Hypomagnesemia in the cancer patient

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Abstract

Hypomagnesemia is a common medical problem that contributes to the morbidity and mortality of cancer patients. 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 by the pathophysiological mechanism: decreased intake, transcellular shift, gastrointestinal losses, and kidney losses. Cancer patients 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-EGFR monoclonal antibodies, human epidermal growth factor 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 on the clinical impact on cancer outcomes, preventing hypomagnesemia in patients receiving high-risk anti-cancer agents, and developing effective therapeutic strategies.
Introduction

Hypomagnesemia is defined as a serum magnesium (SMg) concentration of less than 1.8 mg/dL. It is essential to anticipate, identify, and treat hypomagnesemia in patients with cancer. This review summarizes the mechanisms underlying the disturbances of magnesium (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 and a cofactor for hundreds of enzymatic reactions, as well as structural functions for both proteins and nucleic acids. The range of symptoms associated with hypomagnesemia is consequently expansive; patients can be asymptomatic and exhibit non-specific symptoms like anorexia, nausea, fatigue, and severe symptoms such as tetany, seizures, and lethal arrhythmias. Hypomagnesemia is graded based on serum concentration (Table 1) and 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 cancer patients, and hospitalized or critically ill patients are at enhanced risk for hypomagnesemia, occurring in up to 50-60% of patients. 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. Cardiovascular and renal complications resulting from cancer, cancer therapy, and 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. Childhood cancer survivors are at a particular risk of developing adverse effects caused by multimodal treatment for their malignancy. Studies that have assessed hypomagnesemia in cancer survivors determined a prevalence ranging between 13.2% and 28.6%.

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. Chronic hypomagnesemia has also been implicated in cancer development, possibly related to the induction of chronic inflammation. Hypomagnesemia can result in higher viral titers of Epstein Barr virus-infected patients, which raises the risk for lymphomas and other malignancies. Preclinical data support hypomagnesemia as a contributing factor to metastatic disease, and studies in cancer patients show hypomagnesemia is associated with worse outcomes.

**Physiology of Magnesium Homeostasis**

The physiology of Mg regulation is complex, and the dysregulation of Mg homeostasis is common in cancer patients 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.

_Magnesium Distribution_
The 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 (ECF) compartment. Nearly 30% of the total plasma Mg is bound to proteins, mainly albumin. The remaining 70% is available for glomerular filtration either as Mg cation complexed to anions, including oxalate (10%), phosphate, citrate, and the remainder exists as ionized Mg (60%).

**Magnesium Balance**

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

**Gastrointestinal Absorption**

Mg absorption in the gut occurs via two routes: a saturable paracellular route and a non-saturable transcellular route. 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. 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 Magnesium

In the kidney, non-protein bound Mg is freely filtered across the glomerulus. The proximal tubule (PT) reabsorbs 15% of filtered Mg through a paracellular mechanism. 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 proximal tubule. 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.

Unlike most solutes, most Mg reabsorption occurs in the cortical thick ascending limb of the Loop of Henle (TAL) rather than the proximal tubule. 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. Claudin 14 interacts with claudin 16 in TAL and decreases the cation selectivity of the claudin 16-19 complexes. Also, claudin 10 has been identified as a vital constituent in cation selectivity in TAL, as demonstrated in claudin-10 knock-out mice, showing hypermagnesemia, nephrocalcinosis, and impaired paracellular sodium permeability. 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 sodium, is the lumen positive transepithelial voltage of the TAL determined by the activity of the Na-K-2Cl cotransporter (NKCC2) and the associated potassium recycling via the renal outer medullary K (ROMK) channel. Chloride ions leave the TAL cells via CIC-Kb channels on the basolateral membrane. Mutations in the genes encoding for NKCC2, ROMK, CIC-Kb, and Barttin (a subunit of CIC-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 Bartter’s patients often have normal Mg levels. CIC-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 ROMK30. CaSR also regulates claudin 14 expression and calcium and Mg reabsorption in the TAL by downregulation of two microRNAs, miR-9 and miR-37427.

The site for fine-tuning Mg regulation in the nephron is the DCT (Figure 1), 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 the Epidermal Growth Factor (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 becoming 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 (IRH) due to impaired basolateral sorting of pro-EGF31, therefore preventing TRPM6 activity. The sodium chloride 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 knock-out mice express reduced levels of TRPM6, possibly explaining the renal Mg wasting observed in Gitelman syndrome, although the atrophy of the DCT segment observed in NCC knock-out mice may partially explain this phenomenon32,33. Mg transport via TRPM6 depends almost exclusively on the negative membrane potential in the DCT cells as no significant chemical gradient for Mg exists in this nephron segment. The voltage-gated potassium channel Kv1.1 is primarily responsible for maintaining the necessary negative membrane potential for
Mg reabsorption in the DCT by providing efflux of potassium 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 \(\gamma\)-subunit of the Na-K-ATPase\(^{35}\) cause a defective routing of the protein resulting in Isolated Dominant Hypomagnesemia (IDH). Na-K-ATPase activity is also dependent on potassium recycling via Kir4.1 potassium channels in the basolateral membrane.

**Etiology of hypomagnesemia in cancer**

The causes of hypomagnesemia in cancer are diverse, and their pathophysiological mechanism can categorize them: decreased intake, transcellular shift, gastrointestinal losses, and kidney losses (Table 2).

**Decreased intake**

The recommended daily Mg allowance prescribed by the FDA is 300-400mg/day. Unfortunately, appetite loss and involuntary weight loss are part and parcel of progressive cancer and cancer treatment, occurring in over 80% of diagnosed patients\(^{36}\). Micronutrient deficiency is common, and early in the course, SMg levels may mask deficiency because it 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 and platelets\textsuperscript{38}. Pamidronate is often used to treat hypercalcemia of malignancy and has been found to cause significant hypomagnesemia attributed to the transcellular shift of Mg into cells.\textsuperscript{39} Catecholamines also shift Mg into cells due to the stimulation of beta-adrenergic receptors, commonly observed in critically ill cancer patients who also have other risk factors for hypomagnesemia. Additionally, massive blood transfusions (typically 10 or more units of packed RBCs) may cause low ionized Mg due to the chelation of Mg by citrate\textsuperscript{40}. Lastly, acute pancreatitis can cause hypomagnesemia, presumably from the saponification of Mg in necrotic fat\textsuperscript{41,42}.

\textit{Gastrointestinal losses}

Gastrointestinal (GI) secretions contain a significant concentration of magnesium, and losses via the gastrointestinal tract are frequently observed in cancer patients. Although nausea and vomiting are frequently conflated as causes, magnesium depletion is primarily related to diarrhea\textsuperscript{43}. This is because the magnesium 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. Cancer and cancer therapies can potentiate chronic diarrhea by one or more mechanisms that can be characterized as secretory, osmotic, inflammatory, and dysmotility.

Neuroendocrine tumors can cause diarrhea that is secretory (no osmotic gap between serum and stool), typically causing large-volume stools\textsuperscript{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\textsuperscript{49,50}. 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 gastrointestinal 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 magnesium is retained for each gram of nitrogen. These values indicate that magnesium 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 getting TPN are more likely to develop hypomagnesemia, possibly because of the increased requirements for magnesium in lymphocytolysis of tumor cells, and they must be carefully monitored to prevent this complication.

Cancer patients may suffer from severe gastrointestinal disease and chronic pancreatitis from complications of therapy. In the setting of steatorrhea, magnesium deficiency often develops. 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. Peripheral autonomic neuropathy is a common feature of bortezomib. The gastrointestinal damage is time-dependent and diarrhea is reported in over 30% of patients who receive the drug.

Inflammatory diarrhea has been reported with specific chemotherapy agents such as pemetrexed, carboplatin, and gemcitabine. 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. Pelvic or abdominal
radiation therapy can cause acute injury and chronic enteritis, resulting in diarrhea.\textsuperscript{48} Inflammatory diarrhea can be seen with cytomegalovirus (CMV) and other opportunistic infections, and 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 (GVHD)\textsuperscript{51}.

Proton-pump inhibitors (PPI) use in cancer patients is pervasive and deserve consideration as a potential cause of hypomagnesemia\textsuperscript{45}. PPIs have been demonstrated to reduce claudins 7 and 12 expression in the gut \textsuperscript{46}. PPIs decrease the negative electric field strength within claudin 7 and 12 channels required to strip the Mg ions’ hydration shell before passing through the claudin channel. In a study of 366 hospitalized patients with hypomagnesemia and matched controls\textsuperscript{47}, current PPI use was associated with a 43% higher RR for hypomagnesemia (adjusted OR, 1.43; 95% CI 1.06-1.93) and the risk was significantly increased among patients receiving diuretics (OR, 1.73; 95% CI 1.11-2.70). It appears the sum of experimental and clinical investigations suggests PPI use may contribute to hypomagnesemia, primarily in patients who have other risk factors for hypomagnesemia, and this applies to most cancer patients.

\textit{Renal losses}

Supportive drugs commonly used in cancer cause hypomagnesemia (\textbf{Table 3}). Thiazide and loop diuretics are used in cancer patients and can cause hypomagnesemia via reduced paracellular Mg absorption via claudins 16 and 19\textsuperscript{48,49} and downregulation of TRPM6 in DCT respectively\textsuperscript{48,50}. Infectious disease is also a common complication of cancer and cancer therapy, and several therapies result in hypomagnesemia and are outlined in \textbf{Tables 3 and 4}. Other drugs causing hypomagnesemia include pamidronate, denosumab, and rarely NSAIDS \textsuperscript{46,49,51,52}. 
Cancer-Specific Therapies

Anti-EGFR monoclonal antibodies

Both incidence and severity of hypomagnesemia are high in patients receiving monoclonal antibodies (MAbs) targeting the epidermal growth factor receptor (EGFR), particularly cetuximab and panitumumab. Urine Mg wasting is the causative etiology of hypomagnesemia at the distal convoluted tubule\textsuperscript{53} (Figure 1). Studies show the incidence of hypomagnesemia related to anti-EGFR MAbs was 34.0\% compared with 9.7\% in controls (95\% CI 28.0–40.5\%, P < 0.001)\textsuperscript{54}. Colorectal cancer patients had the highest risk of grade 3/4 hypomagnesemia events among cancer patients: compared with chemotherapy alone, the addition of cetuximab increased the risk of grade 3/4 hypomagnesemia with RRs of 7.14 (95\% CI 3.13–16.27, P < 0.001) while patients receiving panitumumab were even more vulnerable to grade 3/4 hypomagnesemia (RR 18.29, 95\% CI 7.29–48.41, P < 0.001)\textsuperscript{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 SMg level\textsuperscript{55–59}. Hypomagnesemia is seen less frequently with zalutumumab, with an incidence reported to be only 4\%.\textsuperscript{60} 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 incidence overall seems less than with anti-EGFR MAbs\textsuperscript{61}.

Platinum-based chemotherapy

Cisplatin, and to a much lesser extent, carboplatin therapy, is associated with hypomagnesemia, more so than any other electrolyte deficiency\textsuperscript{5,62,63}. Hypomagnesemia affects
40–90% of patients on cisplatin; in contrast, 10% of patients treated with carboplatin or oxaliplatin experience hypomagnesemia. Platinum-induced hypomagnesemia can persist for up to 6 years after cessation of treatment and is primarily attributed to renal Mg wasting.

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 acute kidney injury. and pre-clinical studies have shown a protective effect of normal SMg levels in models of cisplatin-induced nephrotoxicity.

Human Epidermal Growth Factor Receptor 2 target inhibitors (HER2)

Human Epidermal growth factor Receptor-2 (HER2) is a member of the epidermal growth factor (EGFR) family of transmembrane receptors and is overexpressed in ~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. It is hypothesized that renal Mg loss is due to decreased reabsorption from distal convoluted tubule.

Calcineurin inhibitors

Calcineurin inhibitors (CNIs) are also used in cancer patients for several hematologic cancers and post-hematopoietic stem cell transplantation (HSCT) to prevent GVHD. Hypomagnesemia is a well-recognized and common complication of CNI treatment. It has been linked with post-kidney transplant diabetes mellitus (HR, 1.78, 95%, 1.29-2.45, P < 0.001). 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\textsuperscript{76,77}. Tacrolimus treatment increases the fractional Mg and calcium excretion and reduces the expression of TRPV5 and calbindin-D28K.\textsuperscript{78} The transcription for TRPM6 is also reduced by tacrolimus treatment\textsuperscript{79}. These actions were suggested to account for the hypomagnesemia and hypercalciuria that result from CNI treatment\textsuperscript{79}. \textbf{Table 4} summarizes anti-neoplastic agents that have been associated with hypomagnesemia.

5. Clinical manifestations of Hypomagnesemia

Mg is an essential electrolyte that plays a significant role as a co-factor 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\textsuperscript{80}. Neuromuscular manifestations have been well-characterized, but there is emerging evidence that Mg influences blood pressure, specifically low Mg leading to elevated blood pressure, although studies are mixed \textsuperscript{81,82}. The effect of hypomagnesemia on chemotherapy induced peripheral neuropathy also vary \textsuperscript{83,84}. In addition, a systematic review of magnesium infusions to prevent oxaliplatin-induced chronic peripheral neuropathy concluded that there was no benefit to supplemental magnesium in this setting\textsuperscript{85}. Nevertheless, there is data that hypomagnesemia can contribute to atherosclerotic cardiovascular disease and congestive heart failure, which is common in cancer survivors\textsuperscript{86}.

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\textsuperscript{11}. Mild to moderate hypomagnesemia can interfere with mineral metabolism, increasing the secretion of parathyroid hormone (PTH), which can, in turn, inhibit the CaSR in the kidneys and promote Mg reabsorption\textsuperscript{87}. Paradoxically, severe hypomagnesemia can also cause hypoparathyroidism and
secondary hypocalcemia. This is because severe hypomagnesemia interferes with the activation of alpha-subunits of heterotrimeric G-proteins of the CaSR, mimicking its activation.

Chronic hypomagnesemia can cause demineralization of bone and osteoporosis. Chronic hypomagnesemia can also result in hypercalciuria, which can contribute to nephrolithiasis.

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

### 6. Diagnosis

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

The distinction between gastrointestinal 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 with the following formula:

\[
FEMg = \left( \frac{U \times P}{0.7 \times P \times U} \right) \times 100
\]
U and P refer to urine and plasma concentrations of Mg, respectively. If the FEMg is above 2% in someone with normal renal function, then renal Mg wasting is likely. If the FEMg is <2%, it suggests gastrointestinal losses.

7. Management

Magnesium replacement

The management of hypomagnesemia is guided by the magnitude of hypomagnesemia and its etiology. There is a strong rationale for magnesium replacement in symptomatic cases, however, the utility of magnesium 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. Table 5 summarizes the various available oral Mg supplementations and their advantages and disadvantages\(^93\). In severe or symptomatic hypomagnesemia, then parenteral administration is required. Intramuscular (IM) replacement is also an option, but there is delayed absorption by a few hours from muscle depots. In the absence of seizures or lethal arrhythmia, the parenteral replacement rate should not exceed 1 g/hour\(^94\). Magnesium is cleared renally, therefore parenteral or IM replacement should be monitored in patients with advanced CKD to avoid the risk of heart block. However, otherwise normal individuals excrete over 80% of the sizable parenteral load of Mg in the urine within 48 hours, even in the setting of deficiency, making repleting Mg adequately a significant challenge\(^95\). A potential explanation for the latter phenomenon is that intravenous magnesium 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.\textsuperscript{96}

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\textsuperscript{97}. Patients with grade 2 hypomagnesemia in this setting 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 require 6 to 10 g of Mg sulfate daily. An initial strategy of intravenous replacement and frequent (3 times a week) SMg 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 \textsuperscript{97,98}, which usually does not result in recurrence of severe hypomagnesemia.

\textit{Amiloride}

Amiloride is widely used in clinical medicine as a potassium-sparing diuretic. In addition to blocking the sodium reabsorption in the distal tubule and collecting duct, amiloride has an additional property of enhancing renal Mg conservation \textsuperscript{99}. This property has been used to treat patients with renal Mg-wasting of various etiologies, including nephrotoxicity after amphotericin therapy and other refractory hypomagnesemia \textsuperscript{100,101}. Amiloride can be considered in cancer patients with refractory hypomagnesemia and in whom it can be used safely.

\textit{SGLT-2 inhibitors}
Sodium-glucose cotransporter 2 (SGLT2) inhibitors inhibit glucose reabsorption at the proximal tubule, increase urinary glucose excretion, and have been proven to be effective at controlling hyperglycemia in patients with type II diabetes. A meta-analysis of data collected from over 15,000 patients showed significantly higher SMg levels in SGLT2 inhibitor-treated patients than untreated patients\textsuperscript{102}. On average, SMg levels increased by 0.15–0.24 mg/dl, depending on the formulation. The authors hypothesize that elevated SMg 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 SMg in patients with type 2 diabetes\textsuperscript{103}. In cancer patients who meet the indication for SGLT-2 inhibitors and can be safely used, the observation that it can improve SMg might be useful in refractory cases\textsuperscript{104}.

Other therapies

The limitations of oral Mg supplementation are often reached without achieving goal concentration 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\textsuperscript{37,105}, but the magnitude of their effect and applications at higher concentrations have not been well studied(\textbf{Table 5}).

8. Areas of potential research opportunities

More comprehensive descriptive analyses of cancer patients providing information about the incidence, prevalence, and cancer-related risk factors for hypomagnesemia are needed on a fundamental level. Opportunities exist to examine the relationship between Mg and the 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.

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H Rondon-Berrios: Conceptualization; Methodology; Visualization; Writing - original draft; Writing - review and editing
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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

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<thead>
<tr>
<th>Grade</th>
<th>Serum magnesium (mg/dL)</th>
<th>Clinical significance</th>
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<tbody>
<tr>
<td>1</td>
<td>1.2 - 1.7</td>
<td>Mild or no symptoms, fatigue</td>
</tr>
<tr>
<td>2</td>
<td>0.9 - 1.2</td>
<td>Muscle weakness, fasciculations</td>
</tr>
<tr>
<td>3</td>
<td>0.7 - 0.9</td>
<td>Neurologic deficits, atrial fibrillation</td>
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<tr>
<td>4</td>
<td>&lt;0.7</td>
<td>Psychosis, seizures, tetany, nystagmus, lethal arrhythmia</td>
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Table 2: Etiology of Hypomagnesemia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
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<tr>
<td>Dietary deficiency of Magnesium</td>
<td>Starvation, Protein-calorie malnutrition, Total parenteral nutrition, Enteral feeding with inadequate magnesium</td>
</tr>
<tr>
<td>Magnesium Redistribution</td>
<td>Blood transfusions, Acute pancreatitis, Refeeding Syndrome</td>
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<tr>
<td>Gastrointestinal losses</td>
<td>Diarrhea, Vomiting, Nasogastric suction, Malabsorption, Gastrointestinal fistulae, Bowel resection, Drug-related (eg: PPIs, laxative abuse)</td>
</tr>
<tr>
<td>Renal Losses</td>
<td>Ketoacidosis, Hypercalcemia, Hypoparathyroidism, Hyperaldosteronism, Hypervitaminosis D, Chemotherapeutic agents (eg: Cisplatin, Cetuximab), Non chemotherapy drugs (eg: Diuretics)</td>
</tr>
<tr>
<td>Transdermal losses</td>
<td>Burns, Excess sweating</td>
</tr>
</tbody>
</table>

PPI: Proton pump inhibitor, SIADH: Syndrome of inappropriate antidiuretic hormone secretion
### Table 3: Drug induced Hypomagnesemia in a cancer patient: Adjunct Agents used in cancer patients

PPI: proton pump inhibitor, TRPM: Transient Receptor Potential Melastatin, LOH: loop of henle, Mg: magnesium, RANKL: Receptor activator of nuclear factor kappa-B ligand, PTH: Parathyroid hormone, cAMP: cyclic adenosine monophosphate, DCT: distal convoluted tubule

<table>
<thead>
<tr>
<th>Drug Class or Name</th>
<th>Incidence</th>
<th>Mechanism</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td>19.4% of PPI users</td>
<td>Intestinal loss, malabsorption of magnesium. PPIs interfere with TRPM6 and TRPM7 genes, leading to intestinal malabsorption and possible (?) renal Mg loss.</td>
<td>106–108</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Unknown</td>
<td>TRPM6 inhibition, leading to increase in renal Mg loss, Increase in potassium excretion causes hypokalemia, leading to decrease in passive Mg reabsorption.</td>
<td>48,50</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Unknown</td>
<td>Decrease in paracellular reabsorption in thick ascending LOH, increase renal Mg loss, hypokalemia</td>
<td>48,49</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Case reports</td>
<td>Renal impairment, increased Mg excretion and cellular shifting. No other bisphosphate has been reported to cause hypomagnesemia</td>
<td>49</td>
</tr>
<tr>
<td>Drug</td>
<td>Report Type</td>
<td>Mechanism</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>RANKL monoclonal antibody (Denosumab)</td>
<td>Isolated</td>
<td>Unknown</td>
<td>51</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Isolated</td>
<td>Unknown</td>
<td>52</td>
</tr>
<tr>
<td>Aminoglycosides (Amikacin, Gentamicin,</td>
<td>Unknown</td>
<td>Positively charged antibiotics act via a polyvalent cation-sensing</td>
<td>109-111</td>
</tr>
<tr>
<td>Tobramycin, Neomycin, Streptomycin)</td>
<td></td>
<td>extracellular receptor in DCT, leading to inhibition of PTH mediated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cAMP formation and Mg uptake in DCT.</td>
<td></td>
</tr>
<tr>
<td>Antituberculous agents (Viomycin, Capreomycin)</td>
<td>Unknown</td>
<td>Proximal tubular dysfunction, secondary hyperaldosteronism with consequent renal Mg loss</td>
<td>112-114</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Unknown</td>
<td>This drug is a polyene antibiotic, and Mg participates in the polyene-</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sterol binding process, leading to a functional Mg deficiency.</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Unknown</td>
<td>Renal Mg wasting</td>
<td>116</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Unknown</td>
<td>Renal Tubular injury</td>
<td>117-119</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Upto 70%</td>
<td>Chelates divalent ions, thereby leading to acute reduction in ionized</td>
<td>120,121</td>
</tr>
<tr>
<td></td>
<td></td>
<td>magnesium.</td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Drug induced Hypomagnesemia in a cancer patient: Antineoplastic Agents


<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs reported to cause Hypomagnesemia</th>
<th>Incidence</th>
<th>Mechanism</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-EGFR monoclonal antibodies</td>
<td>Cetuximab, Panitumumab, Zalutumumab</td>
<td>34% for cetuximab 4% for zalutumumab</td>
<td>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)</td>
<td>31,54,60,61,70,122</td>
</tr>
<tr>
<td>EGFR Tyrosine Kinase inhibitors</td>
<td>Afatinib, Erlotinib, Gefitinib</td>
<td>None reported</td>
<td>Postulated similar mechanism as EGFR- antibodies</td>
<td>61</td>
</tr>
<tr>
<td>Platinum based agents</td>
<td>Cisplatin, Carboplatin, Oxaliplatin</td>
<td>Cisplatin: 40-90% Carboplatin and Oxaliplatin: 10%</td>
<td>Downregulation of TRPM6/EGF pathway., may lead to persistent distal tubular dysfunction with a Gitelman-like syndrome, can also cause magnesium loss from gut due to anorexia, vomiting, diarrhea.</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>HER-2 inhibitors</td>
<td>Trastuzumab, Pertuzumab</td>
<td>Patients on Pertuzumab: 14% with HypoMg (≥ G1), 9% with HypoMg (≥ G1) in neoadjuvant setting</td>
<td>Inhibition of Mg reabsorption in DCT due to EGF blockade, Secretory diarrhea</td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Cyclosporine, Tacrolimus</td>
<td>Case series and reports</td>
<td>EGF production is downregulated, which in turn inhibits TRPM6 activation. Reduce messenger (m)RNA expression of NCC, Reduce transcript for TRPM6 in DCT</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Interleukin-2</td>
<td>Case reports</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

References:
64,123,124
72
125
126
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Study Type</th>
<th>Effect Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR inhibitors</td>
<td>Rapamycin</td>
<td>Case report</td>
<td>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</td>
<td>127</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>Amsacrine</td>
<td>Case reports only</td>
<td>Unknown</td>
<td>128</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Pegylated liposomal doxorubicin</td>
<td>Case reports only</td>
<td>Unknown</td>
<td>129</td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Ifosfamide</td>
<td>1.2%</td>
<td>Unknown</td>
<td>130,131</td>
</tr>
</tbody>
</table>
Table 5 Common Oral Magnesium Formulations and Dosages
(This data was obtained from Lexicomp Online and Reference # 93

<table>
<thead>
<tr>
<th>SUPPLEMENT</th>
<th>ELEMENTAL MAGNESIUM CONTENT</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium oxide (MagOx)</td>
<td>61% elemental magnesium</td>
<td>Requires higher dosages to meet repletion, diarrhea is limiting complication</td>
</tr>
<tr>
<td></td>
<td>242 mg in 400-mg tablet</td>
<td></td>
</tr>
<tr>
<td>Magnesium hydroxide (Milk of Magnesia)</td>
<td>42% elemental magnesium</td>
<td>Over the counter, avoid in patients with creatinine clearance &lt;30cc/min,</td>
</tr>
<tr>
<td></td>
<td>167 mg in 400 mg per 5 mL oral suspension</td>
<td></td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>16% elemental magnesium</td>
<td>Diarrhea is a concern, used as a laxative, avoid in patients with creatinine clearance &lt;30cc/min,</td>
</tr>
<tr>
<td></td>
<td>48 mg elemental magnesium and 13 mg potassium in 290 mg per 5 mL oral solution</td>
<td></td>
</tr>
<tr>
<td>Magnesium gluconate (Mag-G)</td>
<td>5% elemental magnesium</td>
<td>Over the counter, excessive dosages lead to diarrhea</td>
</tr>
<tr>
<td></td>
<td>27 mg in 500-mg tablet</td>
<td></td>
</tr>
<tr>
<td>Magnesium Compound</td>
<td>Element Mg Content</td>
<td>Absorption/Excretion Characteristics</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Magnesium chloride (Mag-Delay or Slow Mg)</td>
<td>12% elemental magnesium</td>
<td>Slowly absorbed, less renal excretion, Less diarrhea</td>
</tr>
<tr>
<td>Magnesium sulfate (Epsom salts)</td>
<td>10% elemental magnesium</td>
<td>Slowly absorbed, less renal excretion, Less diarrhea</td>
</tr>
<tr>
<td>Magnesium lactate (Mag-Tab SR)</td>
<td>12% elemental magnesium</td>
<td>Sustained release</td>
</tr>
<tr>
<td>Magnesium aspartate hydrochloride (Maginex DS)</td>
<td>10% elemental magnesium</td>
<td>Diarrhea is a side effect</td>
</tr>
<tr>
<td>Magnesium protein complex (Mg plus protein)</td>
<td>133 mg elemental magnesium bound to 26 mg soy protein.</td>
<td>Less diarrhea, used in pediatrics mostly</td>
</tr>
</tbody>
</table>
Figure legend

Figure 1: Kidney Handling of Magnesium and Nephron Site of Action of Magnesiuric Drugs

Na+=Sodium ion, K+=Potassium ion, Cl=Chloride ion, Ca2+=Calcium ion, Mg2+=Magnesium ion, NKCC2=Na+-K+-2Cl- Cotransporter, ROMK=Renal Outer Medullary K+Channel, CIC-Kb=Cl Channel Kb, CaSR=Calcium Sensing Receptor, NCC=Na+-Cl-Contratransporter, TRPM6=Transient Receptor Potential Cation Channel Subfamily M Member 6, Kiv1.1=voltage-gated potassium channel, Pro-EGF=Pro-Epithelial Growth Factor, EGF=Epithelial Growth Factor, EGFR=Epithelial Growth Factor Receptor, SLC41A3=Solute Carrier family 41 member 3, CNNM2=Cyclin And CBS Domain Divalent Metal Cation Transport Mediator 2, FXYD2=FXYD Domain Containing Ion Transport Regulator 2, Kir4.1=, PCBD1=pterin-4a carbinolamine dehydratase, HNF1B=Hepatocyte Nuclear Factor 1β.

Numbers in blue (%) refers to percent Mg that is reabsorbed in the specific segment of the nephron.

Non-protein bound magnesium is freely filtered across the glomerulus. The proximal tubule (PT) reabsorbs 15% of filtered magnesium via a paracellular mechanism. The bulk of magnesium reabsorption occurs in the cortical thick ascending limb of the Loop of Henle (TAL) where approximately 70% of magnesium is reabsorbed via a paracellular route. Claudin-16 and -19 are considered the main claudins responsible for the magnesium 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 magnesium reabsorption is the lumen positive transepithelial voltage of the TAL that is determined by the activity of NKCC2 and the subsequent potassium recycling back into the lumen via ROMK channel at the apical membrane. Chloride ions leave the TAL cells via CIC-Kb channels on the basolateral membrane. Activation of the CaSR in the TAL inhibits paracellular magnesium transport via inhibition of NKCC2 and ROMK. Further, CaSR regulates claudin 14 expression and calcium and magnesium reabsorption in the TAL. Aminoglycosides target the CaSR and foscarnet can chelate the magnesium 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 magnesium reabsorption takes place beyond the DCT. Magnesium reabsorption takes place beyond the DCT. Magnesium is reabsorbed in this nephron segment via the transcellular route through the TRPM6 magnesium 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 becoming 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 magnesium reabsorption in the DCT. Magnesium transport via TRPM6 depends almost exclusively on the negative membrane potential in the DCT cells as no significant chemical gradient for magnesium exists in this nephron segment. Kv1.1 is primarily responsible for maintaining the necessary negative membrane potential for magnesium reabsorption in the DCT by providing 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 magnesium reabsorption. FXYD2 gene encodes for the γ-subunit of the Na-K-ATPase. The
transcription factor Hepatocyte Nuclear Factor 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 magnesium extrusion in DCT has been challenging as there is no chemical gradient for magnesium and the electrical gradient favors magnesium uptake rather than extrusion. Therefore, it is likely that magnesium 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 magnesium transport into the bloodstream. SCL41A3 and CNNM2 have been identified as potential magnesium 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 magnesium within the DCT (not shown in the figure).
Calcineurin inhibitors
mTOR inhibitors
Anti-EGFR monoclonal antibodies
EGFR tyrosine kinase inhibitors
HER-2 inhibitors
Aminoglycosides
Loop diuretics
Thiazide diuretics
Calcineurin inhibitors
mTOR inhibitors

Figure 1