Copenhagen 12.05.2017

We thank the editors and reviewers for their comments in response to our submitted manuscript. In the following document, we have commented on the points raised by the reviewers, and accordingly revised the manuscript. Revisions are marked in red in the manuscript.

All authors approved the revised manuscript.

We do hope that with these revisions, the editors will find the manuscript suitable for publication.

Sincerely,

Synne Semb,

on behalf of the authors

Reviewer: 1

Dear authors. This is a case report regarding PPI-induced hypomagnesemia (PPIH). Reports on PPIH is recently getting increased in the developed countries, and we are requested to pay attention to this adverse effect. Thus, I believe this report is timely and informative. In this report, medical information is well demonstrated, and 1the discussion is carefully written by focusing on PPIH. So, I consider this report is adequate for the publication by the present form. I would like to indicate just one issue that the author may consider the intestinal inhibition of Mg uptake as an only cause of PPIH. It is well known that just 1% of Mg is existed in ECF, and majority of Mg is stored in ICF. Intracellular Mg freely moves-in and out to ECF for the regulation of Mg concentration, and it is hard to imagine that the intestinal Mg absorption directly contribute to the regulation of Mg concentration during the short term. Averaged daily Mg intake is 12 mmol, and 4 mmol of them is absorbed in the intestine and released to ECF. On the other hand, in the kidney, approximately 84 mmol of Mg is daily filtered through glomerulus and 80 mmol of them is reabsorbed in the tubules. Thus, principal organ to regulate the Mg metabolism might be the kidney. Involvement of TRPM6 in the Mg reabsorption in the kidney is approximately 5% of filtered Mg, however, TRPM6-regulated Mg reabsorption in DCT segment of tubules is a final regulatory part of urine Mg excretion, and therefore, Mg reabsorption through TRPM6 is involved in the multiple drug-induced hypomagnesemia such as thiazide, anti-EGFR anti-cancer medications and cyclosporin A which also affects on the Mg reabsorption in TAL segment. Hypothesis of pH-related changes in the intestinal TRPM affinity to Mg ion is very interesting and attractive, however, it is tough to explain the rapid restoring Mg concentration immediately after discontinuation of PPI and its rapid falling in PPI challenge test only by the changes in intestinal Mg absorption. Thus, it is interested how the urine Mg excretion rate, not its urine concentration itself, is changed before and

after discontinuation of PPI or PPI challenge test. If an increase in the urine Mg excretion rate would not be apparent under the condition of continuous administration of PPI and Mg supplementation, the hypothesis might be more persuasive. If some additional data regarding Mg-handling in the kidney is available, they would be a great help to support the author's conclusion. If not, it would be better to refer to the possible involvement of renal Mg loss in the PPI-induced hypomagnesemia. Again, I believe this article is excellent and revision is not indispensable for the agreement of acceptance of this article.

Comments to the Author

- **"If some additional data regarding Mg-handling in the kidney is available, they would be a great help to support the author's conclusion. If not, it would be better to refer to the possible involvement of renal Mg loss in the PPI-induced hypomagnesemia".**

Reply:

We thank the reviewer for the elaborate and interesting comment concerning on the possible underlying mechanism of PPIH. Unfortunately, we do not have additional data regarding Mg handling in the kidney. We have added an additional comment about renal Mg loss as a cause of hypomagnesemia in other cases of drug-induced hypomagnesemia (page 5, highlighted in red).

Reviewer: 2

The manuscript is well written. However patients undergoing fundoplication may also need PPIs at a later date. This may be mentioned in the manuscript. Further, how oral supplementation of magnesium helps in presence of continued usage of PPIs may be discussed since the PPIs act by altering the intestinal absorption of magnesium.

Comments to the Author

- **"However patients undergoing fundoplication may also need PPIs at a later date. This may be mentioned in the manuscript".**

Reply:

The article is merely a case report describing the course of hypomagnesemia in a long-term PPI user, whose hypomagnesemia rapidly improved upon PPI discontinuation and stayed normal following PPI withdrawal after laparoscopic fundoplication. Even though we have not made any conclusions regarding the optimal management of patients with PPIH, we do agree with the reviewers point and have added the following section to the text: "Patients with PPIH and persistent troublesome reflux symptoms after PPI discontinuation could be considered for anti-reflux surgery. It should be remembered, however, that a majority of patients treated with anti-reflux surgery have resumed PPI therapy 10-15 years after the operation[7], and it is mandatory to control for hypomagnesemia if patients resume PPI treatment." (page 5, highlighted in red).

- **"Further, how oral supplementation of magnesium helps in presence of continued usage of PPIs may be discussed since the PPIs act by altering the intestinal absorption of magnesium".**

Reply:

Good point. We have added the following section: "Similar to our case, previous reports have documented only partial effect of oral magnesium supplements in correcting the

hypomagnesemia during ongoing PPI-therapy [2], and only short term relief with intravenous magnesium infusions" (page 4, highlighted in red).