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BRIEF COMMUNICATION

Low Prevalence of Hypomagnesemia in Long-term Recipients of Proton Pump Inhibitors in a Managed Care Cohort

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BACKGROUND & AIMS: **Chronic intake of proton pump inhibitors (PPI) has been associated with hypomagnesemia, but prevalence of PPI-associated hypomagnesemia is not known.**

METHODS: **We examined the prevalence of hypomagnesemia among long-term PPI recipients by using a large health maintenance organization database. We collected data on 10,167 participants eligible for chronic drug prescriptions from 2008 through 2013. Adult subjects receiving continuous PPI therapy for ≥6 months between 2008 and 2013 and ≥1 serum magnesium determination(s) were identified. Patients with any magnesium levels less than 1.6 mg/dL were selected for analysis; those with recognizable causes of altered magnesium homeostasis were excluded.**

RESULTS: **Five hundred ninety participants received long-term PPIs, and 414 (70.2%) met the inclusion criteria for a total exposure of 2293 PPI-years (average, 5.7 years/subject). Of these patients, 57 (13.8%) had ≥1 low serum magnesium; 5 were no longer on PPIs, and 44 had other recognizable causes for hypomagnesemia (25 receiving diuretics, 8 with chronic diarrhea, 8 with chronic kidney disease, and 3 with malignancies). Of the 8 remaining patients (7 female; mean age, 71.2 ± 13.4 years; mean daily medications, 5.4 ± 1.1), mild hypomagnesemia (range, 1.2–1.5 mg/dL) was noted in 13.9% of 289 measurements. All 8 patients had normal serum levels of magnesium at their final measurement.**

CONCLUSIONS: **In the absence of known precipitating factors, chronic PPI use does not appear to be associated with hypomagnesemia.**

Keywords: Magnesium; Acid Suppression; Side Effects; Adverse Events; Diuretics.

Proton pump inhibitors (PPIs) are one of the most frequently prescribed classes of drugs worldwide. Side effects of PPIs are mild and rare (<1%) including headache, diarrhea, and nausea.[1] However, the prolonged use of these drugs on a large scale over the years has uncovered some rare but important putative adverse events. These include a greater risk of *Clostridium difficile* infection,[2] bone fractures, vitamin B_{12} deficiency,[3] community-acquired pneumonia,[4] acute interstitial nephritis, lymphocytic colitis,[5] and rarely hypomagnesemia. The postulated mechanism of PPI-related hypomagnesemia is inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 cation channels.[6] A number of case series, cross-sectional, and case-control studies have reported on the association between PPIs and hypomagnesemia. More recently, however, large case-control studies have suggested that this association is largely limited to patients with chronic kidney disease or to those on concomitant diuretics.[6–8]

The true prevalence of PPI-associated hypomagnesemia is unknown and may, in fact, be difficult to unearth when most patients are asymptomatic. The aim of this study was to evaluate the prevalence of PPI-associated hypomagnesemia in clinical practice by using a large health maintenance organization database, adjusting for confounding factors that may contribute to or result in hypomagnesemia.

Abbreviations used in this paper: **PPI, proton pump inhibitor; TRPM, transient receptor potential melastin.**

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Methods

The study population consisted of health maintenance organization participants eligible for chronic drug prescriptions. Adult subjects receiving continuous PPI therapy for ≥6 months between 2008 and 2013 and ≥1 serum magnesium determination(s) were identified. Patients with any magnesium levels less than 1.6 mg/dL (normal value, 1.6–2.5 mg/dL) were selected, and after informed consent, their records were analyzed for eligibility criteria. Those with conditions associated with disturbed magnesium homeostasis such as use of diuretics, active malignancy, acute or chronic diarrhea, renal impairment (glomerular filtration rate less than 60 mL/min), segmental bowel resection, and chronic laxative intake were excluded. The remaining patients with unexplained hypomagnesemia were contacted for face-to-face interview and offered further evaluation starting with a repeat serum magnesium determination after written informed consent. The study was approved by the Institutional Review Board of the American University of Beirut.

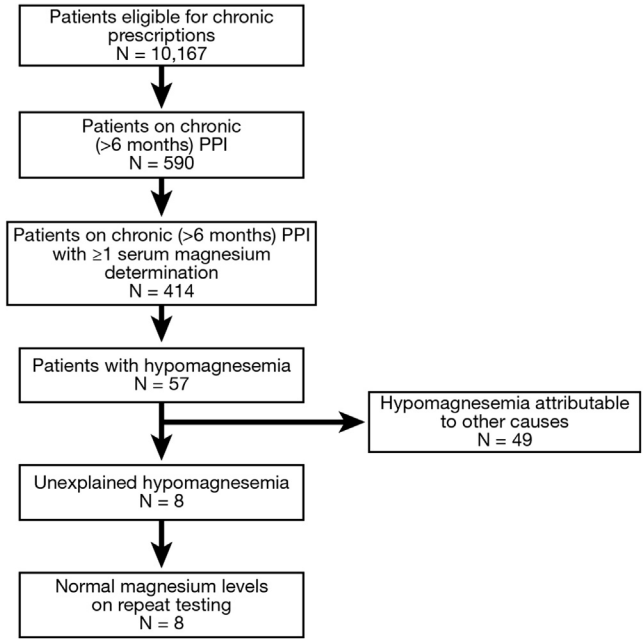

Figure 1. Flow chart of the study subjects.

Results

Of 10,167 eligible participants, 590 received PPIs for more than 6 months (5.8%), and 414 of those (70.2%) had 1 or more serum magnesium determinations for a total exposure of 2293 PPI-years (average, 5.7 years/subject). Of the 414 patients, 57 (13.8%) had ≥1 low serum magnesium level(s) during the 6-year study period. On review of electronic medical records, 5 patients were no longer on PPIs (lack of indication), and 44 had other recognizable predisposing factors for hypomagnesemia. The 8 remaining patients (7 women, 1 man) were elderly (mean age, 71.2 ± 13.4 years), on multiple daily medications (mean, 5.4 ± 1.1), and were frequently hospitalized (mean number of emergency department visits and/or hospital admissions, 25.9 ± 15.7). In those 8 patients, magnesium was measured 289 times (mean, 35; range, 11–100) during the study period. Mild hypomagnesemia (range, 1.2–1.5 mg/dL) was noted in 13.9% of these measurements (range, 1%–29.5%). Most of the magnesium determinations were done in the ambulatory setting, and only 15 (5.2%) were done during hospitalization. When interviewed, all 8 patients were still on PPI and denied symptoms associated with hypomagnesemia (chronic fatigue, muscle spasms or cramps, muscle weakness, numbness, tremors, or palpitations). All patients had normal serum magnesium levels on repeat determination. Figure 1 shows the flow diagram of the study subjects.

Discussion

In this large study cohort of more than 400 patients with a total exposure of >2200 PPI-years, no cases of significant or persistent hypomagnesemia were found when other precipitating factors were carefully excluded. In 2006, Epstein et al[9] first reported 2 patients with symptomatic hypomagnesemia and hypomagnesemic hypoparathyroidism on omeprazole. Other case reports in 2008 described few cases of symptomatic hypomagnesemia and hypocalcemia with long-term PPI use.[10,11] High-dose oral magnesium supplementation during PPI therapy failed to adequately correct the low magnesium levels compared with intravenous infusion, which led to avid renal magnesium retention, and it was consequently suggested that PPIs inhibit active magnesium transport in the intestine.[10] A number of cross-sectional and retrospective studies found that patients with hypomagnesemia were more likely to be using PPIs during the 4-month interval preceding their lowest magnesium levels.[12] In contrast, Faulhaber et al[13] found no difference in magnesium levels between PPI users and nonusers in a cross-sectional analysis of 151 patients. Danziger et al[8] found an association between PPI use and hypomagnesemia only in patients with concurrent diuretic use, and their cross-sectional study on 11,490 individuals found no significant difference between magnesium levels in controls, users of histamine$_2$ receptor antagonists, and PPI users who were not on diuretics. In a recent large case-control study, Zipursky et al[6] found that the risk of hypomagnesemia was only increased in patients receiving diuretics. A systematic review and meta-analysis of 9 studies by Park et al[14] including 115,455 patients identified a modest risk of hypomagnesemia with PPI use (95% confidence interval, 1.077–2.924), but significant heterogeneity was noted, preventing the authors "from reaching a definitive conclusion". Last, a recent small observational study that

Table 1. Fully Published Observational Studies Examining the Association Between PPI Use and Hypomagnesemia

Reference (year)	Type of study	Patients on PPI (n)	Positive association	Comments
Gau et al[23] (2012)	Cross-sectional	207	Yes	• Hospitalized patients >50 y No routine Mg measurements for all patients
Sumukadas et al[7] (2012)	Cross-sectional	82	No (Yes for chronic kidney disease)	• Hospitalized patients >65 y
Danziger et al[8] (2013)	Cross-sectional	2632	No (Yes with diuretics)	• Hospitalized adult patients in intensive care unit Observational study
Faulhaber et al[13] (2013)	Cross-sectional	56	No	• Hospitalized adult patients with no other causes of hypomagnesemia
Koulouridis et al[21] (2013)	Nested case control	402	No	• Outpatient adults only Possible exposure misclassification
Luk et al[24] (2013)	Cross-sectional	66,102	Yes	• Observational study of voluntarily reported adverse event Missing patient demographic data Did not account for other confounding variables such as medication use (diuretics) and other medical conditions causing hypomagnesemia
Biyik et al[15] (2014)	Case control	154	No	• Outpatients only with PPI for >6 mo but with no diuretic/kidney disease
Lindner et al[25] (2014)	Cross-sectional	423	Yes	• Patients admitted to emergency department; possible selection bias
Markovits et al[12] (2014)	Cross-sectional	22,458	Yes	• Possible surveillance bias
Van Ende et al[22] (2014)	Cross-sectional	101	No	• Renal transplant population Duration of PPI use not available Many confounding variables, eg, multipharmacy
Zipursky et al[6] (2014)	Population-based case control	546	No (Yes with diuretics)	• Hospitalized patients ≥66 y
Kim et al[26] (2015)	Retrospective cohort	105	Yes	• PPI use >1 mo. Excluded AKI, chronic kidney disease, and renal replacement therapy patients Hospitalized patients including those receiving cancer chemotherapy (platinum-based therapy was risk factor on multivariate analysis) Small sample size and possible selection bias Diuretic use in 42% of the PPI–low magnesium group vs 9% of controls ($P < .0001$)
Current study	Retrospective cohort	440	No	See Discussion

AE, adverse events; AKI, acute kidney injury; CKD, chronic kidney disease.

used a relatively similar strategy to ours failed to show a difference in mean serum magnesium levels in PPI users and nonusers in a well-defined ambulatory patient cohort without kidney disease, diuretic use, or other risk factors for hypomagnesemia.[15]

Taken together, the totality of the evidence seems to suggest that in the absence of other precipitating factors, PPI use is not a risk factor for clinically significant hypomagnesemia. However, there is evidence to support the notion that in some situations, PPIs do contribute to hypomagnesemia, which may at times be symptomatic and severe, with the best identified clinical risk factor being concomitant diuretic therapy. Magnesium homeostasis depends on a balance between intestinal absorption and renal excretion, and it is conceivable that intestinal absorption of magnesium is affected by long-term PPI therapy, but that magnesium homeostasis remains largely adequate in otherwise healthy individuals. This concept is supported by the fact that PPIs inhibit colonic H^+, K^+-adenosine triphosphatase activity, leading to reduced extrusion of protons into the colon and inhibition of TRPM6/7,[14] and by studies in experimental mice subjected to prolonged omeprazole treatment.[15] We postulate that in the presence of persistent renal magnesium wasting (eg, diuretic therapy), intestinal absorption disturbed by chronic PPI use may be unable to replenish depleted magnesium stores. Whether some PPI users are genetically predisposed to this adverse effect is unknown. It has been postulated that individuals carrying heterozygous mutations of TRPM6/7 may be at high risk, which is evidenced from observations that people with homozygous mutations of TRPM6 manifest severe hypomagnesemia.[16–19] A loss of function mutation of TRPM6 has been shown to result in reduction of intestinal absorption as well as decreased renal reabsorption of magnesium.[20]

Clearly it is impossible to address this association through a large prospective randomized controlled trial. We believe that our study design is arguably better suited to address this putative association by studying a

large cohort of chronic PPI users with measurable serum magnesium during a long period of time. There are a few important limitations to this study that deserve consideration. One is the possibility of selection bias where patients with symptomatic hypomagnesemia identified before 2008 (first year of the study period) were suspected of having a PPI-related adverse event and had their PPI consequently withheld. This possibility is quite unlikely because of the rarity of this phenomenon and a limited awareness by practitioners at the time of this relatively new association (only a few case reports and small case series had been reported before 2008). Another limitation is the possibility of having underestimated the prevalence of hypomagnesemia among chronic PPI users because our study population included only patients with documented low magnesium level. Patients who did not have any magnesium measurements during the study period would not have been captured. However, 70% of individuals receiving long-term PPIs in this managed care cohort had their serum magnesium measured at least once. Conversely, one may argue that the already low prevalence of hypomagnesemia in this study is in fact an overestimate because the study cohort may have been enriched with subjects with a higher pre-test probability for hypomagnesemia (more likely to measure magnesium in subjects with risk factors or clinical symptoms of hypomagnesemia). Last, although study patients refilled their PPI prescriptions regularly, compliance was not ascertained, and although unlikely, exposure misclassification may have occurred.

In summary, this cohort study confirms that in the absence of other risk factors, PPI therapy is not associated with significant hypomagnesemia in clinical practice. This conclusion is in line with most recent large, well-designed observational studies (Table 1).[6–8,13,15,21,22] Routine screening or monitoring of serum magnesium concentrations in patients on long-term PPIs is therefore generally unwarranted. However, clinicians should be cognizant of this potentially serious metabolic derangement particularly in populations at risk such as patients on concomitant diuretics, those with chronic kidney disease, hospitalized patients with multiple comorbidities, and conceivably in individuals at risk for intestinal magnesium wasting (laxative dependence, chronic diarrhea, or malabsorption).

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Conflicts of interest
The authors disclose no conflicts.