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Review Article

Malabsorption-Related Issues Associated with Chronic Proton Pump Inhibitor Usage

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Abstract

Proton pump inhibitor (PPI) drugs are highly effective inhibitors of parietal cell acid secretion. They can raise gastric luminal pH from its normal pH 1.5 level to as high as 6.5. This has ramifications for not only absorption of certain nutrients/minerals, but also for gastrointestinal epithelial barrier function and the microbiome. We examine effects of PPI use on the absorption of the minerals calcium, magnesium, iron, potassium and zinc, as well as vitamin B12 and fat. As the list of potential clinical side effects from PPI use continues to grow in the published literature (hip fractures, dementia, etc.), it is worth examining the primary effects of PPI use on uptake of nutrients/minerals. We distinguish effects of PPIs on absorption from the more medically significant issue of the downstream effects of diminished absorption on actual cellular/tissue stores of affected nutrients.

Keywords: Omeprazole; Zinc; Magnesium; Tight junction; Malabsorption; Proton pump inhibitor

Abbreviations

CAP: Community-Acquired Pneumonia; CDI: Clostridium Difficile Infection; CF: Cystic Fibrosis; CFU: Colony-Forming Units; FDA: Food and Drug Administration (USA); GERD: Gastroesophageal Reflux Disease; GI: Gastrointestinal; GHBT: Glucose-Hydrogen Breath Tests; H_2RA: Histamine$_2$ Receptor Antagonist; ICU: Intensive Care Unit; OR: Odds Ratio; OTC: Over the Counter; PO: by mouth (per os); PPI: Proton Pump Inhibitor; PPIH: PPI-Induced Hypomagnesemia; RR: Relative Risk; RYGB: Roux-en-y Gastric Bypass; SBP: Spontaneous Bacterial Peritonitis; SIBO: Small Intestinal Bacterial Overgrowth; TRPM6: Transient Receptor Potential Melastatin Member 6

Introduction

Proton pump inhibitors (PPI) remain the most potent acid suppression therapy available today and are indicated for the treatment of a broad spectrum of common diseases including gastroesophageal reflux disease (GERD), esophagitis, peptic ulcers and eradication of Helicobacter pylori. With the increasingly widespread use of this class of medications, there has been growing concern about the safety of long-term PPI therapy. PPIs irreversibly bind to the hydrogen potassium ATPase pump on the secretory canaliculus of actively secreting gastric parietal cells, which inhibits hydrochloric acid production. Most of the safety concerns associated with PPIs are direct consequences of this inhibition of acid, which plays an essential role in the digestion and absorption of nutrients and destruction of pathogens. Observational studies in these areas have yielded conflicting results, and few randomized controlled trials exist. We present a review of the literature, focusing on the effects of long-term PPI therapy on magnesium, calcium, iron, vitamin B12, fat, and zinc absorption, as well as the gastrointestinal (GI) epithelial barrier function and the intestinal microbiome.

Two fundamental issues surround the potential phenomenon of PPI-related malabsorption. The first is whether PPI usage actually causes a decreased absorption of a particular nutrient or mineral into the bloodstream. This is a transepithelial transport issue. The second and more medically relevant issue is whether a diminished absorption of a nutrient or mineral actually results in decreased systemic (circulating) levels of said nutrient/mineral in the bloodstream, and/or decreased cellular and tissue levels of the nutrient/mineral at various sites in the body. This involves not only effects on the nutrient's absorption from the GI lumen into the bloodstream, but on secondary adaptive responses, such as renal excretion rates, somatic cellular influx and efflux transport rates, binding protein levels, etc. One can therefore have a malabsorption issue that does not result in decreased systemic levels, and this needs to be addressed.

There is actually a third clinical issue, however, concerning how a "normal" clinical range is determined, what "normal" actually signifies, and whether "normal" is in fact optimal for a variety of physiological/immunological processes. For example, PPIs may cause only a 30% decrease in the blood levels of mineral X, a decrease that does not result in the blood level of X to move out of its established normal range. However, the 30% decrease in X may result in changes in immune function or cancer susceptibility that matter greatly to the organism. Normal ranges of nutrients/minerals are often based upon levels needed for cell growth/restitution and may not consider more specific targeted functions such as immune surveillance or cancer prevention. Therefore the issue of malabsorption must be viewed very broadly to see if more subtle clinical effects can be in play.

Magnesium

Magnesium (Mg) homeostasis is based on intestinal absorption and renal excretion. Reported cases of PPI-induced hypomagnesemia (PPIH) have appropriate renal retention as measured by a low fractional excretion of Mg. Therefore, intestinal malabsorption of

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Mg has been implicated as the etiology of PPIH [1-3]. Normally, Mg absorption occurs via active transport through a transcellular pathway mediated by the protein, Transient Receptor Potential Melastatin Member 6 (TRPM6; transient receptor potential cation channel subfamily M member 6) and passive transport through tight junctional paracellular pathways mediated by claudin-16 and claudin-19. The majority of Mg absorption (70%-90%) proceeds via passive diffusion through the paracellular route of the small intestinal epithelium [2-4]. When luminal Mg concentrations are low there is a greater reliance on the transcellular active transport (TRPM6) predominantly found in the colon [2].

It is hypothesized that both passive and active pathways of Mg absorption are modified by the luminal pH environment. Cundy, et al. [2] showed that high-dose oral repletion of Mg was able to partially restore serum Mg concentrations in cases of PPIH. This suggests that the passive paracellular route of absorption is less affected by the luminal pH. However, Thongon, et al. [4] has shown that omeprazole inhibits passive Mg transepithelial diffusion in the Caco-2 cell culture model. A follow-up in vitro study showed apical acidity actually decreases this inhibitory affect observed by omeprazole [5]. This proposed PPI-inhibition of passive Mg absorption through the paracellular route is that a relatively alkaline pH leads to internalization of the cation pore-forming claudin-19 by the epithelial cell [6].

Magnesium is generally held to be absorbed throughout the entire small intestine by both saturable and non-saturable mechanisms [7]. Colonic, as opposed to small intestinal, absorption of Mg is predominately mediated by active transport through the transcellular route via TRPM6. There exists a colonic H^+/K^+ ATPase pump on the luminal membrane of colonic epithelium known as cHK ATPase-alpha [4,8]. This, like the gastric H^+/K^+ -ATPase, is also inhibited by PPIs [9]. Because it has been observed that active Mg absorption is facilitated when TRMP6 is in the protonated state, one can conclude that colonic absorption of Mg is also pH dependent. Lameris, et al. [8] used a mouse model to compare the serum, urine and stool Mg concentrations of mice treated with omeprazole *vs*. a placebo. While they did not find statistically lower serum Mg concentrations in those mice treated with omeprazole, they did find increased transcription levels of TRPM6 and cHK-ATPase-alpha mRNA ($P<0.05$) in colonic epithelium. This gets to the point that these Mg absorption mechanisms may be pH dependent and that upregulation of these important membrane proteins is a compensatory reaction to rising colonic pH from omeprazole [8].

Case reports of severe Mg deficiency in patients on chronic PPI therapy appeared in the literature starting in 2006. PPIH is now a widely recognized but rare side effect of chronic PPI therapy [3,10]. Severe symptomatic hypomagnesemia from PPIH usually involves serum Mg concentrations of <1.1 mg/dl (normal serum range for healthy adults is 1.7-2.3 mg/dl [Mayo Clinical Labs]). These patients can present with severe manifestations, such as cardiac arrhythmias, hemodynamic instability, tetany and seizures, and are frequently found with concurrent hypocalcemia and hypokalemia. Based on a systematic review of the literature between 2006 and 2012, 36 cases were documented [10]. This is likely an underestimation of the true prevalence, as Luk, et al. [11] found in a cross-sectional study of the FDA's Adverse Event Reporting System database where, of the reported 66,102 adverse events from PPIs, 1% (n=693) were associated with hypomagnesemia. In that systematic review of case reports and case series, Hess, et al. [10] found that Mg levels rebounded to normal within 4 days of PPI-withdrawal and almost universally reoccurred after being re-challenged, despite using a different PPI. From these reported cases, it appeared to be a class effect across all PPIs, and it occurred even with the lowest daily doses. The mean PPIH onset was 5.5 years but varied from 2 weeks to 13 years. Histamine$_2$ receptor antagonist (H_2RA) use was not associated with Mg deficiency in these cases. This association caught more attention in 2011 when the FDA released a warning that long-term PPI users were at risk for severe Mg deficiency and that health care professionals should consider checking baseline Mg and monitoring levels periodically in those individuals who are using concurrent diuretics or other medications that can decrease Mg concentrations (FDA, 2011). Danziger, et al. [12] performed a large single center review of consecutive ICU admissions looking at PPI use and serum Mg concentrations. They found that PPI use was associated with hypomagnesemia only in those using concurrent diuretics. Use of diuretics (primarily loop diuretics) with concurrent PPI use had an odds ratio (OR) of 1.54 (P= <0.001) for having Mg deficiency *vs*. those diuretic users without a concurrent PPI [12]. In diuretic naïve patients on PPIs there was no statistically significant change in serum Mg concentrations. However, in most of the cases reported in the literature, diuretic withdrawal alone did not lead to resolution of PPIH [10]. It has been suggested by the FDA that if considering prolonged or lifelong PPI therapy that serum Mg levels be checked and monitored throughout the treatment course, especially in those patients who are on concomitant medications that can lead to hypomagnesemia [11].

Treatment of PPIH starts with the withdrawal of the PPI and supplementation with Mg until Mg stores are replete. Acid suppression with H_2RA can be used as a surrogate if need be for reflux/gastritis symptoms. Despite this statement released by the FDA and the attention this has received in the literature, PPIH is still a rare occurrence. The American College of Gastroenterology published its most recent practice guidelines on the diagnosis and management of GERD in 2013. In the section entitled "Potential Risks Associated with PPIs," there is no reference to PPI-induced hypomagnesemia or recommendations regarding Mg monitoring while on chronic PPI therapy. This speaks to the infrequency of its occurrence.

However, because mild disease may be asymptomatic but a harbinger for severe manifestation, the medical practitioner should be aware of this entity and should consider following the FDA recommendations of checking baseline serum Mg levels in those who are starting long-term PPI therapy and to consider monitoring periodic serum Mg concentrations if taking concurrent medications that deplete serum Mg concentration such as diuretics [13].

Calcium

Calcium (Ca) absorption is a process that has many dependent variables, including the Ca content of diet, the solubility of Ca salts and the resulting bioavailability of ionic Ca, gastroduodenal pH, and endocrine function of vitamin D and parathyroid hormone. For the scope of this review we will limit our discussion to the gastroduodenal pH and its role in Ca absorption.

Ca is absorbed in its ionic form primarily in the proximal small intestine. Dissolution of Ca salts into their bioavailable components happens primarily in the acidic milieu of the stomach [14]. It has been observed that the solubility of Ca salts such as $CaCO_3$ is 96% in a pH of 1 but falls to 23% in alkaline environment with a pH of 6 [15]. Mice with experimentally induced achlorhydria showed decreased Ca absorption and lower bone mineral content when compared with control mice [16]. Recker, [17] used Ca isotopes to measure fractional absorption of Ca and showed that human subjects with achlorhydria have decreased Ca absorption after fasting, when compared with fasting healthy adults. Following this, Recker [17] measured absorption of Ca isotopes when mixed in a meal and found that both the patients with achlorhydria and healthy controls had equal absorption patterns. A decade later, after the first PPI was introduced, Serfaty-Lacrosniere, et al. [18] studied a small cohort of healthy adults randomized to PPI and placebo and found no significant difference in meal-based Ca absorption using whole gut lavage technique.

In a randomized, double-blind, placebo-controlled, crossover trial, O'Connell, et al. [19] was able to demonstrate that omeprazole decreased Ca carbonate absorption by 41% in a small group of post-menopausal women. Of note, these women were in a fasting state prior to ingestions of Ca isotopes. There appears to be a trend in the literature showing that when using Ca mixed with a meal as opposed to Ca supplements in the fasting state, there is no significant fractional Ca malabsorption despite PPI use or general achlorhydric state. A more recent small, randomized, cross-over clinical trial showed that a standard daily dose of PPI *vs*. placebo showed no Ca malabsorption in young healthy adults as measured by Ca isotope technique [20]. Clearly the literature contains conflicting data on the degree or presence of Ca malabsorption in PPI use, but a key factor may be absorption of Ca from a Ca-supplement *vs*. a standard meal.

PPIs have been shown to affect Ca homeostasis via other mechanisms besides Ca malabsorption. Severe hypocalcemia has been observed secondarily in those patients with PPIH, as Mg is an essential cofactor for the release of parathyroid hormone in response to hypocalcemia states [21]. In addition to this, there exists an osteoclastic vacuolar H^+/K^+ ATPase that plays an important role in bone remodeling. When the osteoclastic H^+/K^+ ATPase is inhibited it prevents localized acidification and bone resorption, therefore leading to an imbalance in bone strength and remodeling [22].

Much of the revitalized attention to Ca malabsorption and PPI use stems from the associations made between chronic PPI use and hip fractures. This is based on a large case control study that found an adjusted OR of hip fracture with PPI use of greater than one year to be 1.44 (95% CI, 1.30-1.59) [23]. Associations of increased hip fracture with chronic PPI use implicate multiple mechanisms that are not exclusive to Ca malabsorption, which makes the topic of hip fractures not entirely within the scope of this review. However, it should be noted that a large observational study looking for associations of chronic PPI use with osteoporosis did not find a positive association with chronic PPI use, and suggested that prior findings linking this class of medications to hip fractures were likely related to other confounding risk factors of hip fracture [24]. Corley, et al. [25] found that drugs inhibiting gastric acid secretion are associated with increased risk of hip fracture; however, this was only in those with at least one additional risk factor for fracture. Since 2006, many investigators have attempted to answer this same question. A meta-analysis of 10 studies found a pooled OR of 1.25 for hip fractures, 1.50 for vertebral fractures and 1.09 for wrist fractures with chronic PPI use. Unfortunately, their conclusions were limited by significant heterogeneity of cohort studies [26]. In May 2010, the FDA placed a warning on labeling of all over-the- counter (OTC) and prescription PPIs to include a possible risk of fractures. However, in March 2011 the FDA retracted this from the labeling of OTC PPIs, stating that fracture risk with low-dose, short course PPI is unlikely [27]. The American College of Gastroenterology published practice guidelines for the management of GERD in 2013. In reference to the subject of Ca malabsorption and risk of fracture, there was insufficient data to recommend Ca supplementation or extra monitoring of bone mineral density beyond what is already standard of care. It is likewise unclear if Ca absorption (with the Ca supplied specifically as a supplement) may be inhibited by a PPI. They also state that osteoporosis is not a contraindication to starting a long-term PPI, nor should the PPI be stopped if there is a new diagnosis of osteoporosis [28]. Adjustment of PPI therapy could be considered in patients with osteoporosis with additional risk factors for hip fracture.

Vitamin B12

B12 (cobalamin) is an essential vitamin that when deficient can lead to nerve damage, anemia and psychological changes, and it contributes to myriad other disease states. Acid-base in the proximal GI tract is imperative for homeostasis of B12 levels. B12 actually gets degraded in acidic environments when not protein-bound. Therefore, free B12 must be bound to chauffeur proteins in the stomach. Haptocorrin, produced by the salivary gland, binds to free dietary B12 initially to protect it from the acidic environment [29,30]. Parietal cells not only control gastric acid secretion via the H^+-K^+ ATPase, but also produce intrinsic factor. B12 forms a complex with intrinsic factor in the duodenum in order to allow absorption of B12 in the ileum. This B12-intrinsic factor complex occurs at the duodenum when the B12-haptocorrin complex is lysed or more B12 is freed from animal proteins. This lysis requires proteolysis via proteolytic enzymes such as pepsinogen. Without an acidic environment pepsinogen cannot be converted to pepsin. PPIs increase the pH of the gastric environment. Pepsinogen secretion has been found to be decreased in rat models with PPI use [31,32]. It is unclear, as far as this author can determine, if pepsinogen or pepsin activation is decreased in humans on PPIs. In one human study, there was a trend toward lower pepsin concentrations in PPI users, but it was not statistically significant ($p=0.54$) [33]. One small, placebo-controlled study (n=16) showed that protein-bound B12 absorption is significantly decreased in hypochlorhydric patients due to PPI use (0.50% dietary B12 absorbed with PPI *vs*. 1.21% without PPI). However, this malabsorption may or may not be clinically significant and was shown to be markedly reversed with an acidic ingestion alone (cranberry juice) [34]. It stands to reason that acid suppression with PPIs could cause possible B12 deficiency. Ever since the first case report of likely PPI-induced B12 deficiency with megaloblastic anemia was reported in 1996, there has been concern about significant B12 deficiency in chronic use of these drugs [35].

In general, most cases of B12 deficiency are in the elderly. Approximately 6% of those who are 70 years and older have B12 deficiency (defined as <148pmol/L) [36]. Daily requirement is only

0.7-2 micrograms, and typical omnivores take in 7.2 micrograms/day, while vegans may take in less than the daily dose of vitamin B12 [37]. B12 deficiency occurs in atrophic gastritis assumedly due to its associated achlorhydria and autoimmune gastritis because of destruction of the parietal cells. PPIs also cause achlorhydria; therefore PPIs carry ongoing concern for associated B12 deficiency. A routine yearly vitamin B12 check in elderly patients seems advisable, given not only the decreased intrinsic factor production, but also this potential effect of PPIs.

The data in human models of B12 deficiency and acid suppression with PPI are conflicting. Long-term use of PPIs (>4.5 years) in Zollinger-Ellison Syndrome was shown to significantly lower B12 levels by 30%, particularly in achlorhydric patients, but only 8% of patients dropped below normal, and there was no significant decrease in hemoglobin [38]. One early study showed that PPIs do significantly decrease B12 absorption at 2 weeks of use in healthy volunteers [39]. Omeprazole (20 mg) decreased absorption from 3.2% to 0.9%, and the 40 mg dose decreased it from 3.4 to 0.4%. The long-term significance was not determined. One early case-control study showed an association of B12 deficiency and acid suppression of greater than 12 months (both H_2RA and PPI) with an OR of 4.45 in patients older than 65 [40].

Another study showed a dose-dependent relationship between PPI use and B12 deficiency [41]. It showed that PPI use for 2 or more years had an OR for B12 deficiency of 1.95, and <0.75 pills/day had an OR of 1.63 compared to non-PPI users. This study also showed a positive relationship of the PPI users, B12 deficiency and dementia (OR of 2.82), which may show significance of PPI-use–related B12 deficiency. However, another later study in elderly patients using PPIs longer than 3 years showed no difference in B12 levels, homocysteine levels or mean corpuscular volume compared with controls [42]. Therefore, PPIs may have an associated malabsorption of B12, but may not significantly affect traditional markers for B12 deficiency. A recent abstract by Dougherty, et al. [43] showed that only 1 out of 90 patients on PPIs longer than 6 months had a B12 deficiency; however, they additionally found only 38.5% of chronic PPI users had their B12 checked.

Small intestinal bacterial overgrowth (SIBO), which appears to be increased in patients on PPIs (see section on Microbiome), increases luminal destruction of dietary B12, thereby decreasing B12 levels. Those with SIBO often have decreased B12 but increased folic acid due to folic acid production by the increased small bowel bacterial load [44]. Despite this known correlation, patients with confirmed SIBO on PPIs have not been found to have a difference in B12 level despite an increase in pH [45]. Although SIBO is a recognized difficult diagnosis, studies using jejunal aspirates were the bases of a SIBO diagnosis here and are the current gold standard in diagnosis.

Although there appears to be some element of B12 deficiency in chronic PPI users, particularly in the elderly, its clinical significance is still not established. There has never been a prospective randomized control trial to show true association that would indicate monitoring B12 levels. Given the little dietary B12 needed to maintain a normal circulating level and the large amount of liver stores that may last years, it is difficult to recommend checking B12 levels in patients solely for the reason of chronic PPI use without other indications [46]. Perhaps as more information is revealed, there will be more compelling data to change this recommendation.

Fat

Fat starts its digestion with oral lipase and emulsifies in the stomach. It then enters the duodenum where bile, lipase and colipase contribute to its digestion and absorption. Most fat digestion and absorption occurs in the proximal small bowel and is mostly complete by the time it arrives in the distal small bowel. Lipase in the gastric contents has little consequence to fat digestion. Fat malabsorption occurs in gastric secreting tumors due to the hypersecretion of acid, causing inhibition of the pancreatic lipase and precipitating bile salts [47]. A higher pH increases lipolytic enzyme activity and may improve fat absorption in patients. Additionally, bile acid is precipitated at an acidic pH. The more alkalotic the environment becomes, the more soluble the conjugated and unconjugated bile acids become [48]. Therefore, more soluble bile acid activity may induce *increased* small bowel dietary fat absorption. Insoluble bile acids can contribute to fat malabsorption. One study showed that PPIs increased small bowel flora and shifted the species to those that can deconjugate bile [49]. Despite this, the study also showed an associated impaired fat absorption only in those with bacterial overgrowth on PPI.

In patients with pancreatic exocrine deficiency, such as those with cystic fibrosis (CF), post-surgical exocrine deficiency or chronic pancreatitis, pH may play a role in fat absorption in an already-depleted lipid-digesting enzyme pool. In those with a depleted lipase pool, a lower pH has been shown to decrease fat absorption. Lipase has been shown to be degraded at a pH of 4 or less. An acidic pH in the duodenum decreases fat absorption. Elevated duodenal pH is known to improve fat absorption in cystic fibrosis patients who have a baseline lower postprandial pH [50]. In terms of gastric pH and fat absorption there is little evidence that increasing pH in a normal healthy adult will alter fat absorption. In one study, hypochlorhydric patients (atrophic gastritis or PPI users) with known SIBO did not show significant fat malabsorption [34].

PPIs are known to improve fat absorption in chronic pancreatitis in up to 40% of patients [51]. They have been shown to be particularly helpful in delivery of pancreatic enzymes as they may decrease deactivation in the stomach due to a low pH. Improved pH with omeprazole in CF patients has been shown to improve fat absorption and weight gain [52]. PPIs significantly decrease steatorrhea and improve fat absorption in children with CF with a combination of PPI and pancreatic enzyme supplementation as well as decrease fecal fat from 13 g/day to 5.5 g/day [53]. The conclusion can then be that PPIs do not alter fat absorption in healthy individuals but may improve fat absorption in those with chronic exocrine pancreatic insufficiency.

Potassium

Potassium is a cation that plays an essential role in multiple physiological processes. It is well known for its influence in the propagation of action potentials in neuronal, muscular and cardiac tissue. However, it also is involved in vascular tonicity, gastrointestinal motility, and acid-base homeostasis. Hypokalemia can therefore result in muscle cramps/weakness (especially below 2.5 meq/L) and cardiac arrhythmias [54]. Given its vasodilatory effects during exercise, a decrease in serum potassium can diminish blood flow to muscles, causing ischemic rhabdomyolysis [55]. The vast

majority of potassium absorption occurs in the small intestine by passive mechanisms, and the average person will absorb about 90% of his or her daily intake [56].

Proton pump inhibitors can cause hypokalemia in alkalemic environments. Maeda, et al. [57] documented hypokalemia as low as 2.3 meq/L in a 69-year-old woman after beginning omeprazole 20 mg PO daily that improved with potassium supplementation and cessation of the PPI. The proposed mechanism was due to intracellular shifts of potassium through H^+/K^+ -ATPase. Alkalemia induces potassium shifts from plasma and interstitial fluids into the Type B intercalated cells in the collecting duct via H^+,K^+-ATPase in exchange for hydrogen ions, resulting in temporary hypokalemia [58]. It is commonly known that PPIs function by irreversibly binding to H^+/K^+-ATPase on gastric parietal cells that, in turn, inhibits HCl production. However, studies have shown that PPIs also inhibit non-parietal H^+/K^+- ATPase. Garg and Narang [59] performed a study in rabbits that demonstrated renal tubular K+ ATPase inhibition by omeprazole. The function of H^+/K^+-ATPase in the distal nephron is, in part, potassium reabsorption, and its expression is enhanced in acidic environments [60]. In acidemia, PPIs have a higher affinity for H^+/K^+- ATPase and inhibit its activity, thereby decreasing potassium reabsorption in the kidney and contributing to subsequent hypokalemia [61]. This mechanism may explain the reported case of hypokalemia in an 80-year-old woman in the setting of metabolic acidosis and omeprazole use that responded to cessation of the PPI [57].

Lastly, PPIH can secondarily cause hypokalemia due to urinary potassium secretion through renal outer medullary potassium channels in the distal nephron [62]. Despite the aforementioned mechanisms of PPI-induced hypokalemia, the incidences documented were isolated case reports. More research will need to be done to confirm the association between PPI use and potassium malabsorption before physicians can incorporate this into practice.

Iron

Iron is an important mineral vital for oxygen delivery and usage in tissue. It makes up the core of hemoglobin in circulating blood and myoglobin in muscle. Iron deficiency can cause anemia and ischemia due to decreased tissue oxygenation. Heme iron (Fe2+) is readily absorbed by heme carrier protein 1 in the duodenum [63]. However, dietary iron exists mostly as non-heme iron (Fe3+) and is poorly soluble in the GI lumen. It is reduced to ferrous iron (Fe2+) by cytochrome B on the apical surface of the duodenum and enters the duodenal mucosal barrier through the transporter DMT1. It is then transported through the basolateral membrane where it is oxidized back to ferric iron (Fe3+) and bound to transferrin in the systemic circulation [64].

The pH of gastric juice has a significant impact on the solubilization and absorption of non-heme iron. Bezwoda, et al. [65] studied the absorption of non-heme iron from food in human subjects. They found that at pH less than 2, there was an inverse relationship between pH and solubilization of non-heme iron. This is due to the role of gastric hydrochloric acid in the reduction of ferric iron to the more soluble ferrous iron [66]. Hutchison, et al. [67] studied humans with hereditary hemochromatosis and observed that administration of a PPI for 7 days led to a significant decrease in the absorption of non-heme iron from a test meal. They also noted there was a significant reduction in the requirements for maintenance phlebotomy to keep ferritin levels approximately 50 mcg/L before and while taking a PPI.

PPI use may also indirectly cause iron malabsorption via the effect on vitamin C and its biologically active form, ascorbic acid. Ascorbic acid is a major contributor to the facilitation of non-heme iron absorption. The compound is present in gastric juice and reduces Fe3+ to the more soluble Fe2+ in the acidic pH of the stomach [68]. It also forms a chelate with ferric iron in acidic pH, which remains soluble at the alkaline pH of the duodenum, and thereby further aids in iron bioavailability [69]. Ascorbic acid becomes less stable at less acidic pH environments and can be easily degraded [70]. Mowat, et al. [71] performed a small study in humans and found that after 4 weeks of omeprazole 40mg PO daily, ascorbic acid levels were decreased from 3.8 mcg/mL to 0.7 mcg/mL ($P<0.0001$).

The PPI-induced reduction in non-heme iron absorption can be significant enough to cause iron deficiency anemia and poor response to oral iron supplementation. Sarzynski, et al. [72] conducted a retrospective study that demonstrated a significant reduction in mean hemoglobin and hematocrit ($P<0.01$) in human patients on chronic PPI therapy (at least 1 year) compared to matched controls (n = 4-5 controls and 18-21 PPI users). Hashimoto, et al. [73] documented a case of iron deficiency anemia in a 59-year-old male after beginning rabeprazole for GERD treatment. Non-heme iron replacement was initiated in the form of ferrous fumarate without improvement in his anemia. Endoscopy of the entire GI tract was negative for hemorrhagic lesions. The patient's hemoglobin returned to normal levels after discontinuation of the PPI, suggesting an association between PPI use and iron deficiency anemia.

The major extrapolate of the current literature is that PPIs can cause iron malabsorption directly by decreasing iron solubility and indirectly by causing ascorbic acid instability. Despite these studies and case reports, there are no current recommendations for routine screening for iron deficiency or treatment with vitamin C supplementation in patients taking PPIs. However, in cases of iron deficiency anemia of unknown etiology, it may be worth considering the PPI as a possible causal agent. In general, it is important for physicians to remain mindful of PPI necessity and discontinue use when appropriate.

Zinc

Efficient absorption of any solute depends on its complete solubilization. For an ionic species such as zinc, we are additionally talking about its presence as a divalent cation in solution. Any conditions that work against this scenario would mitigate against efficient zinc absorption. Since much of our dietary zinc is complexed to protein, one is thus talking about release of zinc from its protein-bound form, as well as its complete dissolution in luminal fluid contents. For supplemental zinc, the zinc may already exist as the divalent ion free of any protein conjugation, but the solubility issue persists. For either source of zinc, however, an elevation of luminal pH is not a propitious event. The near neutral gastric and duodenal luminal pH values seen with PPI use are not contributory to protein digestion and zinc release, nor is neutral pH as amenable to zinc solubility as acidic pH.

Henderson, et al. [74] showed that zinc is more bioavailable at lower gastric pH values, though the exact effect is dependent upon the zinc salt under study. Sturniolo, et al. [75] observed that H-2 blockers will reduce zinc absorption in humans, with zinc administered as $ZnSO_4$. Farrell, et al. [76] observed that acute PPI use inhibited zinc uptake into the bloodstream by almost 70%, when zinc was administered as a zinc gluconate supplement. Long-term PPI use was associated with a near 20% (statistically significant) decrease in plasma zinc levels, with zinc derived from normal dietary sources. This decrease did not, however, result in a clinical zinc deficiency as levels fell from 0.9 to 0.7 mcg/ml. Serum levels of zinc were also found to be significantly lower in a separate study in males placed on a PPI regimen for 8 weeks, a finding that was not observed for copper [77]. In a still earlier study, seven days of omeprazole administration reduced plasma zinc levels by nearly 50% after oral zinc sulfate supplementation [78]. However, zinc absorption from a test meal was observed not to be affected by omeprazole dosages that elevated gastric luminal pH to values over 6 [18].

In addition to the differences involved in zinc absorption from a test meal *vs.* an administered zinc salt, there are other considerations that can introduce variability in zinc uptake studies. First, is that the duodenum is not the only site of gastrointestinal zinc absorption [79]. The cecum and colon can also contribute significantly to overall zinc absorption, and these sites would not be as affected by the luminal pH changes induced by PPI as would the duodenum. In addition, there is a curious effect of zinc in itself elevating gastric and duodenal lumen pH by inhibiting parietal cell acid secretion much like PPIs [80]. Finally, it is worth noting that omeprazole can itself form complexes with divalent transition metal ions such as zinc [81].

Epithelial barrier function

Although not strictly an example of PPIs inducing GI malabsorption, the compromise of epithelial barrier function caused by omeprazole is worth noting here. In rat gastric corpus mucosa mounted in Ussing chambers, omeprazole, esomeprazole and lansoprazole all caused an acute decrease in transepithelial electrical resistance and a simultaneous increase in transepithelial diffusion of ^{14}C-D-mannitol [82]. Both phenomena indicate an induced paracellular leak across the tissue. Induced transepithelial leak to the paracellular probes, ^{14}C-sucrose and ^{14}C-polyethyleneglycol but not to ^{14}C-dextran of 70k molecular weight indicate an induced change in the tight junctional barrier. This induced leak was observed to allow increased transepithelial diffusion of the biologically active peptide bradykinin and the small molecule drug digoxin, exemplifying the potential biomedical significance of the induced leak [83]. Indication that this PPI-generated transepithelial leak is occurring in the upper GI tract of humans in vivo was shown by the use of the sucrose permeability test, which indicated a 300% greater leak in chronic users of this drug class [76,84].

Microbiome

The gut microbiome is very pH-dependent, and given that PPIs induce achlorhydria, there is concern about thereby altering the microbiome of the gut with associated negative sequelae. Aside from the far proximal duodenum, the small bowel and colonic pH is approximately 6.4 to 7.5 [85]. Colonic and small bowel pH is not directly affected by PPIs; however, alterations in proximal microbiome likely affect the distal microbiome. Gulmez, et al. [86] theorized that the inhibition of the protective "acid wall" increases pathogens from invading ante grade and retrograde, causing community-acquired pneumonia (CAP), *C. difficile* and other infections. After correcting for heterogeneity, one large meta-analysis showed that PPI use increases the risk of SIBO with an OR of 7.587 compared to controls by using small bowel aspirate (diagnosed with aspirate of $>10^5$ CFU/cc) [87]. This same meta-analysis showed the studies that used glucose-hydrogen breath tests (GHBT) to diagnosis SIBO were less conclusive. This may be due to the heterogeneity of the results of the breath tests, reinforcing that small bowel aspirate is the gold standard for diagnosing SIBO. The clinical significance of this overgrowth in the setting of PPI use was not assessed. One additional study used GHBT to check for SIBO with chronic PPI use and showed a trend toward significance with increase in positive GHBT (45.4% *vs.* 32.6%, P = 0.31). This study showed a correlation with dosing of the PPI as well. Once-daily PPI use did statistically increase the likelihood of positive GHBT [88]. Another study confirmed SIBO with PPI use; however, it did not show any associated malabsorption (based upon normal lactulose breath H2 tests), which is often a side effect of SIBO [89].

Unlike B12 deficiency, microbiome change due to PPI does not necessarily require chronic use. One study showed that as little as 4 weeks of low-dose PPI (20 mg omeprazole) can increase duodenal bacterial colonization from 330 CFU/mL to 95000 CFU/mL [90]. Another small study showed that over a 21-day course of PPI with confirmed pH increase from 1.8 to 7.5, the median colony count of gastric juice bacterial load went from $1.5x10^4$ to $7.5\text{-}8.7x10^7$ CFU/mL [91]. In one study, 53% of PPI users had 10^5 CFU/ml in their gastroduodenal aspirates as opposed to 17% of H_2RA users, with basal pH higher in PPI than H_2RA (4.2 *vs.* 2) [45]. Normal gastroduodenal bacteria should be between $10^1\text{-}10^3$ CFU/ml [92].

When salivary pH is close to pH 8 regardless of PPI use, altered oropharyngeal milieu is unlikely. Esophageal bacterial load, however, is altered with the use of PPIs. The flora in Barrett's esophagus patients and esophagitis compared to controls is not vastly different at baseline; however, after PPI administration, the flora changed significantly, particularly with an increase in enterobacteriaceae [93]. This finding was observed in the gastric fluid as well. Increased gastric pH increases gastric colonization generally [94]. Non-H. pylori flora was significantly increased in gastric juices and mucosal biopsies in dyspeptic patients on PPIs, but not dyspeptic patients on either H_2RAs or no medications (58.7% *vs.* 22.6% *vs.* 30.6%) [95]. Hypochlorhydric patients (mean pH 6.6) had a mean 10^8 CFU/mL, while normochlorhydric subjects had 10^1 CFU/ml in fasting gastric aspirate. However, these patients had no noted negative clinical side effects. The prominent bacteria here were viridans streptococci, coagulase negative staphylococci and haemophilus species [96]. Another study showed that PPIs have an increase in predominantly Corynebacterium and α-hemolytic streptococcus species [45]. These are typically oral flora. In cirrhotic patients, PPI use increased streptococci in stool (a typical oral bacterium) [97]. It appears clear that increased pH due to PPIs portends higher, altered bacterial content in the proximal gut.

In addition to the gut microbiome being pH-dependent, white cells require pH regulation to help with the immune system.

Alteration of the host's defense system via alterations in the pH of certain cellular mechanisms due to inhibition by PPIs may also alter the gut microbiome. PPIs may decrease lysosomal activity in white blood cells therefore preventing aberrant bacterial colonization. [98] PPIs have been known to decrease natural killer cell's cytotoxic activity as well [98]. Omeprazole has been shown to decrease reactive oxygen species production by neutrophils, which are imperative for neutrophilic respiratory bursts [99]. Lansoprazole has been shown in vitro to inhibit both natural killer cells and polymorphic nuclear cells [100].

The question of whether this altered microbiome has clinical significance has begun to be investigated. In patients with altered anatomy, PPIs and their resulting altered proximal gut flora may lead to true issues. One study (n = 8) found that PPIs post Roux-en-y gastric bypass (RYGB) have an increase of Firmicutes bacterium and a lower abundance of Bacteroides and Akkermansia, which the authors theorized lead to less weight loss post RYGB [101]. Prior studies have shown that bacterial overgrowth in RYGB is common and does have an effect on malabsorption, and therefore PPIs have the potential to worsen this effect [102].

There is concern that PPIs may increase GI infections generally as well. One large cohort of 170,000 patients showed an increase in gastroenteritis amongst omeprazole users with an RR of 1.6, although this effect dissipated to an RR of 1.1 at 1 year. The overall study did not show a significant increase in gastroenteritis amongst all acid-suppressing medications, although omeprazole was the only PPI in use [103]. There also has been reported a 10-fold increase in campylobacter infections in PPI users. This association was not found in H_2RA users [104]. Concomitant PPI and corticosteroid use had an OR of 13.8 for candida esophagitis as opposed to PPI (OR 1.67) or corticosteroid use alone (OR 3.55) [105].

Clostridium difficile infection (CDI) has garnered much attention with regard to PPI use. One single center study found a 6-fold increase in nosocomial CDI in patients who received PPI as an inpatient compared with those who did not [106]. Additionally, PPIs have been shown to increase recurrence of CDI by 20% [107]. That said, PPI use during a patient's first CDI episode has not been shown to increase recurrence at 90 days, even if the patient remains on his or her PPI after treatment [108]. It may be reasonable to consider not giving PPIs to those inpatients unless there is a very clear indication in the acute setting.

An area that has only very recently been addressed is the gut microbiome in cirrhotic patients. Therefore, it has brought some concern for PPI use in cirrhosis, particularly in increasing the incidence of spontaneous bacterial peritonitis (SBP) due to gut translocation. There may be as high as a 2.23- to 3-fold increase of SBP in cirrhotics, according to two meta-analyses [109,110]. A more recent retrospective cohort study showed a significant increase of SBP in cirrhotics and PPI use with an adjusted odds ratio of 1.960 (p=0.008) [111]. However, the only large prospective trial showed no significance between SBP rate in cirrhotics with PPI use within the prior 3 months, and the type of SBP flora was also not different between PPI users and non-users [112]. These conflicting data do promote some concern, and if cirrhotic patients do not have a valid indication for a PPI, the prescriber may want to prescribe judiciously or discontinue it as soon as possible.

Although not the distinct goal of this review, it is worth noting that PPI use increases risk of infection in the respiratory track, likely due to its effect either on GI flora or altered immune response. For instance, CAP due to oropharyngeal flora was 2 times more likely in PPI users than in non-PPI users [113]. Additionally, acid suppressive therapy has been found to have a 2.34-fold increase in patients with manifestations of respiratory infections [114]. In CF patients, however, PPIs delay the time to pulmonary colonization with *Staphylococcus aureus* and *Pseudomonas aeruginosa* [115]. These bacteria have deleterious effects in CF patients, and therefore PPIs may offer a benefit in this population. This may be due to the negative effects of GERD on pulmonary parenchyma in fragile CF patients, which PPIs could improve. Regardless, prescribers must be vigilant about these potential alterations in the GI microbiome and their potential hazards, and must be prudent in starting or keeping patients on these medications.

Conclusion

The ability of PPI medications to very efficiently inhibit parietal cell acid secretion, and thereby elevate gastric luminal pH from values as low as 1.5 to values as high as 6.5, is the "elephant in the room" regarding PPI effects on efficient nutrient/mineral absorption. The malabsorption issues surrounding PPIs are — at their simplest — issues of bioavailability. For example oral intake of calcium as calcium carbonate — a very poorly water-soluble calcium salt — is obviously problematic for absorption of calcium by virtue of its insolubility. However, at the normally very low pH of gastric luminal fluid, the reaction of calcium carbonate with the stomach lumen's abundant HCl, leads to the production of the highly water-soluble calcium chloride, with the reaction being driven forward by the release of CO_2:

$$CACO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

It is a simple example of the manner in which an acidic gastric luminal fluid can profoundly aid bioavailability. It has similar application with regard to Mg, Fe, Cu and Zn salts as well. In addition, there is the consideration of the pH effects per se on the solubility of a specific mineral salt.

A wholly different concern would be the effect of luminal fluid pH -duodenal as well as gastric- on the maximal activity of certain enzymes and transporters involved in absorption. It is worth considering that the processes by which certain nutrients and minerals are absorbed faced evolutionary adaptation of their own over millennia, and such evolutionary adaptation occurred within the context of a gastric luminal pH in the range of 1–2. Along comes a medication such as PPIs that elevates gastroduodenal pH to 5.5-6.5, and it is not entirely surprising that absorption issues arise.

In fact, it is surprising that the pH-elevating effect of PPIs is as benign as it is, concerning nutrient/mineral status. Our summarizing of the situations for various nutrients/minerals shows that the clinical effects are typically either nonexistent or minor/idiosyncratic/conditional. They certainly can't be ignored clinically but they oftentimes require another factor (e.g., genetics, diuretic use) to become medically problematic. This is really due to the body's systemic physiological response to a suboptimal intestinal absorption. For example, blood levels of nutrient/mineral, X, may be normal even

when intestinal absorption of X is reduced by 50% at elevated pH, because of compensatory regulation of transporters in the kidney and in somatic cells generally. The question of the significance of PPIs and malabsorption of X needs to be extended into whether a decreased absorption of X results in decreased circulating levels of X and/or decreased cellular/tissue levels of X that may be critical for certain processes. The answer to that question may vary widely from one cell/tissue type to the next, and must be evaluated cell type by cell type.

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