

Reviewer responses

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Title: Proton-pump Inhibitor-Induced Hypomagnesemia: Current research and proposed mechanisms

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Review #1

This manuscript addresses a newly recognized topic. Although the evidence is limited and the manuscript is largely hypothetical it is still a significant contribution. The manuscript can be shortened significantly. Most of it is description of known physiology about Mg transport which is important to understand the hypothesis but the text can be substituted with a summary figure showing the pathways and also a table. IN addition the limited evidence can be summarized in a table showing all the case reports and clarify the duration of exposure, timing to identify the hypomagnesemia after PPI exposure etc with the appropriate references. Then in a separate table the limited studies can be presented and the duration of exposure and timing to identify low MG should also be clarified. The author does summarize the limitations of the studies and this can be done more specifically per study in a summary table. Is Figure 1 original figure or was copied from another publication? This needs to be clarified.

We very much appreciate your careful review of our manuscript. We agree that the evidence for the mechanisms underlying PPIH is limited and hypothetical. This field will certainly benefit from additional controlled studies to further elucidate which of these mechanisms are most contributory in particular populations, and which are less significant.

Addressing your comments globally...

We aimed for the focus of this review to be a synthesis of magnesium physiology and the proposed specific mechanisms of PPIH. The “current research” sections are included to provide context as to where the body of literature currently stands, but we made attempts to keep these section quite abbreviated. We readily acknowledge that we did not include all of the case reports or observation studies in the literature. Instead, we have taken what we believe to be the most salient findings to summarize within the text, rather than putting together comprehensive tables. We hope you understand this viewpoint and this explanation gives you better context into our manuscript composition.

Furthermore, while additional figures may illustrate these mechanisms more succinctly, we feel that our original Figure 1 does simply demonstrate the most important physiology at play in PPIH. In addition to a lack of funding to support an artist to draw more figures (this figure in the paper is original and was composed in PowerPoint by JHW), we also do not want to distract attention from this existing figure, which was designed to be simple and straightforward. We believe it provides an appropriate amount of detail without overstretching our conclusions about the PPIH mechanism.

Regarding your request to specify duration of PPI exposure, the existing case reports and observational studies detailed within the text and the current literature do not consistently offer this information. We definitely understand this as a major limitation and have included the following statement in that section:

“While the FDA communication states that these effects occur in longer-term PPI use, duration of exposure to PPI therapy has been difficult to quantify in retrospective studies. PPIs are widely available without a prescription and this may lead to under-reporting to medical providers. Additionally, it is likely that some patients may be taking them on an “as-needed” basis rather than daily or twice a day, making any subsequent measurements of hypomagnesemia uninterpretable.”

Reviewer #2

Very nice paper on a well recognized, but not well understood topic. Acronyms on pages 3 and 5 should be spelled out the first time they are used in the paper. The second sentence in the bottom paragraph on page 5 could be reworded for better clarity. All references need to be put in the proper format with DOI and PMID.

Thank you very much for your comments. We have made the adjustments above and spelled out the abbreviations before using them in the text.

The sentence you referred to has been re-worded and now reads as follows:

“While most other ions are predominantly absorbed via the proximal tubule, the majority of filtered magnesium is reclaimed in the thick ascending Loop of Henle (TAL).”

DOI (where available) and PMID have been added to each reference, in accordance with WJN publication standards.