Review Article

Kidney360

Hypomagnesemia in the Cancer Patient

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Abstract

Hypomagnesemia is a common medical problem that contributes to the morbidity and mortality of patients with cancer. This review summarizes magnesium physiology and highlights the mechanisms underlying magnesium disturbances due to cancer and cancer treatment. The causes of hypomagnesemia can be categorized according to the pathophysiologic mechanism: decreased intake, transcellular shift, gastrointestinal losses, and kidney losses. Patients with cancer are at risk for opportunistic infections, frequently experience cardiovascular complications, and often receive classes of medications that cause or exacerbate hypomagnesemia. Also, cancer-specific therapies are responsible for hypomagnesemia, including platinum-based chemotherapy, anti-EGF receptor mAbs, human EGF receptor-2 target inhibitors (HER2), and calcineurin inhibitors. Urinary indices, such as the fractional excretion of magnesium, can provide useful information about the etiology. The management of hypomagnesemia depends on the magnitude of hypomagnesemia and the underlying cause. We recommended checking serum magnesium at the beginning of treatment and as part of routine monitoring throughout cancer treatment. Opportunities exist for potential research and practice improvement, including further characterization of hypomagnesemia regarding the clinical effect on cancer outcomes, preventing hypomagnesemia in patients receiving high-risk anticancer agents, and developing effective therapeutic strategies.

Introduction

Hypomagnesemia is defined as a serum magnesium (Mg) concentration of <1.8 mg/dl (1). It is essential to anticipate, identify, and treat hypomagnesemia in patients with cancer. This review summarizes the mechanisms underlying the disturbances of Mg deficiency due to cancer and during cancer treatment. Although Mg is frequently referred to as the "forgotten ion," it is the second most abundant intracellular cation (after potassium [K]), acts as a cofactor for hundreds of enzymatic reactions, and has structural functions for both proteins and nucleic acids (2). The range of symptoms associated with hypomagnesemia is consequently expansive; patients can be asymptomatic and exhibit nonspecific symptoms (such as anorexia, nausea, and fatigue) and severe symptoms (such as tetany, seizures, and lethal arrhythmias) (2). Hypomagnesemia is graded on the basis of serum concentration (Table 1) and the degree of hypomagnesemia is generally correlated with adverse outcomes. However, it is important to note that clinically significant adverse effects and outcomes can occur with any degree of hypomagnesemia. This review will summarize Mg's physiology and review cancer-related causes of hypomagnesemia.

Epidemiology and Clinical Outcomes

In general, hypomagnesemia frequently develops in patients with cancer, and patients who are hospitalized or critically ill are at enhanced risk for hypomagnesemia, occurring in up to 50%–60% of patients (3). Cancer often results in compromised immunity, predominantly liquid tumors, or those that affect hematopoiesis. Furthermore, most cancer therapies compromise the immune system, and patients are at exceptionally high risk for opportunistic infections. The administration of antibiotics and antiviral drugs contributes to hypomagnesemia (4). Cardiovascular and kidney related complications resulting from cancer and cancer therapy frequently require the use of cardiovascular medications that can contribute to hypomagnesemia. Traditional chemotherapeutic agents cause hypomagnesemia that can persist for months to years after cessation of cancer therapy (5). Patients who survived childhood cancer are at a particular risk of developing adverse effects caused by multimodal treatment for their malignancy (6). Studies that have assessed hypomagnesemia in patients who have survived cancer determined a prevalence ranging between 13% and 29% (7–10).

Hypomagnesemia, in both acute and chronic forms, is associated with poor clinical outcomes. Chronic hypomagnesemia is implicated in developing insulin resistance, diabetes, more rapid progression of diabetic nephropathy, nephrolithiasis, fracture, and increased risk for cancer (11–13). Chronic hypomagnesemia has also been implicated in cancer development, possibly in relation to the induction of chronic inflammation

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Table 1.   Grades of hypomagnesemia according to common terminology criteria used by cancer societies for adverse events reported, version 4.0

Grade	Serum Magnesium (mg/dl)	Clinical Significance
1	1.2–1.7	Mild or no symptoms, fatigue
2	0.9–1.2	Muscle weakness, fasciculations
3	0.7–0.9	Neurologic deficits, atrial fibrillation
4	<0.7	Psychosis, seizures, tetany, nystagmus, lethal arrhythmia

(14). Hypomagnesemia can result in higher viral titers of patients infected with Epstein–Barr virus, which raises the risk for lymphomas and other malignancies (15). Preclinical data support hypomagnesemia as a contributing factor to metastatic disease (16), and studies in patients with cancer show hypomagnesemia is associated with worse outcomes (17).

Physiology of Mg Homeostasis

The physiology of Mg regulation is complex, and the dysregulation of Mg homeostasis is common in patients with cancer and results in frequent complications. Understanding the physiology discussed in this section will clarify the effect of some of the cancer-specific and targeted therapies we will discuss in this review.

Mg Distribution

Total body Mg is close to 24 g for an average adult, and 99% of total body Mg is located in the intracellular fluid compartment (bone, muscle, and soft tissues), leaving 1% present in the extracellular fluid compartment. Nearly 30% of the total plasma Mg is bound to proteins, mainly albumin. The remaining 70% is available for glomerular filtration, either as the Mg cation complexed to anions—including oxalate (10%), phosphate, and citrate—or as ionized Mg (60%).

Mg Balance

Mg is a micronutrient mostly derived from nuts (almonds), green vegetables, cereal, and milk. The intestines absorb 120 mg/d (30%–50%) of Mg and secrete 20 mg/d in bile and pancreatic and intestinal juices, representing a net absorption of 100 mg/d (18). Under conditions of Mg deficiency, the intestines can absorb up to 80% of dietary Mg (19). The kidneys filter approximately 2400 mg/d of Mg, of which they reabsorb 2300 mg/d (90%–95%) for a net excretion of 100 mg/d. In the setting of Mg deficiency, net kidney Mg excretion is reduced to <12 mg/d (20).

Gastrointestinal Absorption

Mg absorption in the gut occurs *via* two routes: a saturable, paracellular route and a nonsaturable, transcellular route (21). The paracellular route is a passive mechanism and accounts for the bulk (90%) of total Mg reabsorption. The paracellular route is modulated by tight junction proteins called claudins. Claudins 2, 7, and 12 are expressed in the intestines and might facilitate Mg reabsorption (22). The final segment for Mg reabsorption occurs in the cecum and colon using the transcellular route, which is an active process and accounts for 10% of Mg reabsorption. Transcellular Mg transport requires the activity of transient receptor potential melastatin 6 (TRPM6) and 7 (TRPM7) Mg transporters in the enterocyte apical membrane.

Kidney Handling of Mg

In the kidney, nonprotein-bound Mg is freely filtered across the glomerulus. The proximal tubule (PT) reabsorbs 15% of filtered Mg through a paracellular mechanism (23,24). Water reabsorption along the early parts of the PT increases Mg concentration in the tubular lumen, creating a favorable gradient for Mg reabsorption in the distal section of the PT. Solvent drag also contributes to Mg reabsorption in this segment of the nephron. Extracellular-fluid volume expansion results in decreased Mg reabsorption along with the PT (25).

Unlike most solutes, most Mg reabsorption occurs in the cortical thick ascending limb of the loop of Henle (TAL) rather than the PT. In the TAL, approximately 70% of the filtered Mg is reabsorbed, mainly through the paracellular route (Figure 1). Claudins 16 and 19 are considered the main claudins responsible for Mg permeability through the paracellular route (26). Claudin 14 interacts with claudin 16 in the TAL and decreases the cation selectivity of the claudin 16–19 complexes (27). Claudin 10 has also been identified as a vital constituent in cation selectivity in the TAL, as demonstrated in claudin 10–knockout mice which demonstrated hypermagnesemia, nephrocalcinosis, and impaired paracellular sodium (Na) permeability (28). In the absence of claudin 10, TAL tight junctions become more permeable to calcium and Mg. The driving force for paracellular Mg reabsorption, along with calcium and Na, is the lumen-positive transepithelial voltage of the TAL determined by the activity of the Na-K–2 chloride (Cl) cotransporter (NKCC2) and the associated K recycling *via* the renal outer medullary K (ROMK) channel (29). Cl ions leave the TAL cells *via* ClC-Kb channels on the basolateral membrane. Mutations in the genes encoding for NKCC2, ROMK, ClC-Kb, and Barttin (a subunit of ClC-Kb) lead to Bartter syndromes type 1, 2, 3, and 4, respectively, all of which are associated with various degrees of hypomagnesemia. Compensation for reduced TAL Mg reabsorption may occur in the distal convoluted tubule (DCT), which explains why patients with Bartter syndrome often have normal Mg levels. ClC-Kb and Barttin are also expressed in DCT, and patients with mutations in these genes frequently exhibit hypomagnesemia. Activation of the calcium-sensing receptor (CaSR) in the TAL by calcium or Mg inhibits paracellular Mg transport *via* inhibition of NKCC2 and ROMK (30). CaSR also regulates claudin 14 expression and calcium
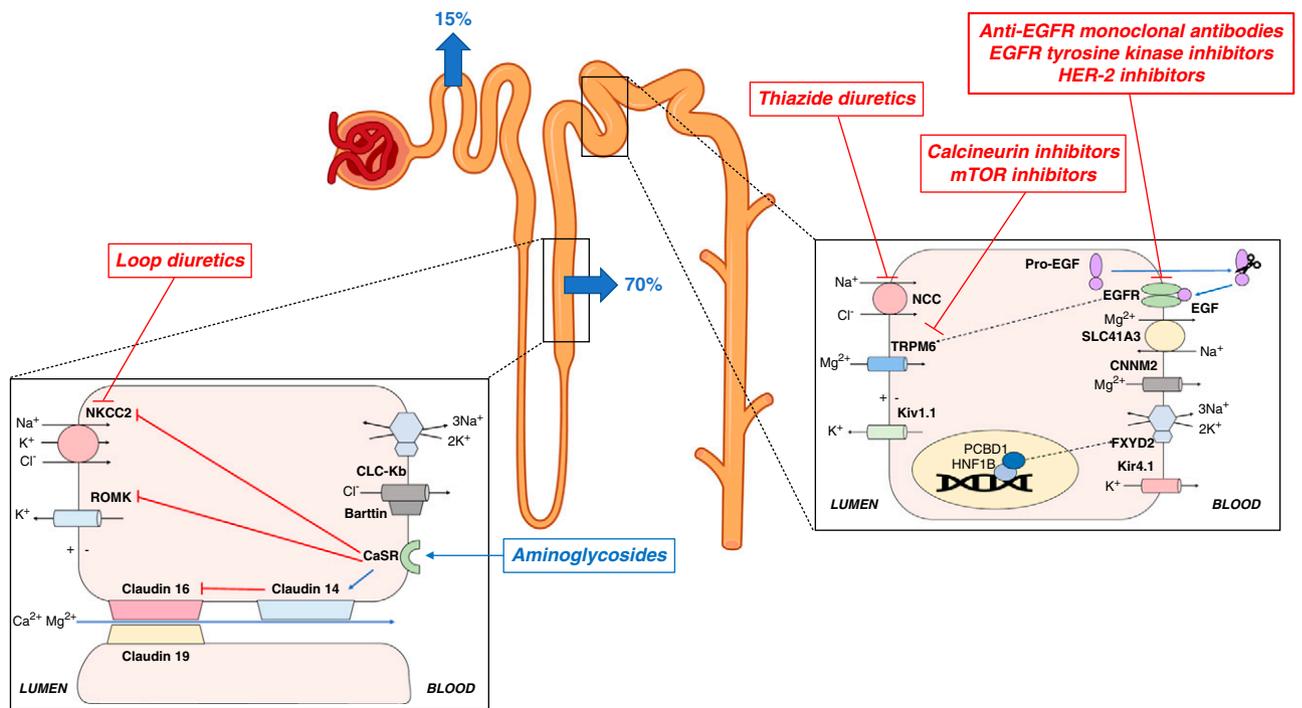
Figure 1. | Kidney handling of magnesium (Mg) and nephron site of action of magnesiuric drugs. Numbers in blue (%) refers to the percent Mg that is reabsorbed in the specific segment of the nephron. Nonprotein-bound Mg is freely filtered across the glomerulus. The proximal tubule (PT) reabsorbs 15% of filtered magnesium *via* a paracellular mechanism. The bulk of Mg reabsorption occurs in the cortical thick ascending limb of the loop of Henle (TAL), where approximately 70% of Mg is reabsorbed *via* a paracellular route. Claudins 16 and 19 are considered the main claudins responsible for the Mg permeability through the paracellular route. Claudin 14 may interact with claudin 16 in TAL and decreases the cation selectivity of the claudin-16 and -19 complexes. Recently, claudin 10 has also been identified as an important factor in cation selectivity in TAL. The driving force for paracellular Mg reabsorption is the lumen-positive transepithelial voltage of the TAL, which is determined by the activity of NKCC2 and the subsequent potassium recycling back into the lumen *via* the ROMK channel at the apical membrane. Cl ions leave the TAL cells *via* ClC-Kb channels on the basolateral membrane. Activation of the CaSR in the TAL inhibits paracellular Mg transport *via* inhibition of NKCC2 and ROMK. Further, CaSR regulates claudin-14 expression and calcium and Mg reabsorption in the TAL. Aminoglycosides target the CaSR and foscarnet can chelate the Mg molecule. The site for fine-tuning magnesium regulation is the distal convoluted tubule (DCT), which is responsible for the reabsorption of 10% of filtered magnesium. No Mg reabsorption takes place beyond the DCT. Mg is reabsorbed in this nephron segment *via* the transcellular route through the TRPM6 Mg channels. EGF regulates TRPM6 by increasing its expression. EGF is synthesized as pro-EGF, which is then secreted by DCT cells to undergo cleavage by extracellular proteases to become EGF. EGF then binds to the EGFR at the basolateral membrane, thereby activating a tyrosine kinase, which stimulates TRPM6. NCC seems to be involved in Mg reabsorption in the DCT. Mg transport *via* TRPM6 depends almost exclusively on the negative membrane potential in the DCT cells because no significant chemical gradient for Mg exists in this nephron segment. Kiv1.1 is primarily responsible for maintaining the necessary negative membrane potential for Mg reabsorption in the DCT by providing an efflux of potassium, resulting in hyperpolarization of the luminal membrane. The activity of the Na-K-ATPase in the basolateral membrane also affects the membrane potential and is the driving force for Mg reabsorption. The FXYD2 gene encodes for the γ-subunit of the Na-K-ATPase. The transcription factor hepatocyte NF 1β (HNF1B) regulates the expression of FXYD2. The PCBD1 gene encodes for pterin-4a carbinolamine dehydratase, which is a dimerization cofactor for HNF1B. The activity of the Na-K-ATPase is also dependent on potassium recycling *via* Kir4.1 channels in the basolateral membrane. The elucidation of the mechanism for basolateral Mg extrusion in the DCT has been challenging because there is no chemical gradient for Mg and the electrical gradient favors Mg uptake rather than extrusion. Therefore, it is likely that Mg extrusion is dependent on the sodium gradient set by the Na-K-ATPase. Several proteins in the basolateral membrane of DCT cells have been postulated to mediate Mg transport into the bloodstream. SCL41A3 and CNNM2 have been identified as potential Mg transporters in the basolateral membrane of DCT cells. Calcineurin and mTOR inhibitors affect the TRPM6 channel, and EGFR monoclonal antibodies and HER-2 inhibitors inhibit the basolateral EGFR. Cisplatin and pentamidine affect the transport of the Mg within the DCT (not shown in the figure). Ca^{2+}, calcium ion; CaSR, calcium-sensing receptor; Cl^-, chloride ion; ClC-Kb, Cl channel Kb; CNNM2, cyclin and CBS domain divalent metal cation transport mediator 2; EGFR, EGF receptor; FXYD2, FXYD domain containing ion transport regulator 2; K^+, potassium ion; Kir4.1, inwardly rectifying potassium channel subtype 4.1; Kv1.1, voltage-gated potassium channel; Mg^{2+}, Mg ion; mTOR, mammalian target of rapamycin; Na^+, sodium ion; NCC, Na^+-Cl^- cotransporter; NKCC2, Na^+-K^+-$2Cl^-$ cotransporter; PCBD1, pterin-4a carbinolamine dehydratase; ROMK, renal outer medullary K^+ channel; SLC41A3, solute carrier family 41 member 3; TRPM6, transient receptor potential cation channel subfamily M member 6.

and Mg reabsorption in the TAL by downregulation of two microRNAs, miR-9 and miR-374 (27).

The site for fine-tuning Mg regulation in the nephron is the DCT (Figure 1), which is responsible for the reabsorption of 10% of filtered Mg. Mg is reabsorbed in this nephron segment *via* the transcellular route through the TRPM6 Mg channels. Insulin and EGF regulate TRPM6 by increasing its expression. EGF is synthesized as pro-EGF, which is then

secreted by DCT cells to undergo cleavage by extracellular proteases to become EGF. EGF then binds to the EGF receptor (EGFR) at the basolateral membrane, thereby activating a tyrosine kinase, which stimulates TRPM6. Mutations in the EGF gene lead to isolated recessive hypomagnesemia due to impaired basolateral sorting of pro-EGF (31), therefore preventing TRPM6 activity. The Na-Cl cotransporter (NCC) seems to be involved in Mg reabsorption in the DCT. Mutations in NCC caused Gitelman syndrome, which is characterized by normotensive hypokalemic metabolic alkalosis and hypomagnesemia. NCC-knockout mice express reduced levels of TRPM6, possibly explaining the renal Mg wasting observed in Gitelman syndrome; however, the atrophy of the DCT segment observed in NCC-knockout mice may partially explain this phenomenon (32,33). Mg transport *via* TRPM6 depends almost exclusively on the negative membrane potential in the DCT cells because no significant chemical gradient for Mg exists in this nephron segment. The voltage-gated K channel Kv1.1 is primarily responsible for maintaining the necessary negative membrane potential for Mg reabsorption in the DCT by providing an efflux of K, resulting in hyperpolarization of the luminal membrane (34).

The Na-K-ATPase activity in the basolateral membrane also affects the membrane potential and is the driving force for Mg reabsorption. For example, mutations in the FXYD2 gene, encoding for the γ-subunit of the Na-K-ATPase (35), cause a defective routing of the protein and results in isolated dominant hypomagnesemia. Na-K-ATPase activity is also dependent on K recycling *via* Kir4.1 K channels in the basolateral membrane.

Etiology of Hypomagnesemia in Cancer

The causes of hypomagnesemia in cancer are diverse, and their pathophysiologic mechanisms can be categorized as follows: decreased intake, transcellular shift, gastrointestinal (GI) losses, and kidney losses (Table 2).

Decreased Intake

The recommended daily Mg allowance prescribed by the Food and Drug Administration (FDA) is 300–400 mg/d. Unfortunately, appetite loss and involuntary weight loss are part and parcel of progressive cancer and cancer treatment, occurring in >80% of diagnosed patients (36). Micronutrient deficiency is common and, early in the course of cancer, serum Mg levels may mask deficiency because they can be drawn from intracellular and skeletal stores (37). Therefore, this condition demands vigilance on the part of providers.

Transcellular Shift

Patients with cancer frequently have periods of low or no caloric intake and can be at risk for refeeding syndrome, which, in addition to other solutes, causes the shift of Mg from plasma into red blood cells (RBCs) and platelets (38). Pamidronate is often used to treat hypercalcemia of malignancy and has been found to cause significant hypomagnesemia, which is attributed to the transcellular shift of Mg into cells (39). Catecholamines also shift Mg into cells due to the stimulation of β-adrenergic receptors, which is commonly observed in patients critically ill with cancer and who also have other risk factors for hypomagnesemia. Additionally, massive blood transfusions (typically ten or more units of packed RBCs) may cause low ionized Mg due to the chelation of Mg by citrate (40). Lastly, acute pancreatitis can cause hypomagnesemia, presumably from the saponification of Mg in necrotic fat (41,42).

GI Losses

GI secretions contain a significant concentration of Mg, and losses *via* the GI tract are frequently observed in patients with cancer. Although nausea and vomiting are frequently conflated as causes, Mg depletion is primarily related to diarrhea (43). This is because the Mg content of lower GI tract secretions is significantly higher (up to 15 mEq/L versus approximately 1 mEq/L for the upper GI tract), and the loss of volume is typically greater, than in the upper GI tract. Cancer and cancer therapies can potentiate chronic diarrhea by one or more mechanisms that can be characterized as secretory, osmotic, inflammatory, and relating to dysmotility.

Neuroendocrine tumors can cause diarrhea that is secretory (no osmotic gap between serum and stool), typically causing large-volume stools (43). A classic example of tumor-induced secretory diarrhea is a carcinoid tumor, which is associated with serotonin syndrome. Other paraneoplastic syndromes can cause secretory diarrhea and subsequent hypomagnesemia (44,45). Traditional chemotherapy drugs, such as 5-fluorouracil and irinotecan, affect cells with rapid turnover, like those typically found in the GI tract, and the epithelial damage results in secretory diarrhea.

Frequently, the treatment plan for cancer involves cytoreductive surgery involving partial resection of the GI tract. This can result in short-gut or dumping syndrome, giving rise to osmotic diarrhea caused by the premature introduction of the undigested nutrients into sections of the small bowel that are not prepared to handle them. Patients after surgery or tumor obstruction may require total parenteral nutrition (TPN). Balance studies in patients on TPN indicate that about 0.5 mEq of Mg is retained for each gram of nitrogen. These values indicate that Mg requirements are substantial in such patients and, in most cases, explain the development of hypomagnesemia during a course of TPN. Patients with solid tumor malignancy who are receiving TPN are more likely to develop hypomagnesemia, possibly because of the increased requirements for Mg in lymphocytolysis of tumor cells, and they must be carefully monitored to prevent this complication (46).

Patients with cancer may suffer from severe GI disease and chronic pancreatitis from complications of therapy. In the setting of steatorrhea, Mg deficiency often develops (47). There are several agents, mainly traditional chemotherapies, that cause pancreatitis, and pancreatic insufficiency can be a cause of chronic hypomagnesemia. A number of agents, such as 5-fluorouracil, are associated with autonomic neuropathy and GI dysmotility, resulting in chronic diarrhea (48). Peripheral autonomic neuropathy is a common feature of bortezomib. The GI damage is time dependent and diarrhea is reported in >30% of patients who receive the drug (49,50).

Inflammatory diarrhea has been reported with specific chemotherapy agents, such as pemetrexed, carboplatin, and

Table 2.   Etiology of hypomagnesemia

Etiology	Causes and Consequences
Dietary deficiency of magnesium	Starvation, protein-calorie malnutrition, total parenteral nutrition, enteral feeding with inadequate magnesium
Magnesium redistribution	Blood transfusions, acute pancreatitis, refeeding syndrome
Gastrointestinal losses	Diarrhea, vomiting, nasogastric suction, malabsorption, gastrointestinal fistulae, bowel resection, drug related (*e.g.*, PPIs, laxative abuse)
Kidney losses	Ketoacidosis, hypercalcemia, hypoparathyroidism, hyperaldosteronism, hypervitaminosis D, chemotherapeutic agents (*e.g.*, cisplatin, cetuximab), nonchemotherapy drugs (*e.g.*, diuretics)
Transdermal losses	Burns, excess sweating

PPI, proton-pump inhibitor.

gemcitabine (51). Novel agents, such as immune checkpoint inhibitors, have also been implicated as a cause of diarrhea. Checkpoint inhibitors are increasingly being used for a broad spectrum of cancers in clinical practice and they have the potential to induce inflammation in the GI tract that is immune mediated (48). Pelvic or abdominal radiation therapy can cause acute injury and chronic enteritis, resulting in diarrhea (52). Inflammatory diarrhea can be seen with cytomegalovirus and other opportunistic infections, and the antimicrobials used for their treatment are another major cause of chronic diarrhea. Lastly, the availability and rate of allogeneic stem cell transplantation has expanded, and diarrhea is a frequent complication as a result of opportunistic infections and in cases of acute graft-versus-host disease (53).

The use of proton-pump inhibitors (PPIs) in patients with cancer is pervasive and deserves consideration as a potential cause of hypomagnesemia (41). PPIs have been demonstrated to reduce the expression of claudins 7 and 12 in the gut (49). PPIs decrease the negative electric-field strength within the claudin-7 and -12 channels required to strip the Mg ions' hydration shell before passing through the claudin channel. In a study of 366 patients hospitalized with hypomagnesemia and matched controls (50), current PPI use was associated with a 43% higher relative risk (RR) for hypomagnesemia (adjusted odds ratio, 1.43; 95% CI, 1.06 to 1.93), and the risk was significantly increased among patients receiving diuretics (odds ratio, 1.73; 95% CI, 1.11 to 2.70). The sum of experimental and clinical investigations appear to suggest that PPI use may contribute to hypomagnesemia, primarily in patients who have other risk factors for hypomagnesemia, and this applies to most patients with cancer.

Kidney Related Losses

Supportive drugs commonly used in cancer cause hypomagnesemia (Table 3). Thiazide and loop diuretics, which are used in patients with cancer, can cause hypomagnesemia due to reduced paracellular Mg absorption *via* claudins 16 and 19 (44,52) and downregulation of TRPM6 in the DCT, respectively (45,52). Infectious disease is also a common complication of cancer and cancer therapy, and several therapies result in hypomagnesemia (these are outlined in Tables 3 and 4). Other drugs causing hypomagnesemia include pamidronate, denosumab, and—rarely—nonsteroidal anti-inflammatory drugs (44,47,49,53).

Cancer-Specific Therapies

Anti-EGF Receptor mAbs

Both incidence and severity of hypomagnesemia are high in patients receiving mAbs targeting the EGFR, particularly cetuximab and panitumumab. Urine Mg wasting is the causative etiology of hypomagnesemia at the DCT (Figure 1) (46). Studies show the incidence of hypomagnesemia related to anti-EGFR mAbs was 34% compared with 10% in controls (95% CI, 28% to 41%; $P<0.001$) (54). Patients with colorectal cancer had the highest risk of grade 3/4 hypomagnesemia events among patients with cancer: compared with chemotherapy alone, the addition of cetuximab increased the risk of grade-3/4 hypomagnesemia with RRs of 7.14 (95% CI, 3.13 to 16.27; $P<0.001$), whereas patients receiving panitumumab were even more vulnerable to grade-3/4 hypomagnesemia (RR, 18.29; 95% CI, 7.29 to 48.41; $P<0.001$) (54). The most important risk factor for hypomagnesemia in patients receiving anti-EGFR mAbs is treatment duration. Other risk factors that have been reported include a patient's age (greater incidence in the elderly) and the baseline serum Mg level (31,55–58). Hypomagnesemia is seen less frequently with zalutumumab, with an incidence reported to be only 4% (59). Hypomagnesemia has been reported with all three EGFR-related tyrosine kinase inhibitors—such as afatinib, erlotinib, and gefitinib—to treat non–small cell lung cancer; the overall incidence of hypomagnesemia with these drugs seems to be less than that with anti-EGFR mAbs (60).

Platinum-Based Chemotherapy

Cisplatin and, to a much lesser extent, carboplatin therapy, is associated with hypomagnesemia, more so than any other electrolyte deficiency (5,61,62). Hypomagnesemia affects 40%–90% of patients on cisplatin; in contrast, 10% of patients treated with carboplatin or oxaliplatin experience hypomagnesemia (63). Platinum-induced hypomagnesemia can persist for up to 6 years after cessation of treatment and is primarily attributed to renal Mg wasting (62,64). Cisplatin causes direct injury to tubular cells in the TAL and DCT and is the likely mechanism by which cisplatin induces hypomagnesemia. Also, cisplatin can lead to Mg loss from the gut because vomiting, diarrhea, and anorexia are common complications of platinum therapy. Importantly, hypomagnesemia can potentiate cisplatin-induced AKI (65), and preclinical studies have shown a protective effect of normal

serum Mg levels in models of cisplatin-induced nephrotoxicity (66–68).

Human EGFR-2 Target Inhibitors

Human EGFR-2 (HER-2) is a member of the EGFR family of transmembrane receptors and is overexpressed in approximately 20% of breast cancers. A recent review of the FDA adverse-events reporting for trastuzumab and pertuzumab has uncovered significant hypomagnesemia rates with HER-2 inhibitors (61,69,70). It is hypothesized that kidney related Mg loss is due to decreased reabsorption from the DCT (71).

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) are also used in patients for several hematologic cancers and post–hematopoietic stem cell transplantation to prevent graft-versus-host disease (72). Hypomagnesemia is a well-recognized and common complication of CNI treatment (73). It has been linked with post–kidney transplant diabetes mellitus (hazard ratio, 1.78; 95% CI, 1.29 to 2.45; $P<0.001$) (74). Treatment with two chemically distinct CNIs, cyclosporine or tacrolimus, was found to reduce the abundance of calbindin-D28K, an effect postulated to account for calcium wasting (75,76). Tacrolimus treatment increases the fractional Mg and calcium excretion and reduces the expression of TRPV5 and calbindin-D28K (77). The transcription for TRPM6 is also reduced by tacrolimus treatment (78). These actions were suggested to account for the hypomagnesemia and hypercalciuria that result from CNI treatment (78). Table 4 summarizes the antineoplastic agents that have been associated with hypomagnesemia.

Clinical Manifestations of Hypomagnesemia

Mg is an essential electrolyte that plays a significant role as a cofactor for nearly every major biochemical pathway. Its deficiency can cause a wide array of acute and chronic clinical manifestations, either solely due to lack of Mg or in association with other electrolyte abnormalities, including hypocalcemia and hypokalemia (79). Neuromuscular manifestations have been well characterized, but there is emerging evidence that Mg influences BP, specifically low Mg leading to elevated BP, although studies are mixed (80,81).

The effects of hypomagnesemia on chemotherapy-induced peripheral neuropathy also vary (82,83). In addition, a systematic review of Mg infusions to prevent oxaliplatin-induced chronic peripheral neuropathy concluded that there was no benefit to supplemental Mg in this setting (84). Nevertheless, there are data showing that hypomagnesemia can contribute to atherosclerotic cardiovascular disease and congestive heart failure, which is common in patients who have survived cancer (85).

The contribution of hypomagnesemia to endocrinopathies and derangements in mineral metabolism is also increasingly recognized. Hypomagnesemia has been linked to impaired glucose homeostasis and may be a risk factor for the development of diabetes (11). Mild to moderate hypomagnesemia can interfere with mineral metabolism, increasing the secretion of parathyroid hormone, which can, in turn, inhibit the CaSR in the kidneys and promote Mg

reabsorption (86). Paradoxically, severe hypomagnesemia can also cause hypoparathyroidism and secondary hypocalcemia (87). This is because severe hypomagnesemia interferes with the activation of α-subunits of heterotrimeric G-proteins of the CaSR, mimicking its activation (86). Chronic hypomagnesemia can cause demineralization of bone and osteoporosis (88). Chronic hypomagnesemia can also result in hypercalciuria, which can contribute to nephrolithiasis (89).

It has been recognized for some time that hypomagnesemia has a critical influence on K homeostasis. It is estimated that >50% of clinically significant hypokalemia has concomitant Mg deficiency (90). Hypomagnesemia results in the release of inhibition of ROMK channels, increasing the secretion of K into the tubular lumen. Correction of K alone will not resolve hypokalemia in these cases, the correction of hypomagnesemia is also required.

Diagnosis

Hypomagnesemia may become evident from the medical history or symptoms listed in Table 1. RBC Mg levels may better reflect total body stores than serum levels. A typical RBC Mg level ranges from 4.2 to 6.8 mg/dl (91). There are other Mg measurement methods, including the ratio of ionized calcium and Mg and the Mg content of hair, muscle, and bone. These alternative measures are not readily accessible to most laboratories, and the normal values are not firmly established.

The distinction between GI and kidney losses can be made by measuring the 24-hour urinary Mg excretion. One can calculate the fractional excretion of Mg (FEMg) on a random urine specimen using the following formula:

$$FEMg \ = \ (U \times P)/([0.7 \times P] \times U) \times 100$$

U and P refer to urine and plasma concentrations of Mg, respectively. If the FEMg is >2% in someone with normal renal function, then renal Mg wasting is likely. If the FEMg is <2%, it suggests GI losses.

Management
Mg Replacement

The management of hypomagnesemia is guided by the magnitude of hypomagnesemia and its etiology. There is a strong rationale for Mg replacement in symptomatic cases; however, the utility of Mg replacement in milder forms has been extrapolated from associative data that we have reviewed, showing adverse outcomes. Hypomagnesemia without acute symptomatology can be treated with oral Mg replacement and by eliminating medications that may be contributing to the hypomagnesemia. Table 5 summarizes the various available oral Mg supplementations and their advantages and disadvantages (92). In severe or symptomatic hypomagnesemia, parenteral administration is required. Intramuscular replacement is also an option, but there is delayed absorption, of a few hours, from muscle stores. In the absence of seizures or lethal arrhythmia, the parenteral replacement rate should not exceed 1 g/h (93). Mg is cleared renally, therefore, parenteral or intramuscular replacement should be monitored in patients with advanced

Table 3. Drug-induced hypomagnesemia in a patient with cancer: adjunct agents used in patients with cancer

Drug Class or Name	Incidence	Mechanism	Reference
PPIs	19% of PPI users	Intestinal loss, malabsorption of magnesium. PPIs interfere with TRPM6 and TRPM7 genes, leading to intestinal malabsorption and possible renal Mg loss	(105–107)
Thiazide diuretics	Unknown	TRPM6 inhibition, leading to increase in renal Mg loss, increase in potassium excretion causes hypokalemia, leading to decrease in passive Mg reabsorption	(45,52)
Loop diuretics	Unknown	Decrease in paracellular reabsorption in thick ascending LOH, increase renal Mg loss, hypokalemia	(44,52)
Pamidronate	Case reports	Renal impairment, increased Mg excretion, and cellular shifting No other bisphosphate has been reported to cause hypomagnesemia	(44)
RANKL mAb (denosumab)	Isolated case report	Unknown	(53)
Ibuprofen	Isolated case report	Unknown	(47)
Aminoglycosides (amikacin, gentamicin, tobramycin, neomycin, streptomycin)	Unknown	Positively charged antibiotics act *via* a polyvalent cation-sensing extracellular receptor in DCT, leading to inhibition of PTH-mediated cAMP formation and Mg uptake in the DCT	(108–110)
Antituberculous agents (viomycin, capreomycin)	Unknown	Proximal tubular dysfunction, secondary hyperaldosteronism with consequent renal Mg loss	(111–113)
Amphotericin B	Unknown	This drug is a polyene antibiotic, and Mg participates in the polyene-sterol binding process, leading to a functional Mg deficiency	(114)
Theophylline	Unknown	Renal Mg wasting	(115)
Pentamidine	Unknown	Renal Tubular injury	(116–118)
Foscarnet	Up to 70%	Chelates divalent ions, thereby leading to acute reduction in ionized magnesium	(119,120)

PPI, proton-pump inhibitor; TRPM, transient receptor potential melastatin; Mg, magnesium; LOH, loop of Henle; RANKL, receptor activator of NF-κB ligand; DCT, distal convoluted tubule; PTH, parathyroid hormone.

Table 4. Drug-induced hypomagnesemia in a patient with cancer: antineoplastic agents

Drug Class	Drugs Reported to Cause Hypomagnesemia	Incidence	Mechanism	Reference
Anti-EGFR mAbs	Cetuximab, panitumumab, zalutumumab	34% for cetuximab; 4% for zalutumumab	Decrease stimulation of TRPM6 in DCT leading to renal Mg wasting (1), inhibition of TRPM6 channels in gut, causing decrease in Mg absorption from gut (2)	(31,54,59,60,69,121)
EGFR tyrosine kinase inhibitors	Afatinib, erlotinib, gefitinib	None reported	Postulated similar mechanism as EGFR antibodies	(60)
Platinum-based agents	Cisplatin, carboplatin, oxaliplatin	Cisplatin, 40%–90%;carboplatin and oxaliplatin, 10%	Downregulation of TRPM6/EGF pathway, may lead to persistent distal tubular dysfunction with a Gitelman-like syndrome, can also cause Mg loss from gut due to anorexia, vomiting, diarrhea	(63,122,123)
HER-2 inhibitors	Trastuzumab, pertuzumab	Patients on pertuzumab: 14% with HypoMg (≥G1), 9% with HypoMg (≥G1) in neoadjuvant setting	Inhibition of Mg reabsorption in DCT due to EGF blockade, secretory diarrhea	(71)
Calcineurin inhibitors	Cyclosporine, tacrolimus	Case series and reports	EGF production is downregulated, which in turn inhibits TRPM6 activation. Reduce mRNA expression of NCC, reduce transcript for TRPM6 in DCT	(124)
Immunotherapy	IL-2	Case reports	Unknown	(125)
mTOR inhibitors	Rapamycin	Case report	Reduction in mRNA expression of TRPM6 at the DCT *via* inhibition of EGF-induced increase in TRPM6 expression, likely by reducing the stability of TRPM6 mRNA	(126)
Topoisomerase inhibitors	Amsacrine	Case reports only	Unknown	(127)
Anthracyclines	Pegylated liposomal doxorubicin	Case reports only	Unknown	(128)
Alkylating agents	Ifosfamide	1%	Unknown	(129,130)

EGFR, EGF receptor; TRPM, transient receptor potential melastatin; DCT, distal convoluted tubule; Mg, magnesium; HER-2, human EGF receptor 2; HypoMg, hypomagnesemia; ≥G1, grade 1 or higher; NCC, renal sodium-chloride cotransporter; mTOR, mammalian target of rapamycin.

Table 5.   Common oral magnesium formulations and doses

Supplement	Elemental Magnesium Content	Advantages/Disadvantages
Magnesium oxide	61% elemental magnesium 242 mg in 400-mg tablet	Requires higher dosages to meet repletion, diarrhea is limiting complication
Magnesium hydroxide (milk of magnesia)	42% elemental magnesium 167 mg in 400 mg per 5-ml oral suspension	Over the counter, avoid in patients with creatinine clearance <30 cc/min
Magnesium citrate	16% elemental magnesium 48 mg elemental magnesium and 13 mg potassium in 290 mg per 5-ml oral solution	Diarrhea is a concern, used as a laxative, avoid in patients with creatinine clearance <30cc/min
Magnesium gluconate	5% elemental magnesium 27 mg in 500-mg tablet	Over the counter, excessive dosages lead to diarrhea
Magnesium chloride	12% elemental magnesium 64 mg in 535-mg tablet	Slowly absorbed, less renal excretion, Less diarrhea
Magnesium sulfate (Epsom salts)	10% elemental magnesium 98.6 mg in 1-g salts	Slowly absorbed, less renal excretion, less diarrhea
Magnesium lactate	12% elemental magnesium 84 mg in 84-mg tablet	Sustained release
Magnesium aspartate hydrochloride	10% elemental magnesium 122 mg in 1230-mg dietary supplement granules	Diarrhea is a side effect
Magnesium-protein complex	133 mg elemental magnesium bound to 26 mg soy protein	Less diarrhea, mostly used in pediatric patients

This data was obtained from Lexicomp Online and Ref. 92.

CKD to avoid the risk of heart block. However, otherwise normal individuals excrete >80% of the sizable parenteral load of Mg in the urine within 48 hours, even in the setting of deficiency, making adequate repletion of Mg a significant challenge (94). A potential explanation for the latter phenomenon is that intravenous Mg administration will result in plasma Mg peaks that may stimulate the CaSR in the TAL, with subsequent inhibition of paracellular Mg transport and magnesiuria. Furthermore, a rapid correction may contribute to other electrolyte losses, including kaliuresis; therefore, chemistries should be closely followed during repletion (95).

The management of cetuximab-induced hypomagnesemia can be challenging and deserves special mention. Firstly, oral Mg supplementation is poorly tolerated in the colorectal cancer population due to diarrhea (96). In this setting, patients with grade-2 hypomagnesemia may require weekly intravenous replacement (4 g of Mg sulfate). Mg replacement in patients with severe (grade-3/4) hypomagnesemia can be very challenging and requires 6–10 g of Mg sulfate daily. An initial strategy of intravenous replacement and frequent (three times a week) serum Mg monitoring helps guide the frequency of replacement until a steady state is reached. An alternative strategy for patients requiring frequent Mg sulfate infusion and who do not have an enormous tumor burden may be a "stop-and-go" approach to anti-EGFR mAb therapy (96,97), which does not usually result in recurrence of severe hypomagnesemia.

Amiloride

Amiloride is widely used in clinical medicine as a K-sparing diuretic. In addition to blocking the Na reabsorption in the distal tubule and collecting duct, amiloride has an additional property of enhancing renal Mg conservation (98). This property has been used to treat patients with renal Mg wasting of various etiologies, including nephrotoxicity after amphotericin therapy and other refractory hypomagnesemia (99,100). Amiloride can be considered in patients with cancer who have refractory hypomagnesemia and in whom it can be used safely.

Na-glucose cotransporter 2 Inhibitors

Na-glucose cotransporter 2 (SGLT2) inhibitors inhibit glucose reabsorption at the PT, increase urinary glucose excretion, and have been proven to be effective at controlling hyperglycemia in patients with type 2 diabetes. A meta-analysis of data collected from >15,000 patients showed significantly higher serum Mg levels in patients treated with SGLT2 inhibitors than in patients who were untreated (101). On average, serum Mg levels increased by 0.15–0.24 mg/dl, depending on the formulation. The authors hypothesize that elevated serum Mg levels might result from osmotic diuresis caused by SGLT2 inhibitors, but the exact mechanism is unknown. A more recent analysis investigated a similar treatment effect with dapagliflozin on serum Mg in patients with type 2 diabetes (102). The observation that SGLT2 inhibitors can improve serum Mg might be useful in refractory cases in those patients with cancer who meet the indication for, and who can safely use, SGLT2 inhibitors (103).

Other Therapies

The limitations of oral Mg supplementation are often reached without achieving goal concentrations because Mg itself can induce diarrhea. Alternatives have been proposed—such as Epsom salt baths (Mg sulfate), Mg oils, and creams—which the patient can absorb transdermally (37,104), but the magnitude of their effects and applications

at higher concentrations have not been well studied (Table 5).

Areas of Potential Research Opportunities

On a fundamental level, we need more comprehensive, descriptive analyses of patients with cancer to provide information about the incidence, prevalence, and cancer-related risk factors for hypomagnesemia. Opportunities exist to examine the relationship between Mg and carcinogenesis, survival, and response to therapy. Preventive strategies in patients receiving high-risk drugs, such as cisplatin and cetuximab, need further corroboration. Finally, the pace of drug development in oncology is unprecedented, and onconephrologists will need to maintain vigilance to identify therapies that induce or exacerbate hypomagnesemia and develop effective preventive and therapeutic strategies.

Author Contributions

K.D. Jhaveri and H. Rondon-Berrios conceptualized the study; K.D. Jhaveri, N.N. Uppal, H. Rondon-Berrios, and B.T. Workeneh wrote the original draft and were responsible for visualization; K.D. Jhaveri, H. Rondon-Berrios, N.N. Uppal, and B.T. Workeneh reviewed and edited the manuscript; H. Rondon-Berrios was responsible for methodology; and B.T. Workeneh was responsible for validation.

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