bias the results. In addition, deterioration of eGFR may have represented an episode of uncaptured acute kidney injury before death (for example, in the setting of congestive heart failure exacerbation) or change in medication regimen, and not specifically a change in kidney function. Hence, the effect of certain medications on eGFR, such as renin–angiotensin–aldosterone system blockers, diuretics, and nonsteroidal anti-inflammatory drugs, known to impact on glomerular hemodynamics, was not assessed.

Finally, one is unable to delineate from this study why increasing eGFR over time would be associated with mortality. The authors speculate that this may be due to lower serum creatinine generation as a result of reduced muscle mass associated with chronic debilitating conditions. Another explanation could be recovery from an episode of acute kidney injury that was not captured or perhaps withdrawal of certain renoprotective medications, such as renin–angiotensin–aldosterone system blockers, in people who were not tolerating these medications because of hypotension or nonadherence to a low-potassium diet. Hyperfiltration observed with very early-stage CKD as in those with diabetic nephropathy could be another explanation.

The rising or falling of GFR may serve as a useful predicting tool to prognosticate future outcomes for CKD patients, provided that estimating equations used to track longitudinal changes in GFR are valid measures of true change in kidney function. There is a need to develop simple prognostic models to guide clinical decision making in CKD patients who are at highest risk for future cardiovascular events and death. The U-shaped association between change in eGFR and death is logical and hypothesis-generating but needs to be confirmed in large studies specifically of CKD patients using validated GFR estimating methods and also assessing the effect of albuminuria progression on outcomes. As muscle mass or exercise can affect endogenous creatinine production in individuals, future studies should consider adjusting for anthropometric measures and levels of physical activity when using creatinine-based estimating equations to evaluate the association of changes in GFR with mortality.

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Proton pump inhibitors and hypomagnesemia: a rare but serious complication

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Proton pump inhibitors (PPIs) promote hypomagnesemia through loss of active Mg^{2+} absorption via transient receptor potential melastatin-6 and -7 (TRPM6/7). Danziger *et al.* confirm the association of PPIs with hypomagnesemia in patients hospitalized at a tertiary medical center. They found that patients taking PPIs, compared with those receiving histamine-2 antagonists or no acid-suppressive medications, had a decline in serum Mg^{2+} after adjusting for several clinical and laboratory factors. The effect was seen only in those concomitantly receiving diuretics.

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Proton pump inhibitors (PPIs) are widely used, both through prescription and over-the-counter, to treat acid-related gastrointestinal disease. These drugs are generally safe, but several adverse effects have been described since their introduction into clinical

practice. Initial concerns of the potential renal effects of intercalated-cell H^+K^+-ATPase inhibition as manifested by hypokalemic distal renal tubular acidosis were quickly dismissed. However, rare cases of hyponatremia, probably from drug-induced syndrome of inappropriate antidiuresis, and interactions with calcineurin inhibitors in organ transplant patients with CYP 450-2C19 enzyme system mutations were described.[1] More commonly, acute interstitial nephritis complicates PPI therapy. On the basis of the sheer number of people exposed, PPIs are one of the most common causes of drug-induced acute interstitial nephritis.[1] Hypomagnesemia is the newest complication noted for this class of medications, first described in 2006.[2] Since the initial recognition of this cation disturbance with PPIs, numerous case reports and series have confirmed the association.[3]

The obvious question to be asked following discovery of the association of hypomagnesemia with PPIs is, what is the pathophysiologic mechanism? Magnesium (Mg^{2+}) homeostasis is determined primarily by two processes—gastrointestinal absorption and renal excretion of magnesium.[4] The vast majority of Mg^{2+}, which is the second most abundant intracellular cation, resides in the mineral phase of bone or within soft-tissue cells. Intracellular Mg^{2+} is an important cofactor for enzymatic reactions and is critical in energy metabolism involving ATP, which explains the clinical syndromes that develop with deficiency. Gastrointestinal magnesium absorption occurs by passive paracellular movement and active transport into the portal venous system (Figure 1a). Mg^{2+} is absorbed passively through tight junctions between enterocytes. Passive intestinal absorption is nonlinear, low-affinity, and concentration-dependent.[4] This pathway of simple diffusion absorbs a constant fraction of ingested Mg^{2+} (about 7%); thus absorption increases with higher luminal concentrations. Active Mg^{2+} transport in the gut occurs through the combined actions of transient receptor potential melastatin-6 and -7 (TRPM6/7) channels, which are present in the apical membrane of enterocytes.[4] These transporters are high-affinity and saturable—they play a particularly important role in Mg^{2+} absorption when luminal concentrations are low, thereby allowing adaptation to low intake.

The kidneys tightly regulate Mg^{2+} excretion. This divalent cation is completely filtered by the glomerulus and then is reabsorbed in the proximal tubules (15–20%) and thick ascending loop of Henle (about 70%), both by passive, paracellular processes driven by positive luminal charge. However, fine-tuning of Mg^{2+} reabsorption occurs in the distal convoluted tubule. As in the intestine, TRPM6 channels located in the apical membrane of the distal convoluted tubule actively transport Mg^{2+} from the lumen to the intracellular space. Once inside the cell, Mg^{2+} crosses the basolateral membrane into peritubular capillaries (Figure 1b). Magnesium deficiency increases the expression of TRPM6/7 inthe intestine and TRPM6 in the kidney—this enhances active Mg^{2+} transport via these channels. For example, the proportion of dietary Mg^{2+} absorbed in the intestine approaches 75%, while renal excretion of Mg^{2+} is reduced to less than 1 mequiv. per day.[4,5]

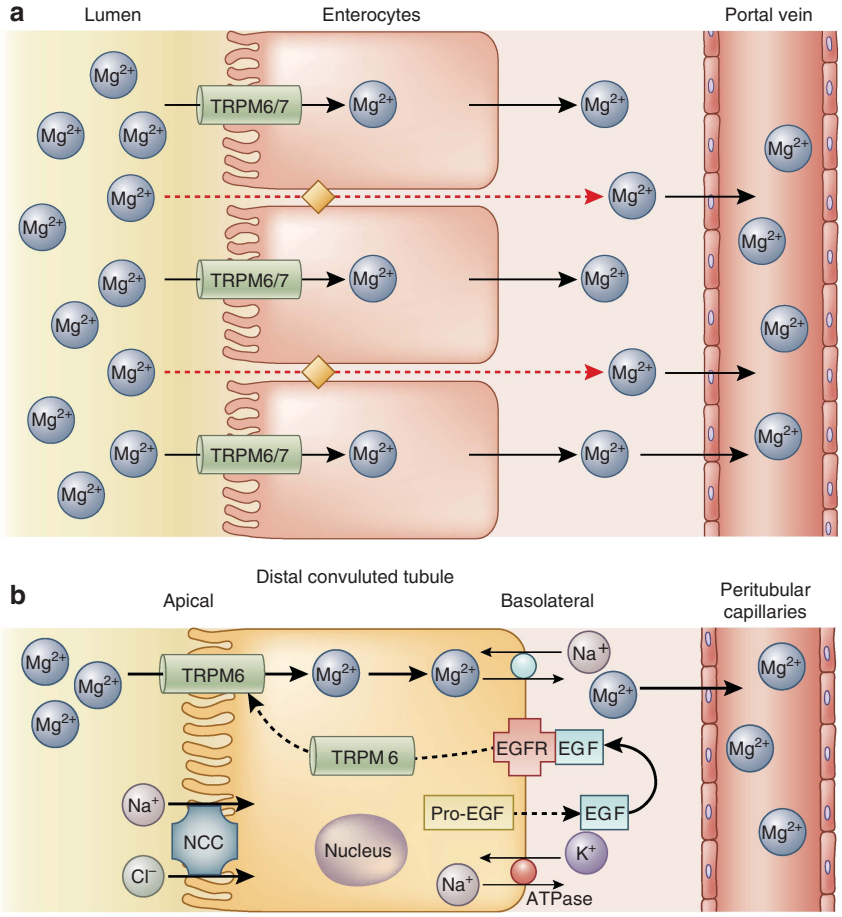

Figure 1 | Intestinal and renal magnesium (Mg^{2+}) transport. (**a**) Mg^{2+} absorption in the gastrointestinal tract. Mg^{2+} is absorbed either passively through paracellular pathways (red dashed lines) or actively through transient receptor potential melastatin-6 and -7 (TRPM6/7) channels (solid black lines) within enterocytes. Mg^{2+} ultimately enters the portal vein. (**b**) Mg^{2+} reabsorption in the renal distal convoluted tubule. Mg^{2+} enters the cell via TRPM6, which is shuttled to the apical membrane following binding of epidermal growth factor (EGF) to its receptor (EGFR). Mg^{2+} then exits the cell via the basolateral membrane into the peritubular capillaries. The sodium chloride cotransporter (NCC) on the apical membrane actively transports NaCl into the cell.

Knowledge of magnesium handling allows one to dissect out the mechanism by which PPIs may cause hypomagnesemia. Several studies demonstrate that renal Mg^{2+} excretion was appropriately reduced in patients with PPI-associated hypomagnesemia, eliminating the kidney as the cause of Mg^{2+} loss. In contrast, impaired intestinal absorption was documented as the primary culprit in PPI-induced hypomagnesemia. What aspect of gastrointestinal Mg^{2+} absorption is impaired, and how do PPIs disturb this process? Studies suggest that passive paracellular Mg^{2+} absorption is intact, but active transport via TRPM6/7 channels is disrupted. Although the pathophysiology has not been definitively determined, it appears that a PPI-induced decrease in intestine luminal pH of 0.5 (a 3.5-fold increase in protons) alters TRPM6/7channel affinity for Mg^{2+}.[6] In TRPM6/7 channel pore-forming regions, two ionized carboxyl side chains of both glutamic and aspartic acid residues are important to Mg^{2+} binding and electrical conductivity. Modeling experiments suggest that increased intestinal protons as seen with PPIs reduce the ionized/un-ionized ratio for these residues, which decreases channel affinity for Mg^{2+} and reduces absorption.[6] These data suggest that PPIs can impair active Mg^{2+} transport via TRPM6/7 channels and lead to hypomagnesemia over time. Superimpose this effect on patients with a heterozygous loss-of-function mutation in TRPM6, and more severe hypomagnesemia may develop.

Given the extent of their use, it is clear that PPIs do not cause hypomagnesemia in most patients, and a spectrum of severity exists, with mild cases probably going unrecognized and unreported. This is not surprising, as this is the case with most medication-related adverse effects. Underlying host characteristics and comorbidities, individual pharmacogenetics, and, in certain cases, dose and duration of drug therapy all contribute to the ultimate severity of clinical presentation. Published cases suggest that hypomagnesemia occurs in the elderly, with females more commonly affected.[3,5,7] Hypomagnesemia develops mainly after chronic PPI ingestion, generally over many years (up to 13 years), with no obvious dose relationship. Approximately half of the reports note concurrent diuretic use, which probably contributes to hypomagnesemia. Symptoms are those expected with hypomagnesemia, and its concomitant electrolyte disorders—these include weakness, ataxia, cramps, tetany, seizures, and arrhythmias/electrocardiographic changes as well as some gastrointestinal symptoms (nausea, vomiting, and diarrhea), which may further exacerbate hypomagnesemia.[3,5,7] Chronic magnesium loss and negative balance may promote efflux of Mg^{2+} from bone into the plasma to maintain levels, perhaps weakening bone structure and increasing fracture risk.[8] Plasma magnesium concentrations are frequently very low (about 0.12–0.85 mg/dl) and are often accompanied by hypokalemia and hypocalcemia. When measured, urinary magnesium levels and fractional Mg^{2+} excretion (<0.2–1.2%) are low.

Danziger and colleagues[9] (this issue) now extend the clinical observations on the association of PPIs with hypomagnesemia by examining a large, fairly sophisticated clinical and laboratory database (MIMIC-II) of hospitalized intensive care unit patients at a tertiary medical center over 7 years.[9] After appropriate exclusions, a total sample of 11,490 patients was included. Information on current outpatient medications and admission serum Mg^{2+} concentrations in patients on PPIs and histamine-2 (H_2) antagonists was available and compared with information on patients not taking such medications (control). Validation of 100 cases assured accuracy. The primary outcome was the first serum Mg^{2+} level recorded within 36 hours of hospitalization, with censoring of extremes and dichotomization of levels at 1.6 mg/dl. Serum phosphate level was used as a secondary outcome as a way to ensure specificity of the observed associations (drug effect rather than unrelated nutritional effect). The data were then analyzed with two different models that corrected for various clinical and laboratory covariates. Although serum Mg^{2+} levels were similar between the three groups before model adjustment, a lower adjusted serum Mg^{2+} level was noted with PPIs compared with H_2 antagonists, but this effect was restricted to diuretic users. In fact, among diuretic users ($n=3286$), PPIs were associated with a lower serum Mg^{2+} concentration (0.028 ± 0.007 mg/dl lower) and an odds ratio of 1.54 (95% CI 1.22–1.95) for hypomagnesemia ($Mg^{2+} < 1.6$ mg/dl). Adjusted serum phosphate was not different between the groups. Although the decrease in serum Mg^{2+} is clinically insignificant and is limited to those receiving concomitant diuretics, the signal is present—PPIs are associated with hypomagnesemia. It is unsurprising that the serum Mg^{2+} decrement is small in a large population of patients—the majority of patients given this drug will not develop clinically significant hypomagnesemia. Furthermore, that it was only significant in those treated with diuretics fits what is seen in reported cases. In reality, most patients have other comorbidities (vomiting, diarrhea, diabetes mellitus, potential TRPM6/7 mutations) or are also receiving concomitant medications (diuretics, stool softeners, and so on) that can exacerbate hypomagnesemia.

So what should we take away from this study and the previously published data on this topic? First, there clearly is an association between chronic, long-term PPI exposure and hypomagnesemia. It is a class effect. Clinicians must be aware of this entity and recognize the potential for this adverse drug effect. This would allow them to intervene quickly and avoid potentially serious outcomes of hypomagnesemia. Second, because PPI-induced hypomagnesemia is due to reduced active Mg^{2+} absorption in the intestine, patients with underlying malabsorption or other intestinal disturbances that increase risk for impaired Mg^{2+}

absorption must be identified before PPI therapy. In these cases, either an H_2 antagonist could be used initially, or, if a PPI is indicated for otherwise refractory acid-related gastrointestinal disease, close monitoring for symptoms of hypomagnesemia (as well as serum Mg^{2+} surveillance) is required. Third, patients at risk for serious complications associated with hypomagnesemia (cardiac arrhythmias, underlying heart disease, and so on) should be preemptively identified and watched closely or switched from a PPI to an H_2 antagonist. For patients who develop hypomagnesemia but truly require continued PPI therapy, it appears that increased oral magnesium supplementation can effectively return plasma levels to normal by enhancing gastrointestinal absorption via the passive paracellular pathway of Mg^{2+} absorption. When all is considered, this potential complication does not eliminate PPIs as a reasonable option; it just requires clinicians to be aware of the data available to use them safely.

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