



International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

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Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE

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CURRENT EVIDENCE ON MECHANISMS, RISK FACTORS,
DIAGNOSIS AND CLINICAL MANAGEMENT

DOI

[https://doi.org/10.31435/ijitss.3\(51\).2026.6661](https://doi.org/10.31435/ijitss.3(51).2026.6661)

RECEIVED

01 August 2026

ACCEPTED

22 September 2026

PUBLISHED

28 September 2026

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PROTON PUMP INHIBITOR-INDUCED HYPOMAGNESEMIA: CURRENT EVIDENCE ON MECHANISMS, RISK FACTORS, DIAGNOSIS AND CLINICAL MANAGEMENT

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ABSTRACT

Objective: Proton pump inhibitors (PPIs) are a group of medicines most commonly used to inhibit gastric acid secretion. Long-term treatment may lead to the development of hypomagnesemia. The aim of this review was to summarise the current evidence on proton pump inhibitor-induced hypomagnesemia (PPIH), focusing on its pathophysiological mechanisms, risk factors, clinical presentation, diagnosis and management.

Methods: A narrative review was conducted of English-language literature published between 2002 and 2026, retrieved from the PubMed/MEDLINE database between June and August 2026.

Results: The data reported in the literature indicate a link between the use of PPIs and an increased risk of hypomagnesemia. However, there is considerable heterogeneity amongst the studies, which makes it impossible to determine the exact extent of this risk. Reduced intestinal absorption of magnesium is considered the most likely mechanism underlying PPI-induced hypomagnesemia (PPIH). This is thought to be associated, amongst other things, with changes in pH and disturbances in magnesium transport across the intestinal epithelium. The risk depends on the dose and duration of PPI use, as well as on the presence of other factors affecting magnesium homeostasis. Clinically, PPI-induced hypomagnesemia (PPIH) may be asymptomatic or may cause neuromuscular, neurological and cardiovascular disorders, as well as leading to hypokalemia and hypocalcemia.

Conclusions: To diagnose PPI-induced hypomagnesemia (PPIH), it is necessary to consider exposure to PPIs and to rule out other causes of magnesium deficiency. Management involves correcting the Mg^{2+} deficiency and assessing whether continued PPI therapy is appropriate. Further prospective studies are needed to better identify at-risk groups and determine the optimal strategies for monitoring magnesium levels in patients on long-term PPI therapy.

KEYWORDS

Proton Pump Inhibitors, Hypomagnesemia, Magnesium, Magnesium Homeostasis, Magnesium Deficiency

CITATION

Sadowska, J., Strzelecka, K., d'Obyrn, Z., Pływak, E. W., Polar, W. P., Kamińska, J., Jagodzińska, E., Stawicka, M., & Szemberg, A. (2026). Proton pump inhibitor-induced hypomagnesemia: Current evidence on mechanisms, risk factors, diagnosis and clinical management. *International Journal of Innovative Technologies in Social Science*, 3(51). [https://doi.org/10.31435/ijitss.3\(51\).2026.6661](https://doi.org/10.31435/ijitss.3(51).2026.6661)

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1. Introduction

1.1 Proton pump inhibitors

Among the drugs that reduce gastric acid secretion, proton pump inhibitors (PPIs) are particularly widely used [1,2]. Their mechanism of action is based on the irreversible inhibition of the $H^+/K^+-ATPase$, located in the parietal cells of the stomach. This results in the inhibition of the final stage of hydrogen ion secretion into the gastric lumen [1,3,4]. Consequently, PPIs lead to a strong and long-lasting inhibition of hydrochloric acid secretion and an increase in the pH of gastric contents. They are more effective than another class of drugs used for similar indications, namely H_2 receptor antagonists [2,4]. The main conditions for which PPIs are used include gastric and duodenal ulcers and gastroesophageal reflux disease. In addition, these medications are prescribed for the eradication of *Helicobacter pylori* as part of combination therapy, as well as for gastroprotection in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) who are at increased risk of gastrointestinal complications [2,3]. There are also indications for the long-term use of PPIs. Among these, particular attention should be paid to severe erosive esophagitis, Barrett's esophagus, and Zollinger-Ellison syndrome [1,2]. PPIs are a class of drugs that are widely used around the world due to their high efficacy and good tolerability [1,2]. A significant problem remains the unjustified prolongation of therapy and its use without clear indications [2,3]. Long-term PPI therapy may cause a range of disorders, such as disturbances in trace element metabolism, gastrointestinal infections, renal dysfunction or fractures. It should be emphasized, however, that a causal relationship has not yet been established for some of these associations [1,2]. Among the conditions mentioned above, hypomagnesemia caused by chronic PPI use has been extensively described. Due to the fact that hypomagnesemia can lead to serious clinical complications, special attention should be paid to it [1,3,4].

1.2 Magnesium homeostasis

Magnesium is the second most abundant intracellular cation and plays a key role in numerous physiological processes occurring in the human body. The most important functions of magnesium include, amongst others, its involvement in energy metabolism and enzymatic reactions, as well as the regulation of ion channels, cell membrane function, and the metabolism of nucleic acids and proteins [5]. The majority of the body's magnesium reserves are found in bones, muscles and other soft tissues, whilst approximately 1 per cent is located in the extracellular space. For this reason, the use of serum magnesium concentration as a diagnostic parameter remains severely limited. Despite its widespread use, it does not always correlate with the body's actual magnesium stores [5,6]. The gastrointestinal tract and the kidneys are jointly responsible for maintaining Mg^{2+} homeostasis. The absorption of dietary magnesium takes place in the intestines via passive paracellular transport as well as active transmembrane transport. In the latter, the TRPM6 and TRPM7 channels play a key role [7,8]. The kidneys regulate Mg^{2+} excretion according to the body's needs by reabsorbing most of the magnesium filtered in the glomeruli in the distal tubule. In this section of the nephron, magnesium transport also depends on TRPM6 and TRPM7 [7,8]. Clinically adequate magnesium levels are essential for the proper functioning of the neuromuscular and cardiovascular systems, as they influence neuromuscular excitability, muscle function and the electrical stability of the heart [6,9]. Consequently, symptoms associated with magnesium deficiency include, amongst others, weakness, cramps, muscle tremors, tetany, convulsions and cardiac arrhythmias [7,9]. Hypomagnesemia is defined as a reduced serum magnesium concentration. However, the cut-off values described in the literature are not consistent with one another. It is worth noting that a normal serum magnesium concentration does not indicate normal total magnesium stores in the body [5,6].

1.3 PPI induced hypomagnesemia

The first reports on the association between proton pump inhibitor use and hypomagnesemia date from 2006 and concerned patients on long-term omeprazole therapy. This was followed by case reports and observational studies demonstrating a link between PPI exposure and reduced serum magnesium levels [10,11,12]. The fact that Mg^{2+} levels returned to normal following discontinuation of PPIs, as well as the recurrence of hypomagnesemia upon resumption of therapy, was consistently observed across clinical observations, supporting the notion that this condition is associated with the entire class of these drugs [10,12,13]. The evidence presented in the literature unequivocally identifies reduced magnesium absorption in the gastrointestinal tract as the main cause of PPI-induced hypomagnesemia. Furthermore, low urinary magnesium excretion has been observed in patients with PPIH (proton pump induced hypomagnesemia), which indicates adequate renal regulation and confirms that the cause of hypomagnesemia is not excessive loss via the kidneys, but rather reduced intestinal absorption of magnesium [11,12,13]. This chronic condition results in a progressive depletion of the body's magnesium stores and ultimately leads to clinically manifested hypomagnesemia. Reports on the mechanism underlying this disorder include both dysfunction of the TRPM6/7 channels responsible for the active transport of Mg^{2+} and impaired paracellular transport of magnesium [11,12,13]. The clinical presentation of PPIH is highly variable. In many cases, the condition is asymptomatic, but it can also cause muscle weakness, muscle cramps and paraesthesia. Severe magnesium deficiency, on the other hand, can cause tetany, convulsions and potentially life-threatening cardiac arrhythmias [10,11,13]. Furthermore, hypomagnesemia may be accompanied by secondary electrolyte disturbances such as hypokalemia and hypocalcemia, which further increase the risk of complications [11,13]. The link between the observed symptoms and the use of PPIs is sometimes recognised with a delay. This is because the symptoms of hypomagnesemia are non-specific and magnesium deficiency develops gradually over many years of drug therapy. Furthermore, normal serum magnesium concentrations do not always reflect the body's total magnesium stores [10,12].

1.4 Research problem, rationale and objective

The association between the use of proton pump inhibitors and hypomagnesemia has already been the subject of systematic reviews and meta-analyses [14,15]. The findings presented in these studies indicate an increased risk of hypomagnesemia in people taking PPIs. However, the wide variety of available studies limits a definitive assessment of the magnitude of this risk. Differences relate, amongst other factors, to the study populations, the threshold values for magnesium concentration adopted, the type and dose of PPIs used, and the duration of treatment [14,15]. Subsequent publications have also analysed in greater detail the mechanisms responsible for the development of hypomagnesemia associated with PPI use. These have focused on changes

in intestinal Mg^{2+} absorption and on the potential role of TRPM6/TRPM7 channels [12,13]. Despite progress in understanding the pathophysiology of this disorder, not all mechanisms have yet been fully elucidated. Key clinical issues remain the identification of factors that increase the risk of hypomagnesemia and the guidelines for monitoring magnesium levels in patients taking PPIs [12,13]. The aim of this review is to summarise the current evidence on proton pump inhibitor-induced hypomagnesemia, with particular emphasis on its pathophysiological mechanisms, risk factors, clinical symptoms, diagnosis and management.

2. Methodology

2.1 Study design and scope

The following paper is a narrative review of the literature on hypomagnesemia associated with the use of proton pump inhibitors (PPIs). The review included data on the association between PPI use and hypomagnesemia, its pathophysiological mechanisms, risk factors, clinical presentation, diagnosis and management. The review was based on human studies, whilst experimental data were included selectively to elucidate the potential mechanisms leading to PPI-induced hypomagnesemia.

2.2 Literature search strategy

The literature review was conducted in the PubMed/MEDLINE database between June and August 2026. The search terms used were as follows: “proton pump inhibitors” AND “hypomagnesemia” and “proton pump inhibitors” AND “magnesium”. In order to identify publications concerning specific aspects of PPIH, the search was expanded to include terms relating to mechanisms, risk factors, clinical presentation, diagnosis, treatment and monitoring, including “TRPM6”, “TRPM7”, “risk factors”, “clinical manifestations”, “diagnosis”, “treatment” and “monitoring”. The publications included in the review were published between 2002 and 2026.

2.3 Eligibility criteria

Peer-reviewed English-language publications on PPIH were considered, including observational studies, systematic reviews, meta-analyses and relevant narrative reviews. Individual case reports and case series were included where they provided clinical information, whilst experimental studies were used to elucidate the potential mechanisms of PPIH. Publications not directly related to the scope of the review, duplicates and non-peer-reviewed material were excluded.

2.4 Study selection and data synthesis

The publications were analysed in terms of study design, study population, exposure to PPIs, data on hypomagnesemia, risk factors and key clinical outcomes. Given the heterogeneity of the available studies, the results were subjected to a narrative synthesis, without conducting a meta-analysis of our own.

3. Results

3.1 Evidence linking PPI use to hypomagnesemia

The first case reports linking the use of proton pump inhibitors (PPIs) to hypomagnesemia date back to 2006. A series of four cases described by Hoorn et al. showed that patients taking various PPIs for periods ranging from one year to 13 years developed severe hypomagnesemia. The existence of a correlation between PPI use and hypomagnesemia was further supported by the fact that magnesium levels returned to normal following discontinuation of PPIs, and that the condition occurred with the use of various PPI medications [16]. Hess et al. conducted a systematic review compiling early observations, and an analysis of the available case reports demonstrated the occurrence of hypomagnesemia following PPI exposure lasting from 2 weeks to 13 years, with a median of 5½ years. The link between PPIs and hypomagnesemia was also supported by the rapid improvement following discontinuation of PPI treatment and the recurrence of hypomagnesemia upon reintroduction of PPIs into the treatment regimen. The median time from both the initiation and discontinuation of PPI treatment to the onset of effects was four days in both cases [10]. Subsequent observational studies made it possible to assess this association in larger populations. However, the conclusions were not unequivocal. In their paper, William and Danziger emphasise that studies on both outpatients and inpatients confirm an association between PPI use and hypomagnesemia. However, they also point out that there is a lack

of controlled prospective studies that would confirm a cause-and-effect relationship [12]. The study by Kim et al. is an example of this ambiguity. In this study, after matching the groups, no significant difference in magnesium concentration was observed between the group taking PPIs and those not taking these drugs (0.85 vs 0.86 mM; $p=0.297$). At the same time, in individuals undergoing long-term PPI treatment lasting over a year, this was independently associated with the development of hypomagnesemia [17]. In a study involving 689 kidney transplant recipients, the use of PPIs resulted in approximately a two-fold increase in the likelihood of hypomagnesemia (OR 2.12; 95% CI 1.43–3.15), and after adjusting for potential confounding factors, the association persisted (OR 2.00; 95% CI 1.21–3.31) [18]. Systematic reviews and meta-analyses of observational studies have provided further information enabling a more comprehensive assessment of this association. Park et al. conducted a meta-analysis which demonstrated an increased risk of hypomagnesemia in individuals taking PPIs (OR 1.78; 95% CI 1.08–2.92), although the results showed considerable variability [20]. Subsequently, a meta-analysis by Srinutt et al., comprising 16 studies involving a total of 131,507 participants, indicated a significant association between the two variables - the adjusted OR was 1.71 (95% CI 1.33–2.19), with heterogeneity of $I^2 = 88\%$ [14]. In contrast, the analysis by Liao et al., which included 15 studies and 129,347 participants, showed an increased risk of hypomagnesemia (RR 1.44; 95% CI 1.13–1.76), but also significant heterogeneity ($I^2 = 85.2\%$). Importantly, in some of the subgroup analyses, the association did not reach statistical significance [15]. Given the available data, they suggest a link between the use of proton pump inhibitors and an increased risk of hypomagnesemia. However, it remains difficult to determine the exact magnitude of this association. Interpreting the strength of this cause-and-effect relationship is difficult due to the considerable heterogeneity of the studies, differences in the study populations and definitions of hypomagnesemia, and the observational nature of the available studies [12, 14, 15].

3.2 Mechanisms of PPI-Induced hypomagnesemia

The correct concentration of magnesium in the human body is maintained in balance by dietary intake, absorption in the gastrointestinal tract and excretion via the kidneys. Approximately one-third of the magnesium consumed is absorbed in the small intestine of a healthy person, whilst the kidneys are responsible for excreting the appropriate amount from the body [19,20]. Magnesium absorption by the intestines occurs via two pathways: active and passive. Passive transport, or paracellular transport, occurs mainly in the small intestine and depends on the concentration of magnesium ions in the intestinal lumen and the permeability of the tight junctions between enterocytes. Active transport, that is, transmembrane transport, takes place mainly in the distal part of the gut, particularly in the large intestine, where the TRPM6 and TRPM7 channels are involved in magnesium transport [20,21,22]. The importance of the TRPM6 channel in magnesium homeostasis has been confirmed by genetic studies. Mutations in the TRPM6 gene lead to severe hypomagnesemia and, consequently, hypocalcemia, which confirms the importance of this channel for the active transport of Mg^{2+} in the gut. TRPM6 and TRPM7 show a high degree of similarity [23]. The most likely mechanism leading to PPI-induced hypomagnesemia is impaired magnesium absorption in the gut, rather than excessive loss via the kidneys. PPIs work by increasing the pH in the upper gastrointestinal tract, which may reduce the solubility of magnesium ions and decrease the amount available for absorption. At a higher pH, magnesium binds more readily to anions, such as phosphates, resulting in a reduction in the amount of magnesium available for transport [21]. However, the action of PPIs may affect both pathways of magnesium ion transport in the gut. In the small intestine, omeprazole may adversely affect paracellular transport by reducing the permeability of tight junctions and altering the expression of transmembrane proteins called claudins. In the large intestine, TRPM6/7 activity may be reduced at higher pH levels, as these channels are more active in an acidic environment [21]. The mechanisms described suggest that PPIs may both reduce the availability of Mg^{2+} in the intestinal lumen and limit its transport across the intestinal epithelium [21]. The influence of the gut microenvironment is increasingly being taken into account. PPIs affect the composition and diversity of the gut microbiota and, consequently, bacterial fermentation, pH, and magnesium solubility. This mechanism is not as well established as the direct effect of PPIs on pH and intestinal transport. Therefore, further research into its effects is needed [21]. A key argument in favour of the intestinal mechanism of PPIs is the fact that urinary magnesium excretion is reduced. A study by William et al. showed that individuals taking PPIs excrete less magnesium in a 24-hour urine collection than those not exposed to PPIs, and this relationship remained unchanged after adjusting for potential confounding factors [24]. When magnesium absorption from the gut is reduced, the kidneys decrease its excretion in an attempt to maintain homeostasis. This can be interpreted as renal compensation. [20,21,24].

3.3 Risk factors

The risk of hypomagnesemia in patients taking proton pump inhibitors is influenced by the characteristics of the treatment, as well as by patient-related factors. The most commonly analysed parameters include the PPI dose and the duration of treatment. Chronic exposure to PPIs has been associated with an increased risk of hypomagnesemia, whilst the duration of treatment preceding its onset has varied across numerous studies [5,14,17]. Kim et al. demonstrated that taking PPIs for longer than one year was independently associated with the onset of hypomagnesemia (OR 5.39; 95% CI 1.06–27.49) [17]. The literature suggests a possible association between PPI dose and the risk of hypomagnesemia [5,14,18]. According to a meta-analysis of observational studies, the use of high-dose PPIs was associated with a higher likelihood of hypomagnesemia compared with low doses (adjusted OR 2.13; 95% CI 1.26–3.59) [14]. A similar pattern was observed in kidney transplant recipients. In the analysed group, the risk was highest in patients receiving more than 20 mg of omeprazole equivalent per day (adjusted OR 2.46; 95% CI 1.32–4.57), and an increase in PPI dose was associated with a significant increase in the risk of hypomagnesemia [18]. The use of other medicines that affect magnesium metabolism at the same time as PPIs may be an additional factor influencing the risk of hypomagnesemia. Diuretics have been identified as one of the medicines that may increase susceptibility to hypomagnesemia. It should be noted, however, that the results of studies in this area are not entirely consistent [5,14]. Kim et al. showed that patients with hypomagnesemia were more likely to be taking diuretics. However, after adjusting for other variables, this was not found to be an independent risk factor (OR 1.77; 95% CI 0.57–5.46) [17]. Similarly, in kidney transplant recipients, it has not been demonstrated that the concomitant use of PPIs and loop or thiazide diuretics significantly alters the risk of hypomagnesemia [18]. The use of other medicines that may increase magnesium loss is also a significant factor. It has been shown that the use of platinum-based drugs is strongly associated with the occurrence of hypomagnesemia in patients treated with PPIs (OR 13.40; 95% CI 2.07–86.95). However, the wide confidence interval suggests that the accuracy of this estimate is limited [17]. In a group of post-transplant patients, PPI treatment remained associated with the occurrence of hypomagnesemia even after taking into account immunosuppressive therapy with tacrolimus and cyclosporine [18]. The impact of age on the development of hypomagnesemia remains inconclusive. Although older age is usually associated with higher morbidity and a greater number of medications taken, the analysed data do not allow this to be considered an independent risk factor for PPI-associated hypomagnesemia. Kim et al. observed contrasting results, where age under 45 years was found to be independently associated with the occurrence of hypomagnesemia (OR 4.71; 95% CI 1.52–14.57). However, it should be noted that the result of this study may have been influenced by the small sample size [17]. Both renal function and comorbidities may independently influence magnesium metabolism, making them important factors in the assessment of this association. In the population of kidney transplant recipients, the association between PPI use and hypomagnesemia persisted after adjustment for eGFR, proteinuria, diabetes, cardiovascular disease, medication use and dietary magnesium intake (OR 2.00; 95% CI 1.21–3.31) [18]. There are no data to suggest a significant interaction between PPI use and diabetes [18]. It is not possible to state definitively that a particular PPI is associated with a higher risk than others. Hypomagnesemia has been observed with various PPIs, suggesting that the effect applies to the entire class of drugs rather than to a specific preparation [5,21].

3.4 Clinical manifestations

Hypomagnesemia associated with PPI use is characterised by a wide range of clinical symptoms. Its clinical presentation depends mainly on the severity and duration of the magnesium deficiency. A mild magnesium deficiency may cause no clinical symptoms or lead to non-specific complaints, such as weakness and fatigue. However, a gradual depletion of magnesium stores in the body increases the risk of symptoms affecting the neuromuscular and cardiovascular systems [13,25,26]. The most commonly reported neuromuscular symptoms include muscle spasms, tremors, paraesthesia and muscle weakness, as well as increased neuromuscular excitability. In cases of severe magnesium deficiency, symptoms such as carpopedal cramps, tetany, ataxia and convulsions may occur [13,25,26]. In a series of clinical cases described by Toh et al., the predominant symptoms in patients were muscle weakness, muscle cramps and lethargy [13]. Souza et al. observed upper limb tremors, muscle weakness and two generalised tonic-clonic seizures in one female patient, which resolved after the electrolyte imbalances were corrected [25]. Complications of hypomagnesemia also include cardiovascular disorders. Various electrocardiographic abnormalities have been described in the literature, such as QT interval prolongation, the presence of U waves, ST-segment depression and premature beats [16]. In addition, cardiac arrhythmias have also been observed, including atrial and

ventricular tachyarrhythmias. Magnesium deficiency affects the electrical stability of the myocardium. Consequently, a significant reduction in its concentration increases the risk of developing arrhythmias [25,26]. A significant clinical manifestation of magnesium deficiency is the associated electrolyte disturbances, primarily hypokalemia and hypocalcemia [13,16,25]. The mechanism underlying the development of hypokalemia in the context of hypomagnesemia is partly due to increased renal potassium loss. Physiologically, intracellular Mg^{2+} concentrations inhibit the activity of renal ROMK channels. Magnesium deficiency weakens this inhibitory effect, thereby increasing the secretion of potassium into the tubular lumen, which in turn leads to kaliuresis [16,25]. This mechanism explains why simultaneous magnesium replacement plays a key role in correcting hypokalemia associated with hypomagnesemia [26]. Hypocalcemia associated with hypomagnesemia develops mainly as a result of impaired secretion and action of parathyroid hormone. A significant magnesium deficiency can lead to a reduction in parathyroid hormone (PTH) release from the parathyroid glands and cause tissue resistance to its action. Consequently, functional hypoparathyroidism occurs [13,25,26]. Furthermore, Mg^{2+} deficiency may impair calcitriol synthesis, which also contributes to the development of hypocalcemia [25]. The clinical consequences of the co-occurrence of hypomagnesemia, hypokalemia and hypocalcemia mainly include increased neuromuscular excitability and an increased risk of cardiac arrhythmias [13,25,26]. The full clinical picture of PPI-induced hypomagnesemia ranges from an asymptomatic condition, detected incidentally, to severe neurological symptoms and even life-threatening cardiac arrhythmias. It should be borne in mind that the occurrence of unexplained hypokalemia or hypocalcemia in a patient on long-term PPI therapy may be secondary to hypomagnesemia and should be an indication for measuring serum magnesium levels [25,26].

3.5 Diagnostic approach

Understanding the mechanism underlying magnesium deficiency in a patient taking proton pump inhibitors is just as important as identifying a reduced magnesium concentration. The key consideration is to distinguish between reduced absorption or loss of this element from the gastrointestinal tract and excessive renal loss [5,26]. Total serum magnesium concentration remains the primary test in the diagnosis of hypomagnesemia. It is worth noting that only a small proportion of the total body magnesium is found in the extracellular space. Importantly, even with normal serum concentrations, a reduction in systemic magnesium stores is possible [5,26]. Electrolyte disturbances such as hypokalemia and hypocalcemia often co-occur with Mg^{2+} deficiency. They are therefore a useful element in the diagnostic process, and simultaneous assessment of potassium and calcium is recommended [25,26]. An important aspect of the correct interpretation of magnesium metabolism is the assessment of renal function, at least by measuring creatinine levels and the estimated glomerular filtration rate. Given the key role of the kidneys in regulating Mg^{2+} excretion, renal failure may affect both serum magnesium concentrations and the interpretation of urinary magnesium excretion [5,26]. An important aspect of the differential diagnosis is the assessment of urinary magnesium excretion. This can be achieved by collecting urine over a 24-hour period or by calculating the fractional excretion of magnesium (FEMg) from a single sample [5,26]. Reduced Mg^{2+} excretion in the presence of hypomagnesemia indicates preserved compensatory renal retention and points to a non-renal cause, such as reduced intestinal absorption. Conversely, disproportionately high excretion suggests renal loss [5,26]. The significance of this relationship in the context of PPIs is confirmed by the results of a study conducted by William et al.. Patients taking PPIs were found to have lower daily urinary magnesium excretion than those not taking these medicines: 84.6 ± 42.8 versus 101.2 ± 41.1 mg/day. After adjusting the results for potential confounding factors, it was shown that PPI use continues to be associated with lower Mg^{2+} excretion by approximately 10.5 mg/day [24]. The results of this study confirm the hypothesis that, in PPI-induced hypomagnesemia, the primary mechanism remains reduced intestinal absorption, whilst the kidneys, as part of a compensatory mechanism, limit magnesium excretion [24]. When a patient is concurrently taking medications that may cause renal magnesium loss, such as diuretics, FEMg becomes a particularly useful parameter. According to Souza et al., FEMg values below 2% in cases of hypomagnesemia indicated a non-renal cause of magnesium deficiency [25]. It has also been noted that intravenous magnesium supplementation may elevate FEMg values and thus suggest renal loss. Therefore, a urine sample should be collected before starting supplementation [25]. Diagnosis should include a detailed analysis of the pharmacotherapy being used and a clinical history. Attention should be paid to the type of PPI, its dose and the duration of treatment, as well as the concomitant use of diuretics, platinum-based drugs, aminoglycosides, calcineurin inhibitors or other agents that may affect magnesium homeostasis [5,26]. It is also important to consider other potential causes of hypomagnesemia including, amongst others, chronic diarrhoea, malabsorption disorders, previous bowel resections, inadequate magnesium intake and alcohol

consumption [5,27]. A study by Ayuk and Gittoes demonstrated that in one patient hypomagnesemia was likely a consequence of the coexistence of short bowel syndrome and PPI therapy. This highlights the multifactorial nature of the etiology of magnesium metabolism disorders in some patients [27]. Consequently, the most characteristic laboratory profile for hypomagnesemia is one characterised by low serum Mg^{2+} concentrations, low urinary magnesium excretion and the absence of convincing evidence of renal magnesium loss, in the context of long-term PPI use and following the exclusion of other significant causes [24,25,26].

3.6 Management

The management of patients with PPI-associated hypomagnesemia primarily involves correcting the magnesium deficiency and assessing the need for continued PPI use and any necessary modification of treatment. The choice of supplementation method depends on the severity of hypomagnesemia and the presence of clinical symptoms. In asymptomatic cases or those of mild severity, oral magnesium preparations are used, whilst patients with severe symptomatic hypomagnesemia may require intravenous supplementation [27]. Once the patient's condition has stabilised, oral preparations are used to further replenish the body's magnesium stores. However, their use is limited due to the occurrence of adverse effects affecting the gastrointestinal tract, in particular diarrhoea [27]. The use of magnesium supplementation alone in cases of PPI-induced hypomagnesemia has not always led to a sustained normalisation of magnesium levels. In cases reported in the literature, hypomagnesemia was observed to persist or recur despite oral and intravenous treatment, as long as PPI therapy was continued [28,29]. Kheir et al. described the case of a patient who achieved a sustained normalisation of Mg^{2+} levels only after completely discontinuing PPIs, despite having previously undergone intensive magnesium supplementation on multiple occasions [29]. Where there is a high likelihood of a link between PPIs and hypomagnesemia, discontinuing drug therapy may be a key element of management. In a systematic review by Hess et al., hypomagnesemia was observed to resolve rapidly following the discontinuation of PPIs, whilst reintroduction of a drug from this class led to its recurrence. The median time to both improvement following discontinuation and to the recurrence of hypomagnesemia following resumption of therapy was approximately four days [10]. This dechallenge-rechallenge protocol reinforces the evidence pointing to a link between PPI use and hypomagnesemia. Similar observations were reported by Hoorn et al. In the case series described, discontinuation of PPI therapy led to the normalisation of magnesium levels within approximately two to three weeks, and normal levels of this element were maintained even after supplementation had ceased [16]. Some patients still required treatment to reduce gastric acid secretion. In such cases, PPIs were replaced with histamine H2 receptor antagonists, such as ranitidine or famotidine, which did not result in a recurrence of hypomagnesemia [16]. A systematic review by Hess et al. also described the use of H2 receptor antagonists as the most common alternative to PPIs, and no recurrence of low magnesium levels was observed following such a change in treatment [10]. However, the data available in the literature regarding the monitoring of magnesium levels remain less conclusive. Famularo et al. emphasise that there is a lack of evidence to justify routine magnesium testing in all patients taking PPIs. The authors do, however, suggest that baseline magnesium levels should be assessed and periodically monitored in patients who require long-term PPI therapy and who have additional risk factors for hypomagnesemia, such as the use of diuretics or other medicines that affect magnesium metabolism [28]. Furthermore, Hess et al. also highlight the lack of sufficient data regarding the necessity and optimal frequency of magnesium level monitoring in all patients undergoing PPI therapy. The authors do, however, emphasise the need to monitor magnesium and other electrolyte levels in cases of already diagnosed PPI-induced hypomagnesemia [10].

4. Discussion

4.1 Principal findings

This review shows that the use of proton pump inhibitors increases the risk of hypomagnesemia. This association has been described in case reports and observational studies, as well as in systematic reviews and meta-analyses [10,12,14]. However, it is difficult to determine the exact extent of this risk due to the considerable heterogeneity of the available studies, differences between the populations analysed, and the lack of uniform definitions of hypomagnesemia [14,15]. An important argument supporting the association between PPIs and hypomagnesemia is the dechallenge-rechallenge pattern observed in case reports. This involves an improvement following the discontinuation of PPI therapy and the recurrence of the condition upon resumption of treatment [10]. The available data therefore point to a genuine association between PPI exposure and hypomagnesemia, although the strength and significance of this association still vary among individual patients. The findings of studies conducted to date on the mechanism of PPI-induced hypomagnesemia suggest that this condition is most likely primarily associated with impaired intestinal absorption of magnesium, rather than its excessive loss via the kidneys [21]. Possible mechanisms include a reduction in the availability of Mg^{2+} in the intestinal lumen and its abnormal transport across the intestinal epithelium. In patients with PPIH, low urinary magnesium excretion is observed, confirming a compensatory renal response to impaired intestinal absorption. At the same time, there are still aspects of the pathophysiology that have not been fully elucidated. Furthermore, the significance of proposed mechanisms, such as changes in the intestinal microenvironment and microbiota, remains the subject of further research [21]. Evidence from the literature suggests that susceptibility to developing hypomagnesemia during PPI therapy varies. Factors influencing the occurrence of this condition include, amongst others, the duration of treatment, the PPI dose and the concurrent presence of other factors affecting magnesium metabolism [14,21]. Consequently, PPI-induced hypomagnesemia is an adverse effect whose occurrence may be determined by both exposure to PPIs and the patient's individual susceptibility. In clinical practice, it is therefore essential to consider PPIs as a potential cause of unexplained hypomagnesemia and to identify more precisely those patient groups at increased risk of developing it.

4.2 Clinical implications

In daily clinical practice, PPIs should be considered in the differential diagnosis of unexplained hypomagnesemia, especially if patients are taking them long-term. Diagnosing PPI-induced hypomagnesemia can be challenging due to its nonspecific or asymptomatic course, the coexistence of other diseases, and the concurrent use of medications that affect magnesium metabolism. Importantly, the time between the start of PPI therapy and the onset of hypomagnesemia varies widely. Therefore, the duration of exposure alone is insufficient to either confirm or rule out the condition [10,26]. In the cases analyzed and presented in the study by Hess et al., establishing a link between electrolyte disturbances and PPI use was delayed, and in asymptomatic patients, the detection of PPI-induced hypomagnesemia may have been incidental [10]. An important diagnostic clue may be the coexistence of hypomagnesemia with hypokalemia or hypocalcemia. Magnesium deficiency can lead to both an increase in renal potassium loss and disturbances in parathyroid hormone secretion and function. Consequently, effective correction of these electrolyte disturbances may be limited without simultaneous replenishment of Mg^{2+} deficiency [25,26]. Patients with neurological and neuromuscular symptoms, as well as cardiac arrhythmias, require particular caution in management. Case reports of PPIH include patients with seizures, tetany, altered consciousness, and electrocardiographic abnormalities and arrhythmias. These are often accompanied by additional electrolyte disturbances [10,16,25]. When PPI-induced hypomagnesemia is suspected, the mere presence of hypomagnesemia is not sufficient to identify the PPI being used as the cause of this condition. It is essential to consider alternative sources of deficiency, such as gastrointestinal losses, malabsorption, renal magnesium loss, and other medications that affect magnesium metabolism [26,27]. Assessment of urinary magnesium excretion is a helpful tool in differential diagnosis, as low excretion in the context of hypomagnesemia suggests a non-renal cause [25,26]. PPI-induced hypomagnesemia should therefore be considered within the appropriate clinical context. Such a diagnosis should not be made based solely on PPI exposure.

4.3 Monitoring of magnesium during PPI-therapy

The issue of routine monitoring of magnesium levels in patients on long-term PPI therapy remains a topic of debate. According to Hess et al., confirmation of a characteristic temporal association between PPI use and hypomagnesemia does not justify regular magnesium testing in all patients taking drugs from this class. The need for further prospective studies has been emphasized, which would allow for determining the actual prevalence of PPI-induced hypomagnesemia and identifying the group of patients who would benefit most from monitoring [10]. Similarly, the American Gastroenterological Association does not recommend routine magnesium testing for all patients on long-term PPI therapy, as there is insufficient evidence to support the benefit of such a practice [30]. At the same time, given the possible severe complications of hypomagnesemia and its potentially asymptomatic course in the early stages, a more selective approach seems warranted. In their study, Famularo et al. emphasize the importance of measuring baseline magnesium levels and monitoring them periodically, particularly in patients on long-term PPI therapy, especially when additional factors that increase the risk of magnesium metabolism disorders are present [28]. This approach is not synonymous with widespread screening but is aimed at monitoring patients who are at higher risk of developing PPIH. The guidelines from the American College of Gastroenterology confirm this ambiguity. The authors point out inconsistencies among recommendations regarding magnesium monitoring and state that the available data are insufficient to establish a definitive recommendation in this regard [31]. Given the current evidence, an individualized approach seems more justified than routine monitoring of all patients taking PPIs. Magnesium testing should be considered particularly in patients with additional risk factors and when symptoms or electrolyte disturbances suggestive of hypomagnesemia are present [10,28].

4.4 Limitations of current evidence

Current evidence linking PPI use and hypomagnesemia faces significant limitations. The ability to establish a cause-and-effect relationship is limited due to the substantial proportion of data derived from observational studies, including retrospective and cross-sectional studies. Meta-analyses have also revealed considerable heterogeneity in the results, despite the observed association between PPI use and hypomagnesemia [14,15,32]. These differences related in particular to the characteristics of the study populations, the study design and the clinical settings in which the observations were made. The lack of a single definition of hypomagnesemia and the use of different cut-off values for magnesium concentration across studies significantly hinder direct comparisons of the incidence of this condition and the magnitude of the observed risk [15,32]. In some studies, information on the type of PPI used, the dose or the duration of treatment was lacking. Consequently, the assessment of causality and the impact of the duration of exposure remains limited [14,15]. Another issue of concern is confounding factors, such as age, comorbidities, renal function, and the use of other medications that may affect magnesium metabolism. These factors were not accounted for to the same extent in all studies [15,32]. Limitations also apply to studies on risk factors. For example, the study by Kim et al. was a single-center, retrospective study. It included a relatively small group of patients and was subject to selection bias due to the lack of routine magnesium testing [17]. Differences among the study populations further complicate the generalization of study results [12,18]. In order to determine the true extent of the risk more accurately and to identify patients at greatest risk of developing PPIH, further research is needed. Well-designed, prospective studies that use a standardised definition of hypomagnesemia and provide detailed information on the type of PPI, the dose, the duration of exposure and any potential confounding factors [15,17].

4.5 Future research

Future studies on PPI-associated hypomagnesemia should focus on better defining the risk of its occurrence and identifying patients who are highly susceptible to developing this condition. There is a need for well-designed prospective studies conducted in larger and more diverse populations, with a consistent definition of hypomagnesemia and a detailed analysis of PPI dosage and duration of use. Such a strategy could reduce the heterogeneity observed in previous studies and allow for a more reliable assessment of the association between PPI exposure and the risk of hypomagnesemia [12,14,15]. Another key priority remains the more precise identification of factors that increase susceptibility to PPIH, including the importance of dose and duration of therapy, chronic diseases, concomitant medications, and genetic predisposition [14,21]. There is also a need for studies to assess whether there are differences in risk among specific PPIs. Current data do not allow for a clear identification of such differences, due to the lack of detailed information regarding the type of medication used in some of the studies [15]. Future studies should also aim to identify the optimal

strategy for monitoring magnesium levels during PPI therapy, particularly to determine which patient groups are likely to benefit most from periodic testing. At the same time, mechanistic studies should be conducted to elucidate the exact molecular basis of magnesium absorption disorders. In particular, attention should be paid to the role of pH changes in the intestinal lumen, transport via TRPM6/TRPM7 channels, paracellular permeability, and the gut microbiota [21]. A precise characterization of these mechanisms may, in the future, contribute both to improved recognition of PPIH and to the development of more effective methods for preventing and treating this condition.

5. Conclusions

Hypomagnesemia resulting from the use of proton pump inhibitors is a clinically significant adverse effect which may manifest as significant neurological, neuromuscular or cardiovascular disorders, or may be asymptomatic. The available evidence indicates a link between the use of PPIs and an increased risk of hypomagnesemia. However, the exact magnitude of this risk cannot yet be determined, as the studies are mainly observational and characterised by considerable heterogeneity. The most likely mechanism underlying PPIH is impaired intestinal absorption of magnesium, whilst renal compensatory function remains normal. A probable mechanism underlying these disturbances is a change in pH within the intestinal lumen and impaired transport of magnesium ions via paracellular and transcellular pathways. However, further clarification of these mechanisms is required. The risk of developing PPIH appears to vary between patients and is likely to depend, amongst other things, on the dose, duration of exposure to PPIs and any co-existing factors affecting magnesium metabolism. In order to diagnose PPIH, exposure to PPIs should be taken into account when investigating unexplained hypomagnesemia, and other causes of magnesium deficiency should be ruled out. Management should include correction of the magnesium deficiency and an assessment of whether PPI therapy should be continued, as supplementation may not be sufficient whilst PPI treatment is ongoing. Current data do not unequivocally indicate a need for routine monitoring of magnesium levels in patients treated with PPIs. Further prospective studies are needed to identify at-risk groups, the mechanism underlying PPI-induced hypomagnesemia, and the best management strategies.

Author Contributions: All authors contributed to the article. All authors have read and approved the final version of the manuscript and agreed to its submission and publication.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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