

# An overview of diagnosis and management of drug-induced hypomagnesemia

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## Abstract

Magnesium (Mg) is commonly addressed as the “forgotten ion” in medicine. Nonetheless, hypomagnesemia should be suspected in clinical practice in patients with relevant symptomatology and also be considered a predisposing factor for the development of other electrolyte disturbances. Furthermore, chronic hypomagnesemia has been associated with diabetes mellitus and cardiovascular disease. Hypomagnesemia as a consequence of drug therapy is relatively common, with the list of drugs inducing low serum Mg levels expanding. Culprit medications linked to hypomagnesemia include antibiotics (e.g. aminoglycosides, amphotericin B), diuretics, antineoplastic drugs (cisplatin and cetuximab), calcineurin inhibitors, and proton pump inhibitors. In recent years, the mechanisms of drug-induced hypomagnesemia have been unraveled through the discovery of key Mg transporters in the gut and kidney. This narrative review of available literature focuses on the pathogenetic mechanisms underlying drug-induced hypomagnesemia in order to increase the insight of clinicians toward early diagnosis and effective management.

## KEYWORDS

adverse effect, drug therapy, hypocalcemia, hypokalemia, hypophosphatemia, magnesium

## 1 | INTRODUCTION

Hypomagnesemia is usually defined as a serum magnesium (Mg) level below 0.65 mmol/L (1.3 mEq/L; 1.5 mg/dl).<sup>1</sup> Serum Mg exists in three forms: (1) free or ionized Mg, the physiologically active form that accounts for 55%–70% of total serum Mg; (2) Mg complexed to anions, including bicarbonates, sulfates, phosphates, and citrates (5%–15%) and (3) Mg bound to serum proteins (primarily albumin), constituting the remaining approximately 30%.<sup>2</sup> Similarly to hypocalcemia, hypoalbuminemia is also related to spurious hypomagnesemia.<sup>3</sup>

Consequently, in hypoalbuminemic states (serum albumin <4 g/dl) corrected serum Mg should be calculated using the formula: corrected Mg (mmol/L) = measured Mg (mmol/L) + 0.005 × (40 – albumin g/L).<sup>4</sup> Correction of Mg for albumin levels is rarely performed in clinical practice, a strategy that should probably change.

The incidence of hypomagnesemia varies considerably from merely 2% among individuals in the community up to as high as 65% in patients hospitalized in intensive care units.<sup>5,6</sup> Discrepancies in the reported incidences of hypomagnesemia are attributed to the fact that serum Mg is not routinely measured and that this ion is

**Abbreviations:** CNIs, calcineurin inhibitors; DCT, distal convoluted tubules; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Mg, magnesium; mTOR, mammalian target of rapamycin; NKCC2 co-transporter, sodium potassium chloride co-transporter; OR, odds ratio; PPIs, proton pump inhibitors; PTDM, post-transplantation diabetes mellitus; ROMK, renal outer medullary K channels; TAL, thick ascending loop of Henle; TRPM6, transient receptor potential melastatin 6.

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commonly “forgotten” in the initial evaluation of electrolytes in either the outpatient or inpatient.<sup>7</sup> This is undeserved, because the clinical importance of hypomagnesemia is underscored by potentially severe symptoms (neuromuscular symptoms and cardiac arrhythmias) and its association with other metabolic abnormalities (hypocalcemia, hypophosphatemia, and hypokalemia), as well as an increased in-hospital mortality rate<sup>8</sup> (Table 1). Furthermore, chronic hypomagnesemia has been associated with an increased risk for the development of diabetes mellitus, hypertension, and cardiovascular disease overall.<sup>1,7</sup>

Among the various causes of hypomagnesemia, drugs feature prominently even in cases of extreme hypomagnesemia, defined as serum Mg concentration below 0.3 mmol/L (0.7 mg/dl)<sup>8,14</sup> (Table 2). Here, our aim was to review the available literature regarding hypomagnesemia as a consequence of drug treatment and discuss the underlying pathophysiological mechanisms which may aid the clinician towards early diagnosis and effective management.

## 2 | MG METABOLISM

Following sodium, potassium, and calcium, Mg is the fourth most abundant cation in mammals and, similar to potassium, mainly stored intracellularly. Mg homeostasis is achieved by an interplay between dietary intake, exchange between intracellular and extracellular pools and excretion via gut and kidneys (Figure 1). Of note, Mg exchange between extracellular and intracellular stores is slow and therefore, ineffective against acute extracellular Mg loss.

**TABLE 1** Consequences of hypomagnesemia

Cardiovascular disorders <sup>9,10</sup>
Electrocardiographic changes: wide QRS complex, prolonged PR interval, inversion of T waves, U waves
Arrhythmias: ventricular arrhythmias, torsade de points, supraventricular tachycardia
Increased incidence of digitalis intoxication
Hypertension
Endocrine disorders <sup>11</sup>
Increased risk for the development of (post transplantation) diabetes mellitus
Impaired release of PTH and skeletal resistance to the action of PTH
Neuromuscular and neuropsychiatric disturbances <sup>12</sup>
Muscle cramps or weakness, carpopedal spasm, tetany, vertigo, ataxia, seizures, depression, psychosis
Bone disorders <sup>13</sup>
Osteoporosis and osteomalacia
Electrolyte disorders <sup>5</sup>
Hypokalemia
Hypocalcemia
Hypophosphatemia

Abbreviation: PTH, parathormone.

Surprisingly, serum concentrations of the other electrolytes, including sodium, potassium and calcium, are tightly regulated by circulating hormones, whereas no truly “magnesiotropic” hormones have been identified. Rare inherited disorders have been pivotal for the understanding of Mg physiology. For example, mutation analysis of patients with familial hypomagnesemia with secondary hypocalcemia led to the discovery of two specialized Mg channels, the transient receptor melastatin (TRPM) channels TRPM6 and TRPM7 that belong to the family of transient receptor potential channels.<sup>15</sup> TRPM6 is mainly expressed in the gut, blood vessels, and the kidney (distal convoluted tubules, DCT) playing a significant role in the epithelial Mg transport. TRPM7 is expressed in virtually all tissues and is possibly involved in cellular Mg homeostasis.<sup>16,17</sup>

The regulation of serum Mg concentrations is mainly achieved via regulated renal reabsorption. The proximal tubule and the thick ascending loop of Henle (TAL) reabsorb 15%–20% and 65%–75% of filtered Mg, respectively.<sup>20,21</sup> This reabsorption is primarily achieved through paracellular pathways. Water reabsorption along the proximal tubule results in an increased luminal Mg concentration and paracellular Mg reabsorption in this kidney segment.<sup>22</sup> Moreover, Mg reabsorption in the TAL is mediated by the favorable electrical (lumen-positive) gradient. This lumen-positive voltage is established by sodium, potassium, and chloride reabsorption via sodium potassium chloride (NKCC2) co-transporter coupled to potassium re-entry into the lumen through the renal outer medullary K channels (ROMK).<sup>23</sup>

This process is facilitated by the tight junction proteins claudin-16 and claudin-19.<sup>21,24</sup> In the DCT, Mg reabsorption takes place in an active transcellular manner in which the TRPM6 channels play a major role.<sup>15</sup> Despite the fact that the DCT is responsible for only 5%–10% of total Mg reabsorption, its contribution to Mg homeostasis is of major importance given that there is no Mg reabsorption beyond this segment.<sup>25</sup>

A close link between Mg, potassium, calcium, and phosphorus concentrations has been demonstrated. For example, Mg deficiency can induce renal phosphate wasting, but the reverse is also true.<sup>26</sup> Hypomagnesemia may induce hypocalcemia and hypokalemia; the proposed mechanisms for these disorders are shown in Figure 2.<sup>8,27,28</sup> Clinically, decreased dietary Mg intake, a “shift” of Mg into cells or increased gastrointestinal or renal losses may contribute to or cause hypomagnesemia.

## 3 | CLINICAL SIGNIFICANCE OF HYPOMAGNESEMIA

Magnesium is essential for life as it is involved in numerous enzymatic reactions, including ATP use, cell membrane and mitochondrial function, as well as protein synthesis. Thus, diverse organ systems are affected by Mg depletion, while the most clinically significant consequences of hypomagnesemia are ascribed to alterations in the function of excitable membranes in nerves, muscles, and the cardiac conducting system. Consequently, hypomagnesemia may present

TABLE 2 Etiology of drug-induced hypomagnesemia

1. Shift of Mg into cells
Insulin therapy
Epinephrine, salbutamol, terbutaline, rimiterol, theophylline
Correction of metabolic acidosis with alkali therapy
Metformin
2. Gastrointestinal Mg loss
Laxative abuse, antibiotics, antineoplastic agents, metformin
Proton pump inhibitors
Patiromer
3. Increased urinary Mg excretion
Antineoplastics
Carboplatin, cisplatin
Monoclonal antibody epidermal growth factor receptor inhibitors (e.g. cetuximab, panitumumab)
Mammalian target of rapamycin inhibitors
Calcineurin inhibitors
Cyclosporine, tacrolimus
Antibiotics
Aminoglycosides
Amphotericin B
Pentamidine
Foscarnet
Diuretics
Thiazides
Furosemide
Digoxin
Theophylline
4. Miscellaneous
Alcohol
Massive transfusions, foscarnet
Teriparatide
Bisphosphonates
Denosumab

Abbreviation: Mg, magnesium.

with neuromuscular (e.g. muscle cramps or weakness, carpopedal spasm, tetany, vertigo, ataxia, seizures, depression, psychosis) and cardiovascular (e.g. ventricular arrhythmias, torsade de points, supraventricular tachycardia, sensitivity to digoxin) manifestations.<sup>12,29</sup> Furthermore, low serum Mg levels can secondarily induce hypokalemia, hypocalcemia, and hypophosphatemia, potentially causing further derangements in neuromuscular and cardiovascular physiology. Interestingly, the Atherosclerosis Risk in Communities study suggests that low levels of serum Mg may be an important predictor of sudden cardiac death.<sup>9</sup> In addition, Mg deficit has been associated with carbohydrate intolerance and insulin resistance.<sup>29</sup> Conversely, dietary Mg intake has been associated with a reduced risk of type 2 diabetes.<sup>11</sup> Therefore, hypomagnesemia should be sought and appropriately managed in clinical practice.

## 4 | DRUGS ASSOCIATED WITH HYPOMAGNESEMIA

### 4.1 | Antibiotics

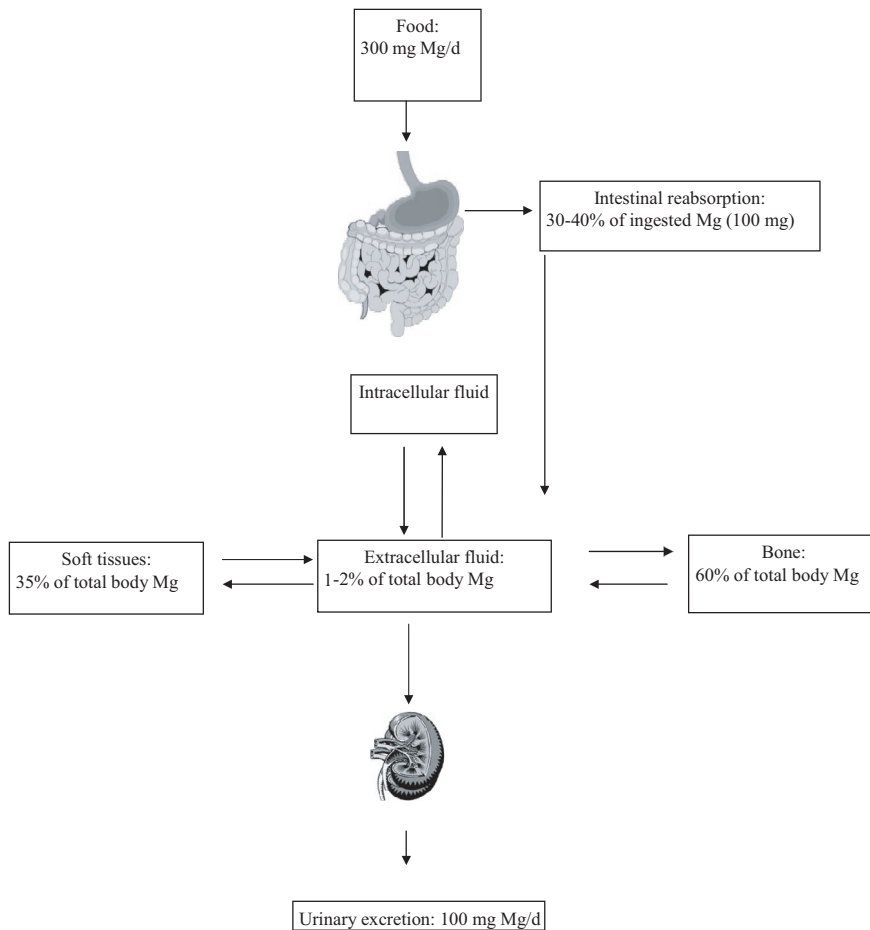
Several types of antibiotics are associated with hypomagnesemia primarily because they cause renal loss of Mg (Table 2). These include aminoglycosides, amphotericin B, pentamidine, and foscarnet.

Hypomagnesemia from aminoglycosides is a class effect, as it has been reported with several agents of this class (gentamicin, amikacin, tobramycin, and capreomycin).<sup>30</sup> The risk of hypomagnesemia with aminoglycoside therapy appears to be related to both duration and dose; hypomagnesemia may develop and persist even after aminoglycoside therapy has been discontinued.<sup>31,32</sup> In healthy volunteers, the administration of a single dose of gentamicin (5 mg/kg) has been reported to result in a transient four-fold increase in fractional Mg excretion.<sup>33</sup>

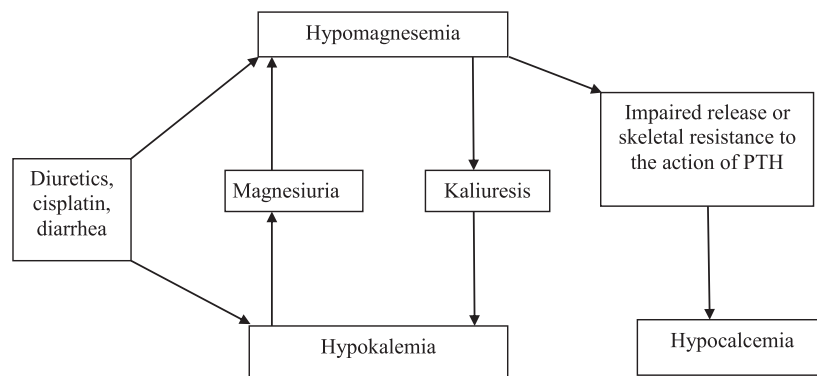
Aminoglycosides are believed to cause hypomagnesemia by stimulating the calcium sensing receptor, which is located on the basolateral membrane of the TAL. Stimulation of this receptor inhibits tubular transport by this segment as well as the paracellular transport of Mg. In fact, complete inhibition of transport in the TAL can cause a Bartter-like syndrome, which, besides hypomagnesemia, is a constellation of renal sodium loss, hypokalemia, hypocalcemia, and low-normal blood pressure.<sup>34,35</sup>

The renal toxicity of amphotericin B usually occurs more distally in the kidney, namely in the DCT. Although the general characteristics of amphotericin B nephrotoxicity are known (increased tubular permeability, necrosis, arterial vasoconstriction), it remains unclear how this drug can specifically perturb renal Mg transport in this nephron segment.<sup>36,37</sup> Hypomagnesemia occurs as frequently as 75% in patients treated with amphotericin B and is more common with the deoxycholate than with the lipid formulation.<sup>38,39</sup> Prolonged or high-dose therapy and the concurrent use of other drugs associated with hypomagnesemia also increase the risk of hypomagnesemia following treatment with amphotericin B.<sup>40</sup> Although hypomagnesemia due to amphotericin B is usually reversible, it may persist for weeks after discontinuation of the drug.<sup>41</sup> It is important to emphasize that both aminoglycosides and amphotericin B have also been associated with acute kidney injury; however, hypomagnesemia may also develop with preserved glomerular filtration rate. Furthermore, both classes of drugs can also cause other renal tubular disorders, including proximal and distal renal tubular acidosis and nephrogenic diabetes insipidus.<sup>36,37,42,43</sup> With regard to other antifungal agents, posaconazole and isavuconazole have also been associated with hypomagnesemia.<sup>44</sup> The exact mechanism has not been elucidated.

Several cases of severe and symptomatic hypomagnesemia have been reported after intravenous pentamidine therapy, and this has been ascribed to renal Mg wasting.<sup>45-47</sup> Pentamidine may also cause acute pancreatitis, which could contribute to hypomagnesemia.<sup>48,49</sup> The main underlying mechanism of



**FIGURE 1** Metabolism of magnesium (Mg). Dietary Mg content normally ranges from 300 to 350 mg/day, of which 30%–40% is absorbed, mainly in the jejunum and ileum. Fifty to 60% of total Mg is stored in bones, about 40% is intracellular (mainly in muscles) and only 1% is found in extracellular fluid.<sup>18</sup> Mg balance is tightly regulated through intestinal and renal absorption and excretion as well as exchange with bone. About 2 g of Mg (8 mmol) is filtered daily by the kidney, of which approximately 100 mg (5%) is excreted in the urine matching the net intestinal absorption<sup>19</sup>



**FIGURE 2** Hypomagnesemia-induced hypocalcemia and hypokalemia. Potassium ( $K^+$ ) depletion is associated with increased urinary excretion of magnesium (Mg), while Mg depletion causes kaliuresis and hypokalemia. It appears that a decrease in intracellular Mg (not Mg deficiency alone), releasing the Mg-mediated inhibition of renal outer medulla  $K^+$  channels, can increase renal potassium excretion leading to potassium depletion.<sup>27</sup> Hypocalcemia is the consequence of Mg-induced impairment in the release of PTH or skeletal resistance to PTH action. PTH, parathormone

hypomagnesemia in acute pancreatitis is presumably similar to that of hypocalcemia: saponification of Mg and calcium in necrotic fat.<sup>49</sup> Foscarnet, used to treat the complications of cytomegalovirus infection, has also been associated with hypomagnesemia. In a small cohort, nine out of 13 patients (69%) developed hypomagnesemia.<sup>50</sup> Renal Mg losses have been implicated; in addition, foscarnet as a potent chelator of divalent ions provokes ionized hypomagnesemia.<sup>51,52</sup>

## 4.2 | Diuretics

Both loop and thiazide diuretics can cause hypomagnesemia by indirectly inhibiting renal Mg reabsorption.<sup>30,53</sup> This is consistent with what is observed in patients with Bartter or Gitelman syndrome, in which the targets of loop and thiazide diuretics is inactivated genetically. The degree of hypomagnesemia seen with loop and thiazide

diuretics is usually mild possibly because the associated volume depletion stimulates Mg reabsorption by the proximal tubule.<sup>30</sup> Loop and thiazide diuretics cause magnesuria indirectly; they inhibit sodium cotransporters in the kidney, subsequently inhibiting paracellular or cellular Mg transport. In the case of loop diuretics, the direct inhibition of the NKCC2 co-transporter disrupts the positive epithelial voltage that is present in this part of the nephron due to the recycling of potassium into the tubular lumen via the ROMK channels. The ensuing loss of voltage inhibits the paracellular transport of Mg and calcium and favors Mg and calcium excretion. Previously, hypomagnesemia following thiazide therapy was mainly attributed to secondary hyperaldosteronism or hypokalemia. More recent experiments in mice, however, have suggested that thiazide inhibition of the sodium chloride co-transporter directly leads to a downregulation of the Mg channel TRPM6.<sup>54</sup> In humans, hypomagnesemia is a dose-dependent adverse effect of thiazides use that is more frequently observed in the elderly.<sup>55</sup> In a general population-based study including 9280 subjects, thiazide use was associated with a two- to three-fold increased risk of hypomagnesemia (defined as a serum Mg  $\leq 0.72$  mmol/L; 1.8 mg/dl).<sup>56</sup> In this study, loop diuretics did not increase the risk of hypomagnesemia. Paradoxically, a slightly higher serum Mg concentration was observed. It should be emphasized that the results of the aforementioned study were predominantly observed in individuals receiving diuretics for more than a year. These results may be explained by the upregulation of TRPM6 in the DCT mediated by chronic loop diuretic therapy. Increased Mg reabsorption by the proximal tubule or increased TRPM6 activity through metabolic alkalosis may also play a role.<sup>57</sup>

Potassium-sparing diuretics (e.g. amiloride or spironolactone) have not been associated with hypomagnesemia. In fact, these diuretics tend to favor renal Mg reabsorption.<sup>56</sup>

### 4.3 | Calcineurin inhibitors

Calcineurin inhibitors (CNIs; i.e. cyclosporine, tacrolimus) are among the most commonly used immunosuppressant drugs for the prevention of graft rejection and sometimes also used in the treatment of autoimmune disease. Tacrolimus more often causes more severe hypomagnesemia than cyclosporine.<sup>58,59</sup> For example, serum Mg concentrations were significantly lower in recipients of allogeneic hematopoietic stem cell transplantation who received tacrolimus compared with cyclosporine.<sup>60</sup> It appears that kidney function plays an important role regarding the hypomagnesemic effect of CNIs, given that serum Mg levels demonstrate a negative correlation with creatinine clearance.<sup>61,62</sup> CNIs cause inappropriate renal Mg loss, likely because they reduce the expression of TRPM6; a shift of Mg into cells may also contribute.<sup>59,63,64</sup> Even though CNI-induced hypomagnesemia is usually mild, severe neurological symptoms have been reported, including altered mental status, seizures, or focal neurological deficits.<sup>59,65,66</sup>

Hypomagnemia has been suggested to contribute to the nephrotoxic and blood pressure increasing effects of CNIs.<sup>67,68</sup> It has also

been linked to the emergence of post-transplantation diabetes mellitus (PTDM), a common metabolic complication after transplantation which unfavorably affects both patient and graft survival.<sup>69,70</sup> Indeed, in a retrospective study of 390 patients who underwent kidney transplantation, CNI-induced hypomagnesemia during the first month post transplantation was associated with the development of PTDM.<sup>71</sup> Similarly, in a series of 169 adults who received tacrolimus for liver transplantation, both pre- and early post-transplant hypomagnesemia was an independent predictor of PTDM.<sup>72</sup> In more than 20% of the kidney transplant patients, hypomagnesemia is present for many years after transplantation and has been associated with incident kidney disease and graft dysfunction.<sup>73,74</sup>

## 4.4 | Antineoplastic drugs

Hypomagnesemia is frequently observed in cancer patients and is ascribed to several mechanisms including malnutrition, diarrhea, hypercalcemia as well as antineoplastic drug therapy.<sup>75,76</sup>

### 4.4.1 | Platin-based anticancer drugs

Hypomagnesemia secondary to chemotherapy has long been recognized with the use of platinum-containing drugs (cisplatin, carboplatin, and oxaliplatin) that are used for a variety of solid cancers (e.g. lung cancer, head and neck cancer, and cervical cancer).<sup>77,78</sup> It is most common with cisplatin, a drug that was approved by the Food and Drug Administration in 1978.

Cisplatin causes hypomagnesemia in a dose-dependent fashion and affects up to 90% of patients if no preventive measures are taken (see Section 5 below).<sup>79</sup> The etiology of cisplatin-induced hypomagnesemia is not completely understood; renal Mg loss is the primary mechanism, but gastrointestinal losses have also been reported.<sup>80</sup> Morphological studies in humans with cisplatin nephrotoxicity demonstrated necrosis of the terminal portion of the proximal tubule and apoptosis of the distal nephron.<sup>81</sup> However, nephrotoxicity associated with cisplatin and the ensuing hypomagnesemia may be more complex implicating several mechanisms of injury, inflammation, repair, recovery, and cell death.<sup>81</sup> It is known that epidermal growth factor (EGF) increases Mg reabsorption in the DCT through the TRPM6 channels. Cisplatin may cause hypomagnesemia by downregulating the TRPM6/EGF pathway. Of note, Mg co-administration mitigates both cisplatin-induced hypomagnesemia by protecting the downregulation of the TRPM6 channels and nephrotoxicity by regulating the expression of renal transporters. Specifically, in rats the Mg-mediated downregulation of the renal organic cation transporter 2 and the upregulation of the renal multidrug and toxin extrusion protein 1 were associated with a significant reduction in renal cisplatin accumulation.<sup>82</sup>

Laurent et al. showed a proliferative response throughout the nephron, indicating incomplete tissue repair, which potentially explains the chronicity of hypomagnesemia.<sup>80</sup> The glomerular damage

linked to cisplatin has been shown to be at least partly reversible compared with tubular damage, which is often permanent. In fact, Schilsky and colleagues showed that 22 of 29 patients (76%) who received cisplatin for non-seminomatous germ cell tumors developed acute hypomagnesemia; eleven (50%) remained hypomagnesemic for at least 3 years.<sup>83</sup> This long-term effect has been corroborated by other investigators as well.<sup>84,85</sup>

In addition to isolated hypomagnesemia, cisplatin can also cause a Gitelman-like syndrome manifesting with renal sodium wasting, hypocalciuria, and hypokalemia. Remarkably, it has been reported that this Gitelman-like syndrome can persist for up to 20 years after treatment with cisplatin.<sup>86</sup> These observations suggest that the DCT may be especially sensitive to cisplatin, although the reason for this predilection is unknown.<sup>87</sup> Severe symptoms have been reported in patients with cisplatin and hypomagnesemia, including tetany, paralysis, seizures, cortical blindness, and arrhythmia, although it is difficult to verify in these cases if hypomagnesemia was the sole culprit.<sup>88-91</sup>

Carboplatin was introduced in oncology in the late 1980s, and was advocated as a less nephrotoxic counterpart of cisplatin. Hypomagnesemia also occurs with carboplatin with lower frequency compared with cisplatin (reported incidence  $\leq 12.5\%$ ).<sup>92,93</sup> However, hypomagnesemia may persist for months after completing a course of carboplatin-containing chemotherapy.<sup>94</sup> Recent evidence shows that hypomagnesemia due to carboplatin is a strong predictor of shorter survival in patients with advanced ovarian cancer.<sup>95</sup>

#### 4.4.2 | Monoclonal antibodies

A meta-analysis of 25 randomized controlled trials (16,400 patients) showed that treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies was associated with high incidence of hypomagnesemia (34%), hypocalcemia (16.8%), and hypokalemia (14.5%).<sup>96</sup> Hypokalemia and hypocalcemia were predominantly hypomagnesemia-mediated.<sup>76</sup> The incidence of hypomagnesemia and hypokalemia was increased with panitumumab compared with cetuximab or bevacizumab,<sup>96-98</sup> whereas zalutumumab has been associated with low rates of hypomagnesemia (4%) and hypokalemia (6%).<sup>99</sup> Certain characteristics of panitumumab, such as longer half-life and higher affinity to human EGFR, may explain the differences regarding the frequency of hypomagnesemia among these drugs. The mechanism of hypomagnesemia induced by anti-EGFR monoclonal antibodies resembles an inherited disorder called isolated recessive hypomagnesemia, in which EGFR is inactivated. This inactivation then leads to a downregulation of TRPM6 causing renal Mg loss.<sup>100</sup>

It has recently been implicated that concomitant administration of proton pump inhibitors (PPIs) or histamine H<sub>2</sub> antagonists increases the rate and severity of cetuximab and panitumumab-induced hypomagnesemia.<sup>101,102</sup> Prolonged administration and concurrent platinum treatment are also risk factors for the emergence of anti-EGFR monoclonal antibodies-induced hypomagnesemia.<sup>103</sup>

Cetuximab-related hypomagnesemia can be symptomatic.<sup>104</sup> It has also been associated with deterioration of peripheral sensory neurotoxicity caused by oxaliplatin.<sup>105</sup> In patients with advanced colorectal cancer, the development of hypomagnesemia with cetuximab- or panitumumab-based chemotherapy has been associated with a later time to progression and a longer overall survival rate.<sup>106</sup> It is yet unknown if these positive outcomes are directly associated with hypomagnesemia (e.g. because intracellular Mg depletion halts tumor growth) or if hypomagnesemia is merely a reflection of effective tissue penetration of the drug.<sup>107</sup> The reason for the opposite associations between the development of hypomagnesemia and the prognosis after cisplatin- and monoclonal antibody therapy is not clear.

#### 4.4.3 | Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin (mTOR) inhibitors can cause hypomagnesemia via renal Mg wasting, although the exact underlying mechanisms are not well defined.<sup>1</sup> The hypomagnesemic and magnesuric effect of mTOR inhibitors is milder than with CNIs. In a retrospective study including 138 renal transplant patients who were converted from CNIs to mTOR inhibitors over a 6-month period, serum Mg concentration significantly increased along with a reduction in the fractional excretion of Mg.<sup>108</sup> It has been proposed that rapamycin (sirolimus) leads to magnesuria by reducing TRPM6 expression in the DCT due to a decrease in TRPM6 mRNA stability.<sup>109</sup> Contrary to these results, however, sirolimus-induced hypomagnesemia accompanied by increased renal expression of TRPM6 has also been reported. It is not entirely clear whether this upregulation of TRPM6 represents a direct stimulatory effect of sirolimus or—more likely—a compensatory response aiming to limit renal Mg loss due to mTOR-mediated downregulation of NKCC2 protein expression which results in magnesuria.<sup>109</sup> Of interest, sirolimus-related renal tubular defects are ameliorated by rosiglitazone (a thiazolidinedione with known renal sodium- and water-reabsorptive properties) potentially via NKCC2 upregulation.<sup>110</sup>

#### 4.5 | Proton pump inhibitors

In 2006, the first two cases of hypomagnesemia associated with the use of PPIs were reported.<sup>111</sup> Since then, numerous case reports and series have confirmed this association,<sup>112,113</sup> and PPI use has now also been associated with hypomagnesemia in the general population.<sup>114</sup> PPI-induced hypomagnesemia seems to be a class effect caused by omeprazole, esomeprazole, pantoprazole, and rabeprazole and resolves with cessation of therapy.<sup>115</sup>

A very recent meta-analysis of all observational studies (N = 16; 131,507 patients) investigated the association between PPIs and the development of hypomagnesemia; this meta-analysis demonstrated that PPI use was significantly associated with hypomagnesemia, with a pooled unadjusted odds ratio (OR) of 1.83



(95% CI [1.26, 2.67];  $p = .002$ ) and a pooled adjusted OR of 1.71 (95% CI [1.33, 2.19];  $p < .001$ ). Interestingly, high-dose PPI use was associated with higher odds for hypomagnesemia relative to low-dose PPI use (pooled adjusted OR 2.13; 95% CI [1.26, 3.59];  $p = .005$ ).<sup>116</sup>

Nevertheless, PPI-induced hypomagnesemia prevalence varies among studies (up to 12.5%) and appears to typically occur in elderly people on long-term treatment.<sup>114,117-119</sup> In contrast, in critically ill patients, even short-term PPI use may cause hypomagnesemia.<sup>120</sup> This probably occurs because hypomagnesemia is already very common in ICU patients and, in this context, PPIs may further decrease Mg levels. Co-administration with diuretics and the presence of Mg lowering comorbidities, such as diabetes mellitus or acute diarrheal states, are risk factors for PPI-induced hypomagnesemia.<sup>119</sup> Diminished active Mg transport in the colon, which is primarily mediated via the ion channels TRPM6 and TRPM7, has been proposed as the main explanation of PPIs-related hypomagnesemia.<sup>121</sup> Although confirmative studies are lacking, changes in intestinal pH or a heterozygous carrier state for TRPM6 and TRPM7 have been implicated.<sup>122</sup> It has recently been reported that both low gut microbiota diversity and dietary Mg intake are related with the development of PPIs-induced hypomagnesemia.<sup>123</sup> Omeprazole treatment for 4 weeks significantly reduced serum Mg levels in mice on a low-Mg diet compared with mice under normal dietary Mg availability. In fact, omeprazole induced a shift in microbial composition, specifically a 3- and 2-fold increase in *Lactobacillus* and *Bifidobacterium* abundance, respectively. The findings of this study imply that both omeprazole and low dietary Mg intake alter the gut internal milieu and probably pose a risk for Mg malabsorption in the colon.<sup>123</sup>

It has also been suggested that a constant low-grade renal Mg leak, possibly due to heterozygous mutations of genes involved in the regulation of distal Mg reabsorption, may play a contributory role in the emergence of hypomagnesemia due to PPIs.<sup>124</sup> However, taking into consideration that urinary Mg excretion is appropriately low in patients with PPIs-induced hypomagnesemia, the contribution of renal Mg losses seems limited.<sup>125,126</sup> A significant association between PPIs use and hypomagnesemia has been found in patients with chronic kidney disease at any stage, indicating that PPIs counterbalance the anticipated increase in serum Mg with declining estimated glomerular filtration rate.<sup>127,128</sup>

Proton pump inhibitors-related hypomagnesemia can cause serious clinical manifestations (e.g. life-threatening arrhythmias) that may occur suddenly after a long asymptomatic interval.<sup>112,129</sup>

## 4.6 | Digoxin

Digoxin reduces serum Mg concentration via increased urinary Mg excretion. It has been proposed that a missense mutation in the  $\gamma$  subunit (FXDY2) of  $\text{Na}^+/\text{K}^+$ -ATPase, which is the pharmacological target of digoxin, might be involved in this process.<sup>130</sup> It appears that FXDY2 is a positive regulator of  $\text{Na}_2\text{K}$ -ATPase in the DCT.<sup>131</sup>

## 4.7 | Miscellaneous

The majority of aforementioned drugs cause hypomagnesemia due to renal Mg loss (Table 2). In addition, any medication that can cause relatively serious diarrhea (e.g. laxatives, antibiotics, and antineoplastic drugs) may be directly associated with the development of hypomagnesemia. Even Mg-containing laxatives can lead to excessive intestinal Mg loss and hypomagnesemia.<sup>132</sup>

Patiromer is a non-absorbed potassium-binding polymer that exchanges calcium for potassium in the gastrointestinal tract and was recently approved for the treatment of hyperkalemia in adults. A meta-analysis of phase II and III clinical trials showed that hypomagnesemia occurred in approximately 7% of patients on patiromer, underlining that it is not completely selective for the potassium ion.<sup>133</sup>

A number of drugs can also produce a "shift" of Mg into cells, including beta-adrenergic drugs and insulin.<sup>30</sup> These drugs also cause a shift of potassium or phosphate into cells.<sup>134</sup> It has been reported that intravenous administration of epinephrine in twelve normal volunteers caused a modest but significant reduction in serum Mg concentrations ( $0.77 \pm 0.02$  to  $0.67 \pm 0.02$  mmol/L;  $1.86 \pm 0.04$  to  $1.63 \pm 0.05$  mg/dl).<sup>135</sup> The involvement of beta-adrenergic mechanisms was suggested since propranolol given simultaneously prevented the hypomagnesemic effect of epinephrine infusion.<sup>136</sup> Other sympathomimetic drugs have also been associated with hypomagnesemia, including theophylline, where a renal effect may also play a role.<sup>137</sup>

Insulin can also promote a shift of Mg from the extracellular to the intracellular compartment and lead to hypomagnesemia.<sup>138</sup> The increased secretion of epinephrine due to insulin-induced hypoglycemia may contribute to this process. The risk of hypomagnesemia is especially high in poorly controlled diabetics due to increased renal Mg loss by osmotic diuresis in the hyperglycemic state.<sup>139</sup>

The use of teriparatide, a recombinant form of parathormone which is used for osteoporosis treatment, has been associated with hypomagnesemia. In a retrospective study of 53 patients treated for severe osteoporosis with teriparatide for 6-24 months, the cumulative incidence of hypomagnesemia (serum Mg  $<0.7$  mmol/L; 1.7 mg/dl) was as high as 35.9%. Old age and lower baseline serum Mg concentration were significantly associated with teriparatide-induced hypomagnesemia.<sup>140</sup> Although the underlying mechanisms are not known, deposition of Mg into bones due to increased bone metabolism and renal Mg losses due to transient hypercalcemia may play a role.<sup>140</sup>

Hypomagnesemia also occurs with bisphosphonates and denosumab due to their binding to Mg cations.<sup>77,141,142</sup>

Hypomagnesemia has been reported in patients treated with metformin.<sup>143</sup> Although the underlying mechanisms have not been fully elucidated, increased Mg concentration in erythrocytes and hepatocytes is probably involved.<sup>144</sup> Symptomatic hypomagnesemia (serum Mg concentration of 0.33 mmol/L; 0.8 mg/dl) has also been reported following metformin-induced diarrhea.<sup>145</sup>

A number of therapies can cause hypomagnesemia owing to chelation of Mg (e.g. massive transfusions) or redistribution of Mg

into bone and soft tissue (during alkali therapy and total parenteral nutrition).<sup>146,147</sup>

## 4.8 | Alcohol

Although alcohol is not a medication, in the sense that it is not used as a remedy, it is considered a drug which frequently causes addiction. In this context, we thought it would be prudent to include alcohol as a cause of hypomagnesemia in this review. Hypomagnesemia is the most common electrolyte abnormality related to chronic alcohol abuse and affects as many as 30% of alcohol-dependent patients.<sup>148,149</sup> Alcohol-induced hypomagnesemia may be profound; specifically Mg levels as low as 0.6 mg/dl (0.24 mmol/dl) have been reported.<sup>150</sup> In a study of 380 patients presenting with alcohol withdrawal syndrome, Mg deficiency (<0.75 mmol/L; 1.8 mg/dl) was associated with significant higher 1-year mortality rate.<sup>151</sup> It has been proposed that ionized Mg concentration in erythrocytes and plasma is more reliable than total Mg in the assessment of Mg homeostasis in alcoholic patients.<sup>152</sup> Decreased Mg intake in malnourished patients, increased gastrointestinal Mg losses in patients suffering from chronic diarrhea, as well as increased Mg entry into cells due to both respiratory alkalosis and excessive catecholamine release in alcohol withdrawal syndrome comprise the major pathogenetic mechanisms.<sup>28,153</sup> In addition, hypomagnesemia in patients with chronic alcoholism is associated with inappropriate magnesuria due to alcohol-induced tubular damage.<sup>148</sup> Increased urinary Mg excretion after acute alcohol ingestion has been demonstrated even in non-alcoholic subjects.<sup>1</sup> Finally, in the course of alcohol abuse, hypomagnesemia can also result from alcohol-related metabolic acidosis, concurrent electrolyte disorders (hypophosphatemia, hypokalemia, hypocalcemia) and acute pancreatitis.<sup>49,149,153</sup>

## 5 | SCREENING, DIAGNOSIS, AND TREATMENT OF DRUG-INDUCED HYPOMAGNESEMIA

Should serum Mg be determined in all patients who receive a drug that has been associated with hypomagnesemia (Table 3)? This question is relevant, because serum Mg is usually not a routine laboratory measurement in hospitalized patients, except for the intensive care setting. Recommendations may vary by drug. Monitoring of serum Mg is justified during therapy with cisplatin or cetuximab/panitumumab, because of the direct relationship and the possibility of developing severe hypomagnesemia. Most oncology services now routinely measure serum Mg or even supplement Mg prophylactically during therapy with platin-based chemotherapy and cetuximab/panitumumab.<sup>154,155</sup>

Conversely, the value of measuring serum Mg is uncertain during treatment with commonly prescribed drugs such as antibiotics, diuretics, CNIs, and PPIs. So when should serum Mg be determined in the course of treatment with one of these agents? The most obvious

**TABLE 3** Diagnosis and treatment of drug-induced hypomagnesemia

### Screening for hypomagnesemia

- Unexplained hypocalcemia or hypokalemia
- Ventricular arrhythmia
- Administration of drugs with a high likelihood of hypomagnesemia
- Administration of drugs associated with hypomagnesemia in combination with another potential cause of hypomagnesemia

### Treatment of hypomagnesemia

- Withdrawal of drugs involved in the development of hypomagnesemia, if possible
- Administration of oral Mg salts in mild, asymptomatic hypomagnesemia
- Administration of Mg sulfate intravenously in severe and/or symptomatic hypomagnesemia, as well as in patients with poor intestinal Mg reabsorption due to gastrointestinal disease or in patients who experience gastrointestinal side effects from oral Mg preparations

Abbreviation: Mg, magnesium.

recommendation would be to rely on the presence of signs or symptoms associated with hypomagnesemia, for example, neuromuscular symptoms and cardiac arrhythmias, or with other electrolyte disorders (e.g. hypocalcemia and hypokalemia). If these symptoms are not present, we would recommend measuring serum Mg when a patient receives a drug known to induce hypomagnesemia and manifests another potential cause of hypomagnesemia such as diarrhea, malnutrition, and diabetes mellitus.<sup>8</sup> Supplementation of Mg will depend on the degree of hypomagnesemia and the presence of symptoms. Severe (0.4 mmol/dl; 1 mg/dl) and/or symptomatic hypomagnesemia should be treated by administration of 25 mmol Mg sulfate intravenously over 12–24 h. In cases of seizures or severe cardiac arrhythmias (e.g. torsade de pointes) an intravenous load of 4–8 mmol Mg sulfate in 100 ml of D5W over 5–10 min, followed by 25 mmol/day, should be administered. Intravenous therapy may also be indicated in patients with poor intestinal Mg absorption due to gastrointestinal disease or in those who experience gastrointestinal side effects with oral Mg preparations. Mild, asymptomatic hypomagnesemia may be treated with oral Mg salts (e.g. Mg oxide, Mg lactate or Mg chloride) in divided doses totaling 15–20 mmol/day. Mg-oxide should probably not be the first choice because of high frequency of diarrhea. Mg gluconate, sulfate, or aspartate could be alternative options.<sup>156</sup>

Special attention should be paid to patients with chronic kidney disease to avoid hypermagnesemia: a 50% dose reduction and more frequent monitoring is recommended.<sup>157</sup> Of note, a high prevalence of hypomagnesemia has been observed in this population, mainly due to proteinuria-associated tubular injuries leading to renal Mg wasting.<sup>158</sup> Potassium-sparing diuretics (amiloride or spironolactone) may be substituted for patients with hypomagnesemia related to thiazide or loop diuretics.<sup>159</sup> Amiloride may also blunt renal Mg losses associated with amphotericin B therapy.<sup>160</sup> Finally, the need for concurrent restoration of calcium, potassium and phosphate



should be considered in patients with hypomagnesemia and concomitant electrolyte disturbances.

## 6 | CONCLUSION

Hypomagnesemia is a frequent electrolyte disturbance and occurs with medications used in everyday clinical practice. It should not be disregarded as it may cause serious neuromuscular symptoms and cardiac arrhythmias and impair overall prognosis. Awareness and clinical suspicion are warranted in the course of therapy with certain drugs. Restoration of Mg and concurrent metabolic abnormalities is recommended, while alternative therapeutic regimens are advised if applicable.

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### CONFLICT OF INTEREST

None declared.

### AUTHOR CONTRIBUTION

GL conceived the idea of this review and wrote a major part of it, while he was in charge of the manuscript editing. EH contributed to the writing and editing of this review. MF contributed to the writing and editing of this review. HM contributed to the writing and editing of this review.

### ETHICAL STATEMENT

Not required for this paper.

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