A Relationship Between Proton Pump Inhibitors and Hypomagnesemia?

To the Editor: In the article published in the February 2018 issue of *Mayo Clinic Proceedings*, Nehra et al[1] suggest a probable causal relationship between treatment with proton pump inhibitors (PPIs) and the occurrence of clinically relevant hypomagnesemia. However, analysis of observational studies has variably confirmed or refuted this hypothesis, and current clinical practice guidelines do not recommend screening PPI-treated patients for hypomagnesemia.[2] This uncertainty may relate to divergent findings resulting from differences among PPIs, duration of treatment, dose, variable quality of studies, confounding factors, and other additional risk factors for hypomagnesemia such as comorbidities, critical illness, and use of medications, ie, loop diuretics and stool softeners, that could also cause hypomagnesemia.[3] As a matter of fact, there is no doubt that some patients have normal serum magnesium (Mg) levels at the time PPIs are started, severe hypomagnesemia and tetany appear during the course of treatment, clinical recovery is paralleled by the return of serum Mg to within the normal range when PPIs are withdrawn, and no other comorbidities or risk factors are found that could at least in part contribute to this sequence of events.[4]

Taken together, available evidence supports the view that hypomagnesemia is not a class effect of PPIs. Most patients taking PPIs will not have development of clinically important hypomagnesemia even after long-term use, and probably only a very small proportion of them are at risk of hypomagnesemia during PPI therapy. Currently, however, there is no answer to the question of why some patients, rather than others, with no risk factors and no confounding factors present with hypomagnesemia while receiving treatment with PPIs. There is no evidence of increased urinary Mg wasting in PPI-treated patients, which rules out a reduced efficiency of Mg renal conservation in this setting, and there is also no clear-cut evidence that PPI-induced hypochlorhydria may substantially impair Mg solubilization and absorption in the small intestine, ultimately depleting Mg body stores.[3] The regulation of serum Mg homeostasis is not well understood. Variant alleles at *TRPM6/TRPM7* loci could explain some variance in serum Mg concentrations among healthy individuals.[5] It has been also postulated that variant alleles of *TRPM6/TRPM7* are associated with subtle malabsorption and/or persistent leak through the kidneys that may be further aggravated by PPIs, thus being responsible for hypomagnesemia in susceptible patients. This hypothesis might explain why only a minority of PPI-treated patients have development of hypomagnesemia, which implicates that heterozygous carriers of certain *TRPM6/TRPM7* mutations could be at a greater risk of PPI-induced hypomagnesemia.

What could be the best approach to the problem of a potential association between use of PPIs and the development of hypomagnesemia under a clinical standpoint? We have no clinically meaningful predictors of the probability of hypomagnesemia in this setting. In the meantime, it seems reasonable to conclude that the proven benefits of appropriately administration of PPIs greatly outweigh any potential risk of hypomagnesemia.

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In Reply—A Relationship Between Proton Pump Inhibitors and Hypomagnesemia?

We thank Dr Famularo for his comments. Currently, there is limited evidence for the association between hypomagnesemia and the use of proton pump inhibitors (PPIs) because most of the information is based on findings from case reports and observational studies.[1,2] The prevalence of PPI-induced hypomagnesemia is unknown, and because it is not routine practice to monitor serum magnesium levels in patients receiving long-term PPI therapy, the incidence of associated hypomagnesemia may be underrecognized. In 2011, based on a review of reports from their Adverse Event Reporting System and the medical literature, the US Food and Drug Administration issued a safety statement about the association between use of PPIs and hypomagnesemia. Reported serious adverse events included seizures, carpopedal spasm, atrial arrhythmias, and abnormal QT interval.[3] The mechanism of PPI-induced hypomagnesemia is unknown, and there are no reliable predictors for the development of hypomagnesemia. Current

practice guidelines by Freedberg et al[4] do not recommend monitoring of serum magnesium levels in patients receiving long-term PPI therapy; however, clinicians should be aware of this association. At this point in time, serum magnesium levels should absolutely be checked in patients with any of the aforementioned symptoms or findings as well as patients with weakness or renal failure.

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Statin-Associated Achilles Tendon Rupture and Reproducible Bilateral Tendinopathy on Repeated Exposure

To the Editor: Recent reports have linked statin use with tendon rupture, but these results are inconsistent. A retrospective study revealed that 34% of patients with statin-associated tendon complications experienced tendon rupture,[1] yet population-based studies have found no association of statins with rupture.[2,3] Importantly, little is known regarding statin reinitiation after tendinopathy or rupture. We describe a patient who experienced severe tendinopathy on restarting statin therapy after presumed statin-associated Achilles tendon rupture, which had recovered fully while the patient was not receiving statin therapy. The patient had severe and additive bilateral tendon symptoms on rechallenge with 2 different statins, suggesting that statins have clinically important effects on healing tendons.

Report of Case. A 40-year old man who had participated in competitive athletics since childhood and was in good health apart from an elevated lipid profile and hypertension was prescribed rosuvastatin (5 mg/d orally) in September 2014 (Figure A). In March 2015, while participating in an indoor soccer match, the patient had a complete rupture of the left Achilles tendon, above insertion. Previously, the patient experienced pain on exertion and palpation of the right Achilles tendon, above insertion. The left Achilles tendon was surgically repaired, along with discontinuation of rosuvastatin. By August 2015, the patient had completed an 18-week physical therapy program, was pain free, and returned to unrestricted exercise.

In December 2015, the patient restarted rosuvastatin (2.5 mg/d orally), and after 7 weeks, he experienced severe tightness and pain upon standing and walking in both Achilles tendons, especially in the repaired side. After 2 more weeks, bilateral tendon pain had worsened considerably, and he discontinued rosuvastatin and initiated coenzyme Q10, 100 mg/d orally. By March 2016, bilateral pain and tightness were unresolved, and the patient underwent physical therapy with slow symptom relief. In July 2016, statins were again recommended, and based on his experiences with rosuvastatin, the patient declined this therapy and initiated the hydrophilic agent pravastatin (20 mg/d orally). After 5 days, he again experienced severe and debilitating bilateral tightness in both Achilles tendons, necessitating statin discontinuation and initiation of colestipol, 4 g/d orally. Over the next 2 months, both distal Achilles tendons appeared severely thickened, particularly at the musculotendinous junction, with the previously repaired left side having a greater degree of thickening (Figure B) than the right. Currently, the patient is limited only by the inability to stand for long durations (>20 minutes), and walking can be performed with minimal discomfort. The patient has not attempted running or more vigorous activities or restarted statin therapy.

Discussion. Reports on the effects of statins on previously ruptured tendons or patients with underlying disease remain elusive. Substantive to this case, post-rupture symptom onset upon the first challenge with rosuvastatin may have been coincidental. However, additive symptomology on further challenge with pravastatin suggests a more conclusive role for statins in this situation. The chronology of symptoms is also highly suggestive of a drug-induced effect, which occurred at lower doses than typical for both agents. Indeed, the Adverse Drug Reaction Probability Score[4] equals 11 in this case, suggesting a definitive association between statin therapy and the adverse event. Given the 77-hour half-life of pravastatin, the patient likely had substantial concentrations for weeks following discontinuation of the drug, consistent with