



Letter and Reply

Is hypomagnesemia associated with using proton pump inhibitors?

**To the Editor:**

Proton pump inhibitors (PPIs) have been very useful in various gastrointestinal diseases. However, hypomagnesemia was reported in patients taking PPIs, and cross-sectional or retrospective studies for a causal relationship between PPIs and hypomagnesemia were carried out. Until now, this question remains unresolved although a recent meta-analysis study concluded that PPI use may increase the risk of hypomagnesemia [1].

In the past issue of this Journal, Park et al [2] added a controversy to the association between hypomagnesemia and the PPI use. This study was interesting because it was performed on a relatively homogeneous population, who was undergoing percutaneous coronary intervention and whose basal serum magnesium level was normal. The authors made an effort to demonstrate the relationship through various subgroup analyses. However, in this study protocol, the definition of PPI group is not sufficient for detailed history about taking PPIs, as it was uncertain when PPI usage began.

The authors may need to show more data regarding previous PPI usage, serum magnesium level before starting PPIs, and the proportion of patients with previous PPI usage before enrollment. Despite previous PPI usage, some patients in the PPI group may consistently maintain magnesium levels in normal range during the study period. Furthermore, in the previous reports [3,4], the association between PPI use and a low serum magnesium level was observed among population with higher prevalence of hypomagnesemia, ranging from 6% to 24%. The authors already pointed out a very low incidence of hypomagnesemia in the study population. Unlike calcium balance, magnesium is not readily mobilized from the bone stores. However, if negative magnesium balance continues, the bone stores help to

maintain serum magnesium concentration [5]. Therefore, PPI exposure may induce only modest or no significant changes in serum magnesium concentration among patients with normal range of serum magnesium.

Conflicts of interest

All authors have no conflicts of interest to declare.

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References

- [1] Park CH, Kim EH, Roh YH, Kim HY, Lee SK: The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. *PLoS One* 9:e112558, 2014
- [2] Park SH, Lee SH, Lee JS, Shin WY, Gil HW, Yang JO, Lee EY, Hong SY: Changes in serum magnesium concentration after use of a proton pump inhibitor in patients undergoing percutaneous coronary intervention. *Kidney Res Clin Pract* 34:98–102, 2015
- [3] Danziger J, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, Howell MD, Celi LA, Mukamal KJ: Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int* 83: 692–699, 2013
- [4] Markovits N, Loebstein R, Halkin H, Bialik M, Landes-Westerman J, Lomnicki J, Kurnik D: The association of proton pump inhibitors and hypomagnesemia in the community setting. *J Clin Pharmacol* 54:889–895, 2014
- [5] Wallach S: Effects of magnesium on skeletal metabolism. *Magnesium Trace Elem* 9:1–14, 1990

In reply:

We appreciate your interest in our recent article entitled “Changes in serum magnesium concentration after use of a proton pump inhibitor in patients undergoing percutaneous coronary intervention” [1]. Danziger et al [2] could demonstrate that combined use of proton pump inhibitors (PPIs) and diuretics may increase the risk of hypomagnesemia, although PPI use was not associated with serum magnesium levels among those not using diuretics. A recently published meta-analysis study suggested that the use of PPIs may be associated with hypomagnesemia [3]. However, our study did not show a relationship between PPI use and the occurrence of hypomagnesemia. In addition, a recent study showed that chronic PPI use does not therefore appear to be associated with hypomagnesemia [4].

Inconsistent study results have prevented us from reaching a solid conclusion. In a recent population-based cohort study, PPI use was associated with hypomagnesemia; serum magnesium level was 0.022 mEq/L lower in PPI users compared with nonusers [5]. In the clinical aspect, this lower level of serum magnesium in PPI users may not be significant. But many case reports suggested that PPIs might be associated with hypomagnesemia. Therefore, I think that further studies should focus on the individual sensitivity of hypomagnesemia after PPI use. Drug-induced hypomagnesemia is not unique to PPIs. Other drugs such as gentamicin, calcineurin inhibitors, platinum-based cytostatics, epidermal growth factor receptor –targeting drugs, and diuretics have all been associated with hypomagnesemia. These drugs affect magnesium active transport channels, transient receptor potential melastatin subtype 6, which is responsible for the absorption of magnesium in the kidney and intestine. Until now, it is not known whether PPI therapy may disturb this transport system in the intestine. Further study should reveal whether PPI affects this transport, which can explain the mechanism of PPI-induced hypomagnesemia.

We agree with your opinion that PPI exposure may induce only modest or no significant changes in serum magnesium concentration among patients with normal range of serum magnesium. In addition, I think that it is not necessary to

routinely measure magnesium levels after or before PPI use in patients without risk factors, although the clinician should know that PPI use could be associated with hypomagnesemia.

Conflicts of interest

The author has no conflicts of interest to declare.

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References

- [1] Park SH, Lee SH, Lee JS, Shin WY, Gil HW, Yang JO, Lee EY, Hong SY: Changes in serum magnesium concentration after use of a proton pump inhibitor in patients undergoing percutaneous coronary intervention. *Kidney Res Clin Pract* 34:98–102, 2015
- [2] Danziger J, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, Howell MD, Celi LA, Mukamal KJ: Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int* 83: 692–699, 2013
- [3] Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, O’Corragain OA, Korpaisarn S, Erickson SB: Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. *Ren Fail* 37:1237–1241, 2015
- [4] Sharara AI, Chalhoub JM, Hammoud N, Harb AH, Sarkis FS, Hamadeh G: Low prevalence of hypomagnesemia in long-term recipients of proton pump inhibitors in a managed care cohort. *Clin Gastroenterol Hepatol* 14:317–321, 2016
- [5] Kieboom BC, Kiefe-de Jong JC, Eijgelsheim M, Franco OH, Kuipers EJ, Hofman A, Zietse R, Stricker BH, Hoorn EJ: Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. *Am J Kidney Dis* 66:775–782, 2015

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