



ORIGINAL ARTICLE

Hypomagnesemia as an Underrecognized Adverse Effect of Long-Term Proton Pump Inhibitor Therapy: A Literature review

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ABSTRAKT

Proton pump inhibitors (PPIs) are among the most widely prescribed medications globally, used for the management of gastroesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* eradication. While generally regarded as safe, long-term PPI use has been increasingly associated with adverse metabolic effects, among which hypomagnesemia remains one of the most underrecognized complications. Evidence consistently demonstrates that long-term PPI use impairs intestinal magnesium absorption through interference with TRPM6 and TRPM7 transporter channels. Prevalence of hypomagnesemia among long-term PPI users ranges from 13% to over 50% across studies, with higher rates in elderly patients, those on diuretics, and from subtle conditions. Safety warning, routine magnesium monitoring remains inconsistent and largely inadequate in clinical practice. Routine monitoring of serum magnesium in patients on prolonged PPI treatment is strongly warranted and should be incorporated into updated prescribing guidelines.

KEYWORDS

hypomagnesemia proton pump inhibitor; long-term; pathophysiological mechanisms; drugsafety; medication; *Helicobacter pylori*

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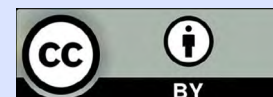
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Aim of the Work

This review aims to comprehensively examine the current evidence regarding the association between long-term PPI therapy and hypomagnesemia, explore the underlying pathophysiolo-

gical mechanisms, describe its clinical manifestations, and evaluate existing monitoring and management recommendations.

Methods

A narrative literature review was conducted using PubMed, Google Scholar, and the Cochrane Library. Search terms inc-

luded „proton pump inhibitor hypomagnesemia,” „PPI magnesium deficiency,” „long-term PPI adverse effects,” „TRPM6 magnesium absorption,” and „omeprazole hypomagnesemia.” Articles published between 2000 and 2024 were considered, with priority given to clinical trials, observational studies, systematic reviews, case reports of clinical significance, and relevant pharmacological mechanistic studies. Between 40 and 60 references were included based on relevance, methodological quality, and contribution to understanding of the topic.

Introduction

Proton pump inhibitors represent one of the most frequently prescribed drug classes in modern medicine. Since their introduction in the late 1980s, their use has expanded dramatically across primary and secondary care settings, driven by the high global prevalence of acid-related gastrointestinal disorders including gastroesophageal reflux disease, peptic ulcer disease, and *Helicobacter pylori* eradication regimens. PPIs are among the top three most commonly dispensed medications worldwide, with hundreds of millions of prescriptions written annually across North America, Europe, and Asia (Forgacs & Loganayagam, 2008; Heidelbaugh et al., 2012). In many healthcare systems they are available over the counter, further contributing to their unrestricted long-term use.

Their widespread adoption has been fueled largely by a perceived favorable safety profile. Compared to H₂ receptor antagonists, PPIs offer superior and more sustained acid suppression with excellent short-term tolerability, leading both physicians and patients to regard them as essentially benign medications suitable for indefinite use. However, a growing body of evidence over the past two decades has challenged this assumption, linking long-term PPI therapy to *Clostridioides difficile* infection, chronic kidney disease, bone fractures, vitamin B12 deficiency, and clinically significant hypomagnesemia (Lazarus et al., 2016; Gomm et al., 2016; Cheungpasitporn et al., 2015).

Magnesium participates in over 300 enzymatic reactions and plays fundamental roles in neuromuscular transmission, cardiac electrophysiology, and glucose metabolism. Despite this importance, magnesium status is infrequently assessed in routine clinical practice, and hypomagnesemia is often overlooked as a contributor to nonspecific symptoms including fatigue, muscle cramps, and cardiac arrhythmias (Grober et al., 2015; Workinger et al., 2018). This creates a danger-

ous diagnostic gap when patients are simultaneously exposed to a drug that chronically impairs magnesium absorption.

The first case reports linking PPI use to severe hypomagnesemia emerged around 2006 to 2009, describing patients whose electrolyte levels normalized upon PPI discontinuation and recurred upon rechallenge (Shabajee et al., 2008; Cundy & Mackay, 2011). These prompted the FDA to issue a formal drug safety communication in March 2011, advising clinicians to consider measuring serum magnesium before and periodically during long-term PPI therapy (FDA, 2011). Despite this, subsequent studies have consistently demonstrated that routine magnesium monitoring remains alarmingly infrequent in clinical practice (Janett et al., 2015; Zipursky et al., 2014).

The clinical consequences of unrecognized PPI-induced hypomagnesemia can be severe, including life-threatening ventricular arrhythmias, seizures, and refractory electrolyte disturbances, all entirely preventable with appropriate monitoring (Regolisti et al., 2010). This review consolidates current evidence on the mechanism, epidemiology, clinical manifestations, diagnosis, and management of this underrecognized complication, advocating for routine magnesium surveillance in all patients receiving long-term PPI therapy.

Background on Proton Pump Inhibitors

Proton pump inhibitors were first introduced into clinical practice with the approval of omeprazole in 1989, representing a landmark advance in the management of acid-related gastrointestinal diseases. The class subsequently expanded to include lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole, each sharing a common mechanism while differing in pharmacokinetic profiles and clinical indications (Sachs et al., 2006).

PPIs act as prodrugs that require activation in the acidic environment of gastric parietal cell secretory canaliculi, where they are converted to their active sulfenamide form. Once activated, they irreversibly inhibit the hydrogen-potassium adenosine triphosphatase enzyme, the gastric proton pump, by forming covalent disulfide bonds with cysteine residues on the enzyme. Because this inhibition is irreversible, acid secretion can only resume after new pump proteins are synthesized, accounting for the prolonged duration of acid suppression that distinguishes PPIs from the reversible competitive inhibition of H₂ receptor antagonists (Sachs et al., 2006; Strand et al., 2017).

Approved indications include GERD, erosive esophagitis, peptic ulcer disease, NSAID-associated ulcer prevention, Zollinger-Ellison syndrome, and *Helicobacter pylori* eradication regimens. Guidelines consistently recommend the shortest effective duration of therapy, with long-term maintenance reserved for specific conditions such as Barrett's esophagus or severe erosive esophagitis (Katz et al., 2013). Despite this, epidemiological studies have documented that between 25% and 70% of PPI prescriptions lack an evidence-based indication or are continued beyond recommended durations (Forgacs & Loganayagam, 2008; Heidelbaugh et al., 2012). PPIs initiated for stress ulcer prophylaxis during hospital admissions are frequently continued indefinitely following discharge, and short-term prescriptions in primary care routinely become permanent through physician inertia and patient familiarity (Reimer et al., 2009). This culture of unrestricted long-term use has critical implications for the recognition of metabolic complications. When a medication is perceived as inherently safe, the threshold for investigating drug-related adverse effects is inevitably lowered, and patients may experience symptoms attributable to hypomagnesemia for months or years before the connection to their PPI is ever considered.

Magnesium: Physiology and Biological Importance

Magnesium is the fourth most abundant mineral in the human body and the second most prevalent intracellular cation after potassium. Of the approximately 24 to 25 grams of total body magnesium in a healthy adult, roughly 60% is stored in bone, with the remainder distributed within intracellular compartments of soft tissues and muscle, and less than 1% circulating in extracellular fluid including serum (Grober et al., 2015).

This distribution has important diagnostic implications: serum magnesium represents only a small fraction of total body stores and does not reliably reflect intracellular or skeletal reserves. A patient may have significantly depleted intracellular magnesium while maintaining a serum level within the normal reference range, a state known as chronic latent magnesium deficiency (Workinger et al., 2018).

Normal serum magnesium levels fall between 0.70 and 1.10 mmol/L, though reference ranges may vary slightly between laboratories. Hypomagnesemia is defined as a serum magnesium level below 0.70 mmol/L, and can be further classified as mild (0.50–0.70

mmol/L), moderate (0.25–0.50 mmol/L), or severe (below 0.25 mmol/L), the latter carrying the highest risk of life-threatening cardiac and neuromuscular complications (Topf & Murray, 2003).

At the biochemical level, magnesium serves as a co-factor in over 300 enzymatic reactions fundamental to cellular energy metabolism, DNA and RNA synthesis, and protein production. Its role as an essential component of the magnesium-ATP complex means that depletion has far-reaching consequences for cellular energy utilization across all organ systems (Gröber et al., 2015; de Baaij et al., 2015). In the cardiovascular system, magnesium functions as a natural calcium channel antagonist, modulating calcium influx into cardiac myocytes and vascular smooth muscle. Deficiency increases myocardial excitability, predisposing to atrial fibrillation, ventricular tachycardia, and torsades de pointes (Dyckner & Wester, 1982). In the neuromuscular system, magnesium regulates acetylcholine release and NMDA receptor activity, with deficiency producing cramps, tremors, tetany, seizures, and neuropsychiatric symptoms including depression, anxiety, and cognitive impairment (Serefko et al., 2013; Rajizadeh et al., 2017).

Magnesium is also intimately linked to calcium and potassium homeostasis. Significant depletion impairs parathyroid hormone secretion and induces peripheral PTH resistance, causing hypocalcemia refractory to calcium supplementation alone (Rude, 1998). Simultaneously, magnesium deficiency impairs renal potassium channel function, causing urinary potassium wasting and hypokalemia that similarly fails to correct without magnesium repletion (Huang & Kuo, 2007). These interdependencies mean that unexplained refractory hypokalemia or hypocalcemia should always prompt evaluation of magnesium status.

Dietary magnesium is obtained primarily from green leafy vegetables, nuts, seeds, whole grains, and legumes. The recommended daily allowance for adults ranges from 310 to 420 mg per day depending on age and sex, yet average dietary intake in Western populations falls at approximately 250 to 350 mg per day, meaning many individuals already have marginal magnesium reserves before any drug-induced impairment of absorption is superimposed (Institute of Medicine, 1997).

Magnesium Absorption Mechanisms in the Gut

The body maintains magnesium homeostasis through a tightly regulated interplay between intestinal

absorption, renal reabsorption, and skeletal buffering. Approximately 30% to 40% of dietary magnesium is absorbed in the gastrointestinal tract, primarily in the ileum and jejunum, with the colon contributing a smaller but meaningful proportion (Quamme, 2010; Konrad et al., 2004). Magnesium absorption occurs via two distinct pathways: passive paracellular transport and active transcellular transport.

Passive paracellular transport occurs between adjacent epithelial cells through tight junctions, driven by simple diffusion along the electrochemical gradient. It is non-saturable, concentration-dependent, requires no cellular energy, and predominates when luminal magnesium concentrations are high. Crucially, this pathway is insensitive to changes in luminal pH, which becomes important when considering how PPIs disrupt magnesium absorption (Quamme, 2010; Schuchardt & Hahn, 2017).

Active transcellular transport becomes dominant when luminal magnesium concentrations are low, such as during dietary restriction or increased physiological demand. This pathway is saturable, energy-dependent, and subject to precise physiological regulation. Its molecular machinery centers on two transient receptor potential melastatin channels: TRPM6 and TRPM7. TRPM6 is expressed predominantly on the apical surface of intestinal epithelial cells and on renal tubular cells in the distal convoluted tubule, positioning it as the primary gatekeeper of magnesium entry at both major sites of body magnesium regulation. TRPM7 is more ubiquitously expressed and forms functional heteromeric complexes with TRPM6 that are essential for normal channel activity (Schlingmann et al., 2002; Walder et al., 2002).

TRPM6 functions as a bifunctional protein combining ion channel and serine-threonine kinase activity. Once magnesium enters the intestinal epithelial cell through the apical TRPM6 channel, it is extruded across the basolateral membrane into systemic circulation, a process involving the sodium-dependent exchanger SLC41A1 (de Baaij et al., 2015; Goytain & Quamme, 2005). Channel activity is regulated by intracellular magnesium concentration, hormonal signals including estrogen and insulin, and importantly, luminal pH (Groenestege et al., 2006).

Luminal pH is a critical determinant of active magnesium absorption. TRPM6 activity is optimal under mildly acidic to neutral conditions and is significantly impaired when luminal pH rises, providing the direct mechanistic link between PPI-induced acid suppression and reduced magnesium absorption (Hess et al., 2012; Lameris et al., 2015). Renal magnesium handling, also mediated largely by TRPM6 in the distal

convoluted tubule, provides a complementary conservation mechanism but cannot fully compensate when intestinal absorption is chronically impaired, making progressive depletion inevitable with long-term PPI use (Quamme, 2010).

Mechanism of PPI-Induced Hypomagnesemia

Current evidence strongly supports a model in which chronic PPI-mediated gastric acid suppression produces sustained elevation of intestinal luminal pH that directly impairs TRPM6 and TRPM7 magnesium transport channel function, reducing active transcellular absorption to a degree that cannot be compensated by passive paracellular mechanisms or renal conservation (Hess et al., 2012; Lameris et al., 2015; Cundy & Mackay, 2011).

Under normal conditions, gastric acid produces a luminal pH of 1 to 2 in the stomach, which is progressively neutralized to approximately 6 to 7 in the jejunum and ileum. PPI therapy significantly reduces the acid load delivered from the stomach, raising luminal pH throughout the small intestine and creating an environment suboptimal for TRPM6 function (Sachs et al., 2006; Hess et al., 2012). In vitro studies have demonstrated that luminal alkalinization significantly reduces TRPM6 channel conductance and magnesium uptake efficiency through pH-dependent conformational changes that reduce channel open probability and ion permeability (Lameris et al., 2015; Schlingmann et al., 2002). TRPM7, forming heteromeric complexes with TRPM6, is similarly affected, with the net result being a significant reduction in active magnesium transport that, sustained over months to years of PPI therapy, leads to progressive total body depletion.

Passive paracellular transport cannot compensate for this deficit. Under normal dietary conditions, luminal magnesium concentrations are insufficient to drive meaningful passive absorption in the absence of functioning active transport, explaining why dietary modifications alone cannot correct PPI-induced hypomagnesemia (Hess et al., 2012; Danziger et al., 2013).

Hypomagnesemia develops slowly and insidiously in this context, as skeletal magnesium reserves buffer falling serum levels and renal conservation reduces urinary losses. Most published studies report a median duration of PPI use before overt hypomagnesemia becomes apparent of one to five years, con-

tributing significantly to diagnostic delay (Cundy & Mackay, 2011; Cheungpasitporn et al., 2015).

Not all long-term PPI users develop hypomagnesemia, suggesting genetic susceptibility modulates individual risk. Polymorphisms in the TRPM6 gene have been associated with lower baseline magnesium absorption efficiency, predisposing carriers to clinically significant hypomagnesemia at lower PPI doses and shorter treatment durations (Groenestege et al., 2006; Konrad et al., 2004). A compelling line of supporting evidence comes from patients switched from PPIs to H2 receptor antagonists, who demonstrate normalization of serum magnesium without dietary changes or supplementation, a class-specific effect strongly implicating luminal pH elevation rather than any off-target molecular effect of the PPI itself (Shabajee et al., 2008; Regolisti et al., 2010). Additional proposed mechanisms including PPI-related gut microbiome alterations and potential renal tubular effects remain less well characterized and require further investigation (Lameris et al., 2015; Janett et al., 2015).

Epidemiology and Prevalence

The epidemiology of PPI-induced hypomagnesemia has evolved from isolated case reports in the mid-2000s to large population-based studies firmly establishing the magnitude of this association. Early case reports described patients with severe symptomatic hypomagnesemia whose electrolyte levels normalized upon PPI discontinuation and recurred upon rechallenge, with a common pattern of prolonged PPI exposure before the electrolyte abnormality was detected (Shabajee et al., 2008; Broeren et al., 2009).

Systematic quantification followed in the early 2010s. A cohort study by Danziger et al. (2013) examining around 11,000 patients demonstrated that PPI use was independently associated with significantly lower serum magnesium concentrations, particularly in patients on concurrent diuretics.

A meta-analysis by Cheungpasitporn et al. (2015) found that hypomagnesemia occurred in approximately 19.4% of long-term PPI users compared with 13.5% in non-users, with individual study estimates ranging from 13% in community outpatient populations to over 50% in elderly inpatients with multiple comorbidities and diuretic use.

Consistently identified risk factors include duration of therapy, with risk increasing substantially after one year of continuous use, higher daily doses, advanced age, and concurrent diuretic therapy. Thiazide diuretics are particularly significant, impairing renal

magnesium reabsorption in the distal convoluted tubule and compounding the intestinal absorption deficit, with studies estimating a two to threefold increase in hypomagnesemia risk when PPIs and thiazides are combined (Zipursky et al., 2014; Danziger et al., 2013). Other high-risk groups include patients with type 2 diabetes, solid organ transplant recipients on calcineurin inhibitors, and those with inflammatory bowel disease with reduced intestinal absorptive surface area (Hoorn et al., 2010; Broeren et al., 2009).

Considered against the scale of worldwide PPI prescribing, the available prevalence data suggest a substantial and largely preventable burden of electrolyte morbidity among long-term PPI users, the majority of whom are never screened for this complication (Cheungpasitporn et al., 2015).

Clinical Manifestations

The clinical presentation of PPI-induced hypomagnesemia is highly variable, influenced by the absolute serum magnesium level, rate of decline, duration of depletion, and presence of concurrent electrolyte disturbances. Mild hypomagnesemia is frequently asymptomatic and detected only incidentally, while moderate to severe depletion produces neuromuscular, cardiac, and neuropsychiatric manifestations ranging from mildly debilitating to immediately life-threatening (Grober et al., 2015; de Baaij et al., 2015).

Muscle cramps, particularly affecting the legs and feet, are among the earliest and most common symptoms, often preceding diagnosis by months or years. Tremor, fasciculations, and weakness are also common, and in more severe cases Chvostek's and Trousseau's signs may be elicited on examination. Tetany and generalized seizures represent the most extreme neuromuscular consequences and have been documented in case reports of PPI-induced hypomagnesemia. Importantly, hypomagnesemia-associated seizures are refractory to standard anticonvulsants and respond only to magnesium repletion (Broeren et al., 2009; Hoorn et al., 2010).

Cardiac complications represent the most immediately life-threatening dimension of this condition. Hypomagnesemia increases myocardial excitability and prolongs the QT interval, predisposing to atrial fibrillation, ventricular tachycardia, and torsades de pointes, particularly when concurrent QT-prolonging medications are present (Dyckner & Wester, 1982; Regolisti et al., 2010). New-onset or refractory atrial fibrillation that resolves following magnesium correction has been documented in multiple case reports,

and any patient on long-term PPI therapy presenting with unexplained arrhythmia or QT prolongation should have magnesium status promptly evaluated (Tay et al., 2024).

One of the most diagnostically important features of significant hypomagnesemia is refractory hypokalemia that fails to correct despite aggressive potassium supplementation. Magnesium depletion impairs renal potassium channel function, causing inappropriate urinary potassium wasting that persists until magnesium is repleted (Huang & Kuo, 2007; Danziger et al., 2013). Similarly, impaired PTH secretion and peripheral PTH resistance in the setting of hypomagnesemia produces hypocalcemia refractory to calcium supplementation. The clinical triad of hypomagnesemia, hypokalemia, and hypocalcemia occurring simultaneously in a patient on long-term PPIs is a well-recognized syndrome representing a clear indication for urgent PPI discontinuation and electrolyte repletion (Rude, 1998; Shabajee et al., 2008).

Depression, anxiety, irritability, cognitive impairment, and fatigue have all been described in association with hypomagnesemia, reflecting magnesium's role in NMDA receptor modulation and central nervous system homeostasis (Serefko et al., 2013; Rajizadeh et al., 2017). These symptoms are particularly prone to misattribution in long-term PPI users, leading to unnecessary psychiatric referrals and prolonged patient suffering that is avoidable with routine magnesium monitoring. Asymptomatic hypomagnesemia, while clinically silent at baseline, still confers increased susceptibility to arrhythmias under physiological stress, reinforcing the importance of biochemical surveillance regardless of symptom burden (Janett et al., 2015).

Hypomagnesemia and Associated Comorbidities

Beyond its direct clinical manifestations, chronic magnesium depletion exerts broad adverse effects on systemic health that are particularly relevant in long-term PPI users, who are often elderly patients with multiple existing comorbidities (de Baaij et al., 2015; Grober et al., 2015).

Chronic hypomagnesemia is associated with endothelial dysfunction, increased vascular smooth muscle tone, and a proinflammatory vascular state contributing to hypertension and atherosclerosis. Epidemiological studies consistently demonstrate an inverse association between dietary magnesium intake and risk of hypertension, coronary artery disease, and

cardiovascular mortality. In patients with established cardiovascular disease, hypomagnesemia may worsen hemodynamic control, increase arrhythmia burden, and reduce the efficacy of antihypertensive and antiarrhythmic medications (Dyckner & Wester, 1982; Grober et al., 2015).

Magnesium is an essential cofactor for insulin receptor tyrosine kinase activity and glucose transporter function. Hypomagnesemia impairs insulin-mediated glucose uptake, worsens insulin resistance, and is associated with poorer glycemic control in established type 2 diabetes. A bidirectional relationship exists whereby diabetic patients are predisposed to urinary magnesium wasting, and hypomagnesemia in turn further worsens insulin resistance, creating a cycle that complicates metabolic management (Barbagallo & Dominguez, 2015). In long-term PPI users with diabetes, the compounded effects of urinary wasting and impaired intestinal absorption may produce particularly pronounced depletion.

Long-term PPI therapy independently increases fracture risk through impaired calcium absorption and direct effects on osteoclast function. Hypomagnesemia adds further skeletal risk, as magnesium is essential for osteoblast and osteoclast activity, PTH regulation, and vitamin D hydroxylation. Deficiency impairs bone matrix synthesis and contributes to reduced bone mineral density, compounding the skeletal risk already associated with PPI-induced calcium malabsorption (Rude et al., 2009).

Patients with mild to moderate CKD may have impaired tubular magnesium reabsorption that increases susceptibility to depletion, while evidence from Van Laecke et al. (2013) suggests that hypomagnesemia may independently accelerate CKD progression through promotion of vascular calcification and endothelial dysfunction. Additionally, patients requiring long-term PPI therapy already carry elevated rates of depression and anxiety related to their underlying gastrointestinal conditions. Superimposed hypomagnesemia may worsen mood disturbance and reduce responsiveness to antidepressant therapy, and correction of magnesium deficiency in this population may carry meaningful mental health benefits beyond purely metabolic improvement (Serefko et al., 2013).

Diagnosis and Laboratory Evaluation

The diagnosis of PPI-induced hypomagnesemia is complicated by limitations of available laboratory tools and the absence of a universally agreed diagnostic protocol. Accurate assessment of magnesium sta-

tus requires understanding the strengths and weaknesses of different measurement approaches in their clinical context (Workinger et al., 2018).

Serum total magnesium is the most widely used clinical measure, being inexpensive, widely available, and easily incorporated into standard electrolyte panels. However, it represents less than 1% of total body magnesium and does not reliably reflect intracellular or skeletal compartments. A patient may have depleted intracellular reserves and clinically relevant deficiency while maintaining a normal serum level. Despite this limitation, serum magnesium remains the practical first-line screening test, and a confirmed level below 0.70 mmol/L is a reliable indicator of significant total body depletion (Workinger et al., 2018; Grober et al., 2015).

Urine magnesium collection helps differentiate renal from extrarenal causes of hypomagnesemia. In PPI-induced hypomagnesemia, where the primary defect is intestinal malabsorption, urinary magnesium is typically low as the kidney conserves magnesium in response to depletion. A combination of low serum and low urinary magnesium points toward impaired intestinal absorption consistent with PPI-induced disease, whereas inappropriately elevated urinary magnesium alongside low serum levels suggests renal wasting as the primary mechanism (Quamme, 2010; de Baaij et al., 2015).

The magnesium tolerance test involves intravenous administration of a standard magnesium load followed by measurement of the proportion retained versus excreted in urine. Retention of more than 20% of the administered load is considered indicative of significant total body depletion and represents the most sensitive clinical tool for detecting subclinical deficiency not captured by serum measurement. However, its cumbersome nature limits its use to specialized settings (Van Laecke et al., 2013). Red blood cell magnesium and ionized serum magnesium offer potentially more sensitive reflections of functional magnesium status, but lack standardized reference ranges and have not been prospectively validated in PPI-induced hypomagnesemia specifically (Workinger et al., 2018).

PPI-induced hypomagnesemia should be considered in any long-term PPI user presenting with unexplained muscle cramps, tremors, cardiac arrhythmias, or refractory hypokalemia or hypocalcemia. Initial evaluation should include serum magnesium, potassium, calcium, and phosphate, supplemented by twenty-four hour urine magnesium if the diagnosis remains uncertain. Confirmation requires demonstration of serum magnesium normalization follo-

wing PPI discontinuation, with recurrence upon rechallenge representing the clinical gold standard for establishing causation (Cundy & Mackay, 2011; Shabjee et al., 2008).

Current Guidelines and Monitoring Recommendations

Despite accumulating evidence, translation of the PPI-hypomagnesemia association into standardized clinical monitoring guidelines has been slow and incomplete, representing one of the most significant shortcomings in long-term PPI safety management (Janett et al., 2015; Zipursky et al., 2014).

The most influential regulatory guidance came from the FDA drug safety communication of March 2011, which advised clinicians to consider obtaining baseline serum magnesium before initiating long-term PPI therapy and to repeat measurement periodically during treatment, with particular vigilance in patients receiving digoxin or diuretics (FDA, 2011). European regulatory bodies similarly concluded that hypomagnesemia is a recognized class effect of PPIs, recommending prescriber awareness and consideration of magnesium monitoring in patients on prolonged treatment (Hess et al., 2012). However, neither body mandated specific monitoring intervals or defined a standardized protocol, leaving implementation entirely to individual clinical judgment.

Multiple studies following the 2011 FDA communication have documented a troubling gap between regulatory recommendation and actual clinical practice. Audits have reported serum magnesium checked in as few as 10% to 20% of eligible long-term PPI users in some clinical settings (Janett et al., 2015; Zipursky et al., 2014). Identified barriers include lack of physician awareness, the nonspecific nature of hypomagnesemia symptoms, absence of magnesium from standard electrolyte panels in many laboratory ordering systems, and the widespread perception that PPIs are too benign to warrant systematic metabolic surveillance.

Based on available evidence, a reasonable approach would include baseline serum magnesium before initiating PPI therapy, with repeat measurement at six to twelve month intervals during ongoing treatment. More frequent monitoring every three to six months is warranted in high-risk patients including those on concurrent diuretics, elderly patients, and those with diabetes, chronic kidney disease, or concurrent QT-prolonging medications. Any patient found to have hypomagnesemia should prompt review of ongoing

PPI necessity, consideration of switching to an H2 antagonist, and initiation of magnesium repletion as indicated by severity and clinical symptoms (Hess et al., 2012; Lameris et al., 2015).

Management and Treatment

Management of PPI-induced hypomagnesemia encompasses three complementary strategies: addressing the pharmacological cause, repleting the existing deficiency, and correcting concurrent electrolyte disturbances. The appropriate approach depends on severity of hypomagnesemia, presence of symptoms, and clinical necessity of ongoing acid suppression (Cundy & Mackay, 2011; Hess et al., 2012).

Discontinuation of the causative PPI is the most effective and definitive treatment, with multiple studies documenting normalization of serum magnesium within one to four weeks of stopping therapy, typically without the need for ongoing supplementation (Shabajee et al., 2008; Regolisti et al., 2010). Where PPI discontinuation is not clinically feasible, substitution with an H2 receptor antagonist represents a practical alternative. H2 antagonists produce significantly less sustained acid suppression and do not raise intestinal luminal pH sufficiently to impair TRPM6-mediated absorption. Published cases hypomagnesemia following PPI-to-H2 antagonist substitution without dietary changes or additional supplementation, making this a valuable option for patients with milder acid-related conditions (Broeren et al., 2009; Hoorn et al., 2010). For conditions mandating indefinite PPI therapy such as Zollinger-Ellison syndrome or Barrett's esophagus, long-term magnesium supplementation combined with regular monitoring represents the most appropriate strategy.

Oral supplementation is the most practical approach for correcting mild to moderate asymptomatic hypomagnesemia. Available formulations include magnesium oxide, citrate, glycinate, lactate, and chloride, which differ substantially in bioavailability and gastrointestinal tolerability. Organic salts such as magnesium citrate and glycinate demonstrate superior intestinal absorption and better tolerability compared to inorganic formulations such as magnesium oxide, with lower rates of osmotic diarrhea, which is the most common dose-limiting adverse effect (Schuchardt & Hahn, 2017). An important limitation is that the same impaired TRPM6-mediated absorption mechanism responsible for initial depletion may reduce the efficacy of oral supplementation when PPI therapy continues, potentially requiring higher doses or in-

travenous repletion to maintain adequate levels (Hess et al., 2012).

Intravenous magnesium sulfate is indicated for severe or symptomatic hypomagnesemia, particularly in patients presenting with cardiac arrhythmias, seizures, tetany, or serum magnesium below 0.50 mmol/L. Intravenous administration bypasses the compromised intestinal absorption mechanism entirely, allowing rapid correction of severe deficiency. Standard clinical protocols typically involve infusion of 4 to 8 grams of magnesium sulfate over several hours, with subsequent oral maintenance supplementation and regular biochemical monitoring. Concurrent hypokalemia and hypocalcemia must be actively managed alongside magnesium repletion, as these will not fully correct until magnesium deficiency is adequately addressed. Following resolution of acute hypomagnesemia, ongoing monitoring at regular intervals is essential in patients remaining on PPI therapy to detect recurrence and guide continued management (Regolisti et al., 2010; Cundy & Mackay, 2011).

Gaps in Current Knowledge and Future Directions

Despite substantial progress in characterizing PPI-induced hypomagnesemia, several important knowledge gaps remain that limit development of optimal prevention and management strategies.

The most significant methodological limitation is the absence of large randomized controlled trials. The majority of available data derives from observational studies, case reports, and case series, which cannot establish causality with the rigor of prospective interventional designs. Randomized trials examining the impact of routine magnesium monitoring and supplementation on clinical outcomes in long-term PPI users are needed to drive meaningful changes in prescribing guidelines (Hess et al., 2012; Cheungpasitporn et al., 2015).

Whether different PPI agents carry differential risk for hypomagnesemia remains incompletely resolved. While the complication has been reported with all available PPIs, comparative data are limited and head-to-head trials comparing agent-specific magnesium-lowering effects are lacking (Lameris et al., 2015). Clarification of differential risk profiles could inform more targeted prescribing decisions in susceptible patients.

The role of genetic factors deserves further investigation. Preliminary data on TRPM6 polymorphisms suggest pharmacogenomic profiling could identi-

fy high-risk patients before PPI initiation, enabling preemptive monitoring strategies tailored to individual susceptibility (Groenestege et al., 2006; Konrad et al., 2004). The potential contributions of PPI-induced gut microbiome alterations and renal tubular effects to magnesium depletion also remain mechanistically plausible but inadequately characterized and warrant dedicated investigation.

Finally, development and implementation of a universally accepted evidence-based monitoring protocol represents the most immediately actionable priority. A standardized approach embedded within electronic prescribing systems, incorporating automatic prompts for magnesium measurement at defined intervals in long-term PPI users, could substantially reduce the burden of unrecognized and preventable hypomagnesemia at a population level (Janett et al., 2015; Zipursky et al., 2014).

Conclusion

Hypomagnesemia is a clinically significant, mechanistically well-understood, yet persistently underdiagnosed complication of long-term PPI therapy. Chronic PPI use impairs intestinal magnesium absorption through disruption of TRPM6 and TRPM7 transporter channels, producing consequences ranging from subtle neuromuscular symptoms to life-threatening cardiac arrhythmias. The condition is further complicated by its tendency to cause refractory hypokalemia and hypocalcemia that will not resolve without prior correction of the magnesium deficit. Despite the FDA safety communication of 2011, routine magnesium monitoring in long-term PPI users remains inconsistently practiced, representing a significant gap between evidence and clinical care. This review strongly advocates for baseline and periodic serum magnesium measurement in all patients on long-term PPI therapy, with more frequent monitoring in high-risk groups including elderly patients, those on diuretics, and those with diabetes or chronic kidney disease. Where clinically feasible, switching from a PPI to an H2 receptor antagonist should be considered as first-line management, as this alone frequently restores normal magnesium levels. Ultimately, preventing this complication requires nothing more than awareness, a routine blood test, and willingness to reassess the ongoing necessity of PPI prescriptions.

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AI Disclosure: Artificial intelligence tools were employed in this study in three main capacities. First, they supported the analysis of clinical reasoning narratives by identifying recurring linguistic patterns associated with specific logical fallacies. Second, they assisted in refining the manuscript's academic language, enhancing clarity, coherence, and alignment with established scientific writing standards. Third, they facilitated the organization and preprocessing of data, helping to streamline the overall analytical workflow. Throughout the research process, AI functioned exclusively as a supportive resource under continuous human supervision. The interpretation of findings, identification and classification of reasoning errors, and formulation of conclusions remained entirely the responsibility of experts in clinical medicine and formal logic. AI was used primarily to improve efficiency in tasks such as data handling, pattern detection, and language editing, and it did not replace human judgment at any stage of the analysis.