measurements were recorded (the median time on dialysis overall was 32 months, with an interquartile range of 20-63 months in the PPI users, and 16-43 months in the non-users). There is evidence to suggest that HD patients tend to lose their RRF relatively quickly - for example, in a study by Moist et al (JASN 2000) looking at predictors of loss of RRF, 69% of patients on HD has urine volume <200cc/24 hours at 1 year. Therefore, it is very unlikely that the patients in our study had significant renal Mg losses (even among those on diuretics).

We thank the reviewer for making the point about hypomagnesemia being a possible marker of chronic inflammation or poor nutritional status. Unfortunately, due to the retrospective nature of the study, we do not collect data on CRP or albumin. We have added this to the limitations section in the discussion.
Reviewer: IOANNIS TZANAKIS

Reviewer's report: General comment I think that it is a very interesting article that provides very useful information of clinical importance. The idea to examine the hypothesis that PPIs probably increase the intestinal loss of magnesium and subsequently cause hypomagnesaemia by studding patients with no or limited renal magnesium excretion such as the ESRD patients is very good. Probably the prolonged use of PPIs is the cause of an otherwise unexplained low serum magnesium levels in hemodialysis patients. I think it is a worth published article but after elucidating and revising some points.

Specific comments (according to MBC Nephrology Quidlines). No revisions The question posed by the authors is well defined. All data and figures are genuine and not manipulated. I think that that the authors clearly acknowledge the study (ref. 10) Alhosaini M, Walter JS, Singh S, Dieter RS, Hsieh A, Leehey DJ. Hypomagnesemia in Hemodialysis patients: role of proton pump inhibitors. Am J Nephrol 2014; 39:204-9. To the best of my knowledge this is the only study published in the English literature that evaluates the role of PPIs in ESRD patients concerning the development of hypomagnesemia. The present study confirms the results of the above study and enhances the information on this field. The statistical analysis is proper and acceptable. The conclusions are well balanced and adequately supported by the data. The writing style of the manuscript is quite acceptable for a medical article; English is the author’s mother language so I have not any comment on spelling or on syntax.

Major Compulsory Revisions A. Patients and Methods In generally the methods are appropriate and well described, however I think that the authors have to provide some more information concerning patients’ data: a) Adequacy of dialysis (mean K.t/v index) b) Did (and how many) patients were receiving Mg containing compounds either as phosphate-binders or as laxatives or as alimental suplementations? c) Were among the examined patients some preserving a residual diuresis i.e. more than 600 ml daily or receiving diuretics? d) Mean serum Albumin, Calcium, Phosphate, iPTH levels e) Estimated dietary protein intake (if possible) All these data must be included in the statistical analysis

We thank the reviewer for these comments. While we did not collect information on the adequacy of dialysis, the standard of care in our dialysis unit is 4 hours 3 times per week (with rare exceptions), and assuming reasonable blood flows, most patients would have achieved adequacy targets. With regard to Mg-containing compounds, none of the patients were receiving Mg-based phosphate binders or other Mg-based preparations. We have now added a statement regarding the standard HD prescription and the use of Mg-containing compounds
to the methods section. With regard to diuretics and residual renal function, this is an important question that has been addressed in our comments above to the other reviewers. Finally, with regard to other electrolytes as well as dietary protein intake, unfortunately we did not collect this information, and have now acknowledged this in the limitations section of the discussion.

B. Results

Tables 1. There is not any table in the manuscript with patient’s laboratories. Table 1 contains only patient’s demographic data as well as data concerning hemodialysis (duration and dialysate Mg concentration). So, the authors must either incorporate the patient’s laboratories, which they have included in to the analysis, in to the Table 1, or to construct a new one table. 2. Furthermore table 1 must be modified as follows: a) A column showing the p-values and the statistical significance must be added. b) The percentage sign (%) must be seen only in the first column beside the qualitative variables but not in the other columns beside the values. 3. One more table showing the chi-square test analysis for the categorical variables is need. 4. Each table should have a title (above the table) that summarizes the whole table. 5. Figure. I think that the columns that shows the patients’ (both PPIs abusers and not) average serum Mg levels should be appeared side by side in a single schema.

We thank the reviewers for these suggestions. We did not collect specific lab data other than serum Mg (which is discussed extensively in the results section and illustrated in the figure), so we have not added an additional table. We have added p values to table 1, and have moved the % sign to the first column. We have now added a table for the chi square testing when we dichotomized Mg levels. We have added titles to the tables.

Minor Essential Revisions
A. Abstract

The title of the article describes accurately the examined topic and the abstract is well constructed. However I have a notion: In the first sentence of the abstract “It is known that serum magnesium (Mg) concentration is inversely related to vascular calcification and hyperparathyroidism among patients with end-stage renal disease (ESRD)”, the remark and hyperparathyroidism is according to my opinion “too much” for an opening phrase. The association between low serum magnesium and hyperparathyroidism is confirmed but is weak.

We thank the reviewer for pointing this out. Instead of saying “It is known that…”, we have changed the wording to “Observational data suggest that…” to highlight the fact that the data on this topic is observational and only suggestive of an association.
B. Discussion 1. Note clearly in the discussion that the PPIs cause a decrease of the intestinal fluid PH which subsequently inhibits the TRPM 6/7 affinity to the magnesium and impair its absorption. (Bai J, Hausman E, Lionberger R, Zhang X: Modeling and simulation of the effect of proton pump inhibitors on magnesium homeostasis. 1. Oral absorption of magnesium. Mol Pharm 2012; 9: 3495–3505). 2. When studying magnesium we should have in mind that: a) Magnesium is a predominately intracellular ion, b) Serum albumin levels alter serum magnesium levels, c) Ionized magnesium fraction is the biological active form of this element So I think that the authors should to note and comment these issues in the discussion. 3. The limitations of the work are clearly stated; however I think that the authors have to add that it is a single center study. 4. Use the term PPIs (plural) instead of PPI.

We have added the reference above to the discussion, and we have re-iterated in our conclusion that it is a single center study. We have also now added in the limitations section that we focused on serum Mg and not ionized Mg. (While this is definitely an important point worthy of further exploration, most, if not all, of the existing observational studies on the relationship between PPIs and Mg have focused solely on serum Mg levels. Hopefully this is something that future studies will better address).