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Hypomagnesaemia leading to parathyroid dysfunction, hypocalcaemia, and hypokalaemia as a complication of long-term treatment with a proton pump inhibitor — a literature review

Małgorzata Bobrowicz[1, 2], Janusz Pachucki[1], Michał Popow[1]

[1]*Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Immunology, Medical University of Warsaw, Warsaw, Poland*

Abstract

Proton pump inhibitors (PPIs) are one of the most frequently used medications worldwide. The side effects of this class of drugs have been widely studied. However, their impact on the electrolyte balance is frequently forgotten. Long-term PPI administration can lead to profound electrolyte disturbances, namely hypomagnesaemia as well as, secondary to very low magnesium levels, hypocalcaemia and hypokalaemia. In this paper we comprehensively review the complexity of the mechanisms contributing to electrolyte imbalance following PPI (proton pump inhibitors) by changing the pH in the intestinal lumen, interfering with the active cellular transport of magnesium regulated by the transient receptor potential melastatin cation channels TRPM6 and TRPM7. The accompanying hypomagnesaemia causes unblocking of the renal outer medullary potassium channel (ROMK), which results in increased potassium loss in the ascending limb of the loop of Henle. Hypokalaemia caused by hypomagnesaemia is resistant to potassium supplementation because the loss of this element in urine increases with the supply of potassium. Additionally, within the calcium-sensitive receptor (CASR), dissociation of magnesium from the alpha subunit of G protein caused by hypomagnesaemia increases its activity, leading to inhibition of PTH secretion and hypocalcaemia resistant to calcium supplementation. All this means that in some patients, chronic use of proton pump inhibitors by affecting the absorption of magnesium, may lead to life-threatening electrolyte disorders.

Key words: *proton pump inhibitors; hypomagnesaemia; hypocalcaemia; hypokalaemia; parathyroid dysfunction*

Introduction

Role of magnesium

Magnesium is the fourth most abundant cation in the body and an essential cofactor in many cellular processes. It plays a crucial role in numerous enzymatic reactions (including those generating ATP), transport processes, cell adhesion, and synthesis of proteins, DNA, or RNA [1]. Magnesium is thus required for controlling glucose utilisation, synthesis of fatty acids, muscle contraction and relaxation, normal neurological function, release of neurotransmitters, platelet-activated thrombosis, and bone formation. Up to 60% of total magnesium is stored in bones, approx. 40% is located intracellularly (mainly in the muscles), and only 1% circulates in extracellular fluid.

The reference values for serum magnesium levels range between 0.65 and 1.05 mmol/L for total magnesium and 0.55 to 0.75mmol/L for ionised form, so hypomagnesaemia is diagnosed when serum total magnesium levels are lower than 0.65 mmol/L. Hypomagnesaemia is a frequent laboratory finding associated with diabetes, chronic gastrointestinal diseases, alcoholism and use of certain drugs that promote renal magnesium waste (digoxin, loop and thiazide diuretics, aminoglycosides, amphotericin, cisplatin, cyclosporine, pentamidine, and foscarnet) [2, 3]. The symptoms of hypomagnesaemia are non-specific (Tab. 1). The general condition of the patient worsens as concurrent metabolic disorders appear, i.e. hypocalcaemia and hypokalaemia occur secondary to hypomagnesaemia. Therefore, hypomagnesaemia is potentially fatal, being a risk factor for a collapse with possible secondary encephalopathy, arrhythmias, seizures, or pulmonary and glottic oedema [4]. Decreased magnesium level is a frequent finding in critically ill patients [5], and it is considered a negative prognostic factor associated with increased mortality, mechanical ventilation requirement, and increased length of stay in intensive care unit (ICU) [6–8]. Moreover, supplementation of this element may protect against sepsis development by blocking the membrane organisation of gasdermin D,

Dr Michał Popow, MD, PhD, Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Banacha 1 Str., 02–097, Warsaw, Poland, email: mpopow@wum.edu.pl

Table 1. Symptoms occurring in hypomagnesaemia.

These symptoms are non-specific and only associated with hypomagnesaemia. In many cases, the pathomechanism responsible for them cannot be clearly identified.
Loss of appetite
Fatigue
Weakness and along with deterioration of magnesium deficiency neuromuscular disturbances (numbness, cramps, seizures, tetany)
Gastrointestinal disturbances (nausea, vomiting, diarrhoea)
Personality changes
Cardiac complications (arrhythmias and coronary spasms)

a protein forming membrane pores, leading to cytokine release and inflammatory cell death (pyroptosis), as demonstrated in murine models [9].

Proton pump inhibitors

Proton pump inhibitors (PPI) are commonly used in clinical practice for the prevention and treatment of peptic ulcer, gastroesophageal reflux disease (GERD), nonsteroid-inflammatory drugs (NSAID) or glucocorticoid-associated gastritis, Zollinger-Ellison syndrome (ZES), and functional dyspepsia. PPIs are an integral part of eradication therapy for *Helicobacter pylori*. PPIs are lipophilic weak bases that are protonated in the gastric parietal cells to form sulphenamide. This activated form of the drug reacts with the sulfhydryl group of cysteines at the active site of the proton pump, which covalently inhibits the H^+-K^+ ATPase in gastric parietal cells and subsequently irreversibly blocks acid secretion [10]. Although the use of PPIs is registered only in specific indications, a considerable proportion of these prescriptions are based on no appropriate indication [11]. PPIs remain one of the most frequently prescribed medications, estimated to account for approx. 10% of annual prescribing costs in Europe and the United States [12]. Another issue leading to their overuse is their over-the-counter availability (OTC). In recent years a body of evidence on the adverse effects off PPIs was documented, and it seems clear that their inappropriate use can result in increasing healthcare costs, morbidity, and even mortality [13]. There are several well-documented risks of long-term use of PPIs including *Clostridium difficile*-associated diarrhoea, pneumonia, reduced bone density, malabsorption of iron, nutrients, and vitamins, acute interstitial nephritis, and dementia [14].

In this paper we focus on the commonly forgotten deleterious influence of long-term PPI use on the balance of magnesium and other electrolytes. Although the incidence of hypomagnesaemia in PPI users is not sufficiently studied because magnesium levels are not routinely checked in patients either hospitalised or seen at out-patient units [15], at least 5 large meta-analyses have demonstrated a significant increase in the risk of hypomagnesaemia in long-term PPI-users [16–20]. Based on those studies, PPI-associated hypomagnesaemia is a class effect because it has been reported in patients using different agents, substitution of one PPI by another led to recurrence [4], and the incidence of hypomagnesaemia increases with long duration of the treatment. According to those studies, hypomagnesaemia is present in about 20% of PPI users *vs*. approx. 13% in non-users. Nevertheless based on reviewal of the reports from the Adverse Event Reporting System (AERS) and case studies reported in the medical literature, in 2011 the US Food and Drug Administration (FDA) issued an announcement recommending measurement of serum magnesium levels prior to initiation of prescription PPI treatment in patients expected to be on these drugs for a longer time, as well as in patients who take PPIs with medications such as digoxin, diuretics, or drugs that may cause hypomagnesaemia [21].

Long-term use of PPI and electrolyte imbalance

The first report on PPI-mediated hypomagnesaemia published by Epstein et al. [22] described 2 patients on long-term omeprazole treatment, who were admitted to the hospital due to carpopedal spasm, severe hypomagnesaemia with avid Mg^{2+} retention, and hypocalcaemia with supressed PTH levels. The levels of magnesium in serum and urine normalised after omeprazole discontinuation and remained within normal range without supplementation. Over the years similar cases were reported by Kuipers et al. [23], Druce et al. [24], Shabajee et al. [25], and Cundy et al. [26] and were elegantly summarized by Florentin et al. [4]. An interesting case was presented by Semb et al., which reported a PPI-dependent patient due to severe reflux that consequently needed weekly intravenous magnesium infusions and in whom no further supplementation was needed following laparoscopic fundoplication [27]. In all the analysed cases urinary magnesium was low, and gastrointestinal investigations identified no structural cause of hypomagnesaemia or malabsorption syndromes including sprue.

The role of magnesium in regulating electrolyte balance

The state of profound hypomagnesaemia poses substantial risks *per se*, but it has to be kept in mind that low magnesium levels are accompanied by other abnormalities in electrolyte balance, i.e. secondary hypocalcaemia and hypokalaemia. The impact of Mg^{2+}

on calcium metabolism is complex [28]. The release of PTH that governs calcium balance is regulated by calcium-sensing receptor (CaSR), a G-protein coupled receptor stimulated by extracellular cations, i.e. calcium and magnesium, but also other physiological cations (e.g. spermine, beta-amyloid, cationic amino acids) and pharmacological agents (e.g. aminoglycosides), which results in conformational changes in the receptor leading to initiation of phospholipase C pathway. The latter increases intracellular calcium levels that in turn inhibit exocytosis of PTH by blocking exocytic vesicles. In contrast, hypocalcaemia and hypomagnesaemia in physiological conditions result in a lack of CaSR stimulation and activate the release of PTH from storage vesicles. However, this is only valid for a reduction in magnesium serum levels down to 0.5 mM, as a more severe hypomagnesaemia results in a paradoxical block of PTH secretion and consequently to hypocalcaemia that is resistant to calcium substitution. Moreover, calcium levels can be restored by substitution of magnesium alone [28], and this effect is immediate, i.e. serum PTH increases within minutes after magnesium application. The mechanism of inhibition of PTH secretion by very low magnesium levels has been extensively studied and has been proven not to rely on the extracellular binding of Mg^{2+} to CaSR, because the receptor mutants with altered (both decreased and increased) activity were equally sensitive to low magnesium [29]. In contrast, as shown in experimental models, the PTH response to hypomagnesaemia requires intact CaSR constitutive activity and relies on the interaction between CaSR and its coupled G-protein [29]. Magnesium ions have a well characterised binding site at the Gα-subunits [30] of various G-proteins. Their binding suppresses the release of GDP leading to inhibition of Gα-subunits. Thereby low intracellular magnesium disinhibits Gα-subunits that mimics the activation of the CaR, consequently causing arrest of PTH secretion [29]. To sum up, both very low as well as high serum magnesium levels block PTH release and diminishes serum calcium levels by 2 different mechanisms: a) by activating Gα-subunits when Mg^{2+} concentration is below 0.5 mM and b) by directly activating CaSR when Mg^{2+} concentrations exceed 1 mM. Secondary to hypomagnesaemia, PTH/PTHrP receptor resistance to PTH is another mechanism leading to hypocalcaemia. The underlying cause of this phenomenon is the decrease in the intracellular magnesium concentration resulting in abnormal activity of adenylate cyclase, of which magnesium is an important cofactor [31].

Another clinical feature frequently encountered in patients with severe hypomagnesaemia is hypokalaemia. Approx. 50% of patients with hypomagnesaemia have hypokalaemia, and inversely around 50% of patients with clinically significant hypokalaemia have concomitant magnesium deficiency [32]. Secondary hypokalaemia refractory to potassium supplementation in individuals with very low magnesium levels is a consequence of disinhibition of the renal outer medullary potassium channel (ROMK) [33]. ROMK is an inward-rectifying K^+ channel responsible for basal K^+ secretion in the distal part of nephron. Its activity is blocked by magnesium ions and the concentration inhibiting ROMK varies depending on the membrane voltage and the extracellular concentration of K^+. Renin–angiotensin–aldosterone axis is also involved [34, 35].

Magnesium metabolism

Magnesium metabolisms is tightly regulated through intestinal and renal absorption and excretion. The average daily intake of Mg^{2+} amounts to approx. 360 mg, while approx. 100 mg of magnesium is ultimately absorbed through the intestine. Because magnesium stored in the skeleton cannot be quickly mobilised, kidneys control the magnesium balance by controlling its urinary reabsorption.

Magnesium absorption in the intestine

Magnesium is absorbed in the intestine via 2 independent mechanisms. The first one — a passive non-saturable paracellular diffusion between the enterocytes of the small intestine — accounts for around 90% of Mg^{2+} absorption, and it increases linearly along with magnesium uptake. The driving force behind passive Mg^{2+} absorption is the high luminal Mg^{2+} concentration. The functioning of the paracellular passive pathway is intermediated by the composition of the tight junction (claudins) [36]. Distal jejunum and ileum are the most permeable towards magnesium cations [37]. The presence of claudin proteins at the tight junctions has been suggested to facilitate Mg^{2+} transport by removing the hydration shell [37].

Another 10% of magnesium ions are absorbed via the transcellular active transport mechanism relying on the expression of transient receptor potential melastatin (TRPM) cation channels — TRPM6 and TRPM7 — that transport magnesium and calcium ions into the cell using the transmembrane electrochemical gradient. The main player in providing intestinal magnesium absorption seems to be TRPM6, which, besides its expression in the gastrointestinal tract, is expressed in kidney, testis, and lungs, whereas TRMP7 is ubiquitously expressed [38]. Importantly, the active transport system guarantees increased magnesium reabsorption at low magnesium intake [38] (Fig. 1).

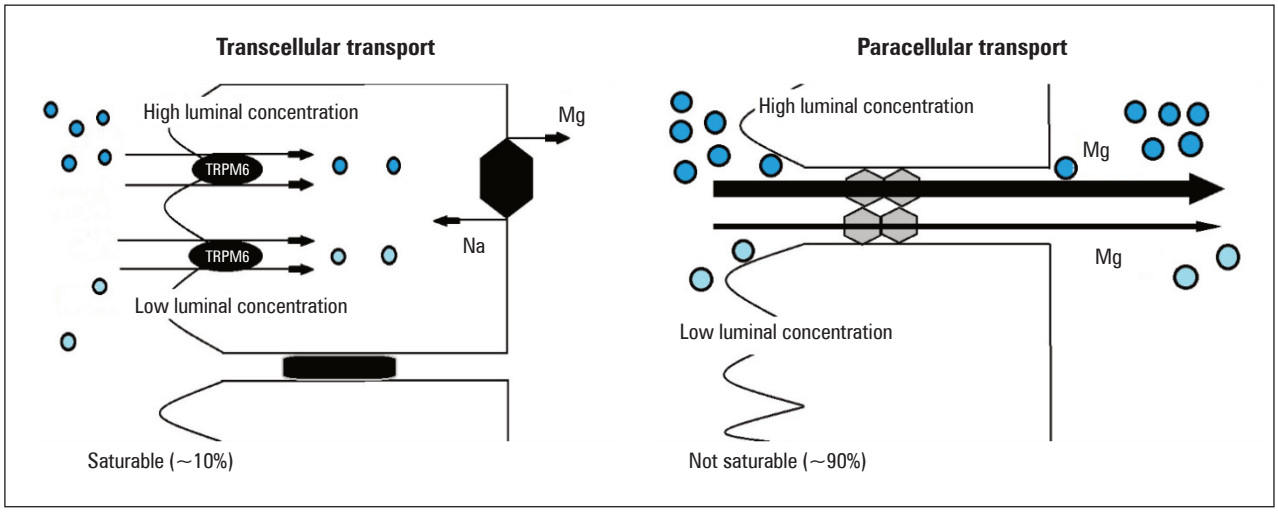

Figure 1. *Mechanisms of active (left) and passive (right) transport of magnesium (Mg) in intestine. TRPM6 — transient receptor potential melastatin type 6; Na — sodium*

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Magnesium reabsorption in the kidney

Magnesium reabsorption in the kidney is regulated in similar mechanisms partially involving the same players as in the intestinal absorption. Approx. 95% of filtered magnesium is collectively reabsorbed in the nephron. Contrary to other cations, which are rather reabsorbed in the proximal tube (PT), which is responsible for only 15–20% of magnesium handling, magnesium ions are most predominantly reabsorbed in the thick ascending limb (TAL), responsible for 65–70% of filtered load. However, it is the distal convoluted tubule (DCT) reabsorbing only a tiny amount (3–7%) of Mg^{2+} that is responsible for controlling magnesium homeostasis [39]. The reabsorption of magnesium in PT is passive, linear, and unsaturable over a wide range of Mg luminal concentrations and is probably driven through claudin-2 [39]. In the TAL magnesium ions are reabsorbed in a paracellular way driven by electrochemical voltage involving the presence of claudin-16 and claudin-19, a tight junction protein. In fact, mutations in the *CLDN16* gene, encoding claudin-16, cause the rare autosomal recessive disease familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC), due to renal Mg^{2+} and Ca^{2+} wasting. Similar syndromes (plus additional severe visual impairment) are caused by mutations in CLDN19, encoding claudin-19. It has been demonstrated that claudin-16 and claudin-19 directly interact with each other, and disease-causing mutations can disrupt these interactions, so the presence of both of them is crucial for magnesium reabsorption [40]. The next step in magnesium reabsorption is the active transport mechanism that occurs in DCT, where it is determined by the already presented TRPM6 protein. The functioning of TRPM6-dependent reabsorption is crucial for maintaining magnesium homeostasis, because inactivating mutations including stop mutations, frame-shift mutations, splice-site mutations, and exon deletions were shown to cause life-threatening hypomagnesaemia with secondary hypocalcaemia [34, 38] (Fig. 2) The surface expression of TRPM6 is maximised by the presence of its partner protein TRPM7. Another factor crucial for TRPM6 functioning is the activity of NaCl cotransporter (NCC) in the DCT, because the inactivating mutations in SLC12A3 gene (encoding NCC) in Gitelman syndrome or abrogation of its activity by thiazide diuretics lead to renal magnesium wasting. Most probably low or absent NCC leads to lower TRPM6 expression by causing DCT atrophy [39].

Finally, EGFR activation is crucial for TRPM6-mediated Mg^{2+} reabsorption. In particular, EGFR stimulation have been shown to increase the expression of TRMP6 by increasing its distribution to transport vesicles [41], and by increasing TRPM6 transcription. Mutations in pro-EGF cause isolated recessive renal hypomagnesaemia (IRH), a rare disorder characterised by low serum Mg^{2+} levels and mental retardation [42]. Moreover, a metanalysis of the tumour patients treated with anti-EGFR monoclonal antibodies (cetuximab, panitumumab) revealed a substantial increase in the risk (with overall RR amounting to 5.83) of hypomagnesaemia due to excessive renal loss [43]. However, a recent *in vitro* study suggested that EGFR-blocking immunotherapy may also affect the absorption of magnesium cations in the intestine [35]. Several other factors affecting renal magnesium reabsorption have been elegantly reviewed by Ellison et al. [39]. Among them are some widely used drugs, e.g. cisplatin, cyclosporin,

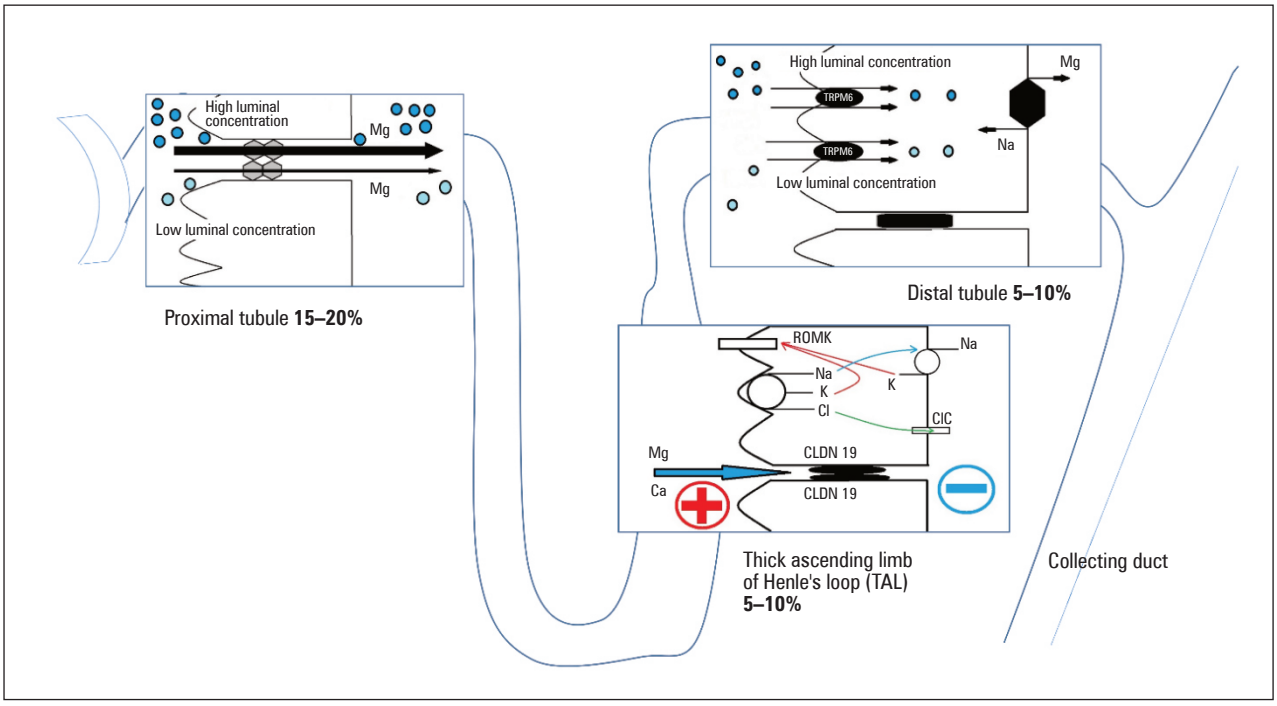

Figure 2. *Mechanisms of magnesium (Mg) reabsorption in the nephron. TRPM6 — transient receptor potential melastatin type 6; Na — sodium; ROMK — renal outer medullary potassium channel; K — potassium; Cl — chloride; Ca — calcium; ClC — chloride channels; CLDN19 — claudin 19*

or tacrolimus, that have been shown to decrease TRPM6 transcription.

Mechanism of PPI-induced hypomagnesaemia

The presented reports shed some light on the possible mechanism of hypomagnesaemia following PPI use. As demonstrated in the cited case reports, PPI users showed low urinary magnesium levels, suggesting avid magnesium retention, so the mechanism of PPI-induced hypomagnesaemia probably relies on the impairment of intestinal magnesium absorption [4]. Given the fact that high doses of oral/intravenous magnesium supplementation were able to increase magnesium serum levels, it seems that PPI treatment does not significantly impair the mechanisms of passive Mg^{2+} absorption but rather impede the functioning the active transport via TRPM channels [4, 44, 45].

To understand the effect of PPIs on TRPM-induced magnesium absorption it is crucial to investigate the effect of PPI administration on the pH in the intestine. In a small study on 20 healthy individuals in whom 40 mg of esomeprazole was administered twice daily, a reduction of luminal pH by 0.5 units, equivalent to a 3-fold increase in proton concentration throughout the mid to distal intestine, has been observed [46]. In physiological conditions the alkaline pH in the intestine is guaranteed by the secretion of bicarbonate that is secreted along with digestive enzymes by the pancreas. The secretion of bicarbonate relies on the presence of $H^+/HCO3^-$ transporters along the pancreatin duct epithelium, and that the function of these transporters is dependent on gradients created by the Na^+/K^+-ATPase. However, as demonstrated by a study using rat pancreatic ducts, the latter are also reached in functional H^+-K^+-ATPases that significantly contribute to ductal bicarbonate secretion [47]. Moreover, these hydrogen-potassium pumps are inhibited by PPI, as demonstrated by the use of omeprazole [47], which results in a decrease in intestinal pH.

So how exactly does proton excess affect the function of TRPM6/7? As mentioned before, TRPM 6 and 7 confer a unique feature of permeability to divalent Ca^{2+} and Mg^{2+}, which is determined by well-defined, negatively charged residues (namely glutamic acid E^{1024} aspartic acid D^{1031}) within the channel pore [48, 49]. It has been suggested that proton excess decreases the functionality of TRPM6 by destabilising its structure [48]. Interestingly, short-term administration of omeprazole to C57BL/6J mice significantly increased TRPM6 mRNA expression in colon cells, suggesting a compensatory mechanism induced by reduced currents through TRPM6 [50].

However, given the fact that hypomagnesaemia is not presented by the majority of PPI long-term uses, probably additional players predispose certain individuals to decrease in Mg^{2+} serum levels. Some

probable players contributing to lowering of magnesium levels include mutations in one of the identified determinants of TRMP6 permeability E^{1024} or D^{1031}. Moreover, it has been demonstrated that a single amino acid substitution in I^{1030} decreases the diameter of the pore of the TRPM6 channel [48]. Also, since TRPM6 localisation in the membrane has been demonstrated to rely on the presence of TRPM7, with which it hetero-oligomerises, and a S141L missense mutation in TRPM6 causing a disruption of the complex has been shown to cause hypomagnesaemia with secondary hypocalcaemia [34, 51]. Therefore, it seems plausible that mutations or factors regulating the expression or localisation of the partner protein TRPM7 may have consequences on magnesium disorders. Because some of the widely used drugs have already been shown to regulate TRPM6 expression, it seems probable that concurrent use of prescribed medications, OTC drugs, and even diet supplements need to be taken into account as factors contributing to hypomagnesaemia.

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Conclusions

PPI inhibitors are one of the most commonly used drugs. However, their prolonged use can lead to profound and potentially life-threatening electrolyte imbalances. Moreover, the alterations in electrolytes following PPI use can mimic hypoparathyroidism, a condition with important clinical consequences [52]. Therefore, understanding of the mechanisms of PPI-induced electrolyte disturbances, active monitoring, and adequate supplementation of electrolytes in PPI-treated patients and switching to H2-inhibitors in selected patients are crucial.

Author contributions

M.B. played the main role in the preparation of the paper, J.P. was involved in the manuscript preparation, and M.P. provided expert guidance and was involved in the manuscript preparation.

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Conflict of interest

Authors declare no conflict of interests.

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