Magnesium Disorders: Core Curriculum 2024

Emmanuel A. Adomako and Alan S.L. Yu

Magnesium is ubiquitous in nature. It sits at the origin of the food chain, occupying the center of chlorophyl in plants. In humans, magnesium is critical to diverse molecular and catalytic processes, including energy transfer and maintenance of the genome. Despite its abundance, hypomagnesemia is common and often goes undiagnosed. This is in spite of epidemiologic data linking low magnesium with chronic diseases including diabetes mellitus. Clinically significant hypermagnesemia is encountered less frequently, but the presentation may be dramatic. Advances in molecular biology and the elucidation of the genetic causes of magnesium disorders have enhanced our understanding of their pathophysiology. Treatment approaches are also changing. The repurposing of newer medications, such as sodium/glucose cotransporter 2 inhibitors, offers new therapeutic options. In this review we integrate knowledge in this rapidly evolving field to provide clinicians and trainees with a resource for approaching common clinical scenarios involving magnesium disorders.

Complete author and article information provided at end of article.

Correspondence to A.S.L. Yu (ayu@kumc.edu)

Am J Kidney Dis. 83(6):803-815. Published online February 17, 2024.

doi: 10.1053/j.ajkd.2023.10.017

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Magnesium is the fourth most common element on earth and plays a critical role in biology. In humans, magnesium is significant in the function of excitable tissue and as a cofactor in hundreds of enzymatic reactions. Disorders of magnesium thus result in protean manifestations.

Distribution of Magnesium

The total mass of magnesium in a 70 kg man is about 30 g. This is less than the contribution of other minerals like calcium and phosphate, which make up 2% and 1% of the body, respectively. Up to two-thirds of the total body magnesium is present in bone, with most of the rest found in muscle and soft tissue. Less than 1% of the total body magnesium is present in blood, with the larger portion in erythrocytes. Of the fraction in plasma, about 32% is protein bound (25% is bound to albumin, and 8% is bound to globulin). Most of the magnesium in the body (99%) resides in the intracellular compartment, where it is second in abundance only to potassium. Because of the percentage of bound magnesium in both the intracellular and extracellular compartments, cells do not generally maintain a large transcellular free magnesium gradient.

Physiologic Role of Magnesium

Magnesium is a required cofactor for about 600 enzymes in diverse critical catalytic reactions. It is a cofactor for adenosine triphosphate (ATP) and thus plays an integral role in energy extraction and utilization. Other key roles include reactions required for the maintenance of the genome (replication, transcription, translation, and DNA repair). Additionally, magnesium is key to stabilizing the structure of nucleic acids and proteins.

Although magnesium is not considered a major contributor to the resting membrane potential, it affects the membrane potential of cells and excitable tissue through the modulation of various ion channels and transporters. Similarly, modulation of ion channels and transporters can affect the whole-body flux of electrolytes. For instance, magnesium gating of renal outer medullary K^+ (ROMK) channels in the distal nephron is important for potassium homeostasis.

In bone physiology, magnesium plays a significant function in the formation, turnover, and maintenance of the skeleton by regulating parathyroid hormone secretion and by its indirect effect on vitamin D metabolism.

Magnesium Handling in the Gastrointestinal Tract

From balance studies, the minimal daily requirement of magnesium ranges from 165 mg to 240 mg. The Institute of Medicine recommended daily allowance is 310-320 mg for women and 400-420 mg for men. The intake for most individuals falls below these recommendations. In the United States, the average daily intake of magnesium in adult men and women is about 329 mg and 207 mg, respectively. Agricultural practices have resulted in magnesium-poor farmlands, and food processing techniques further deplete the magnesium content of popular staples.

Intestinal absorption is influenced by the presence of other dietary components, such as

oxalate, phytate, and insoluble fiber, and high levels of minerals including zinc, iron, and calcium, all of which can negatively impact magnesium absorption. In a regular diet, just under 50% of dietary magnesium is absorbed. Magnesium absorption occurs largely in the distal small intestine, with some absorption in the colon as well. In patients with intestinal resection, both the body stores of magnesium and the urinary excretion decrease as the extent of resection increases.

Intestinal magnesium transport involves both paracellular and transcellular transport. The paracellular route is responsible for the bulk of absorbed magnesium and is the predominant or sole route in the small intestine. It is assumed that claudins play a role, but the specific proteins have yet to be elucidated. In the colon and cecum, transcellular absorption of magnesium is mediated by apical entry through TRPM6 and TRPM7 channels. The expression of TRPM6 is induced under conditions of high dietary magnesium. Surprisingly, proton pump inhibitors (PPI) also induce the expression of TRPM6. This may be compensatory for the diminished function of the transporter. CNNM2 functioning independently or in cooperation with CNNM4 mediates the basolateral extrusion of magnesium in the intestine.

In steady state, 2% of the absorbed magnesium may be secreted as part of pancreatic, biliary, and intestinal secretions. In renal failure, gut excretion of magnesium increases.

Additional Readings

- De Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev*. 2015;95(1):1-46. doi:10.1152/physrev.00012.2014
- Lameris AL, Nevalainen PI, Reijnen D, et al. Segmental transport of Ca^{2+} and Mg^{2+} along the gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol*. 2015;308(3):G206-G216. doi:10.1152/ajpgi.00093.2014
- Schuchardt JP, Hahn A. Intestinal absorption and factors influencing bioavailability of magnesium—an update. *Curr Nutr Food Sci*. 2017;13(4):260-278. doi:10.2174/1573401313666170427162740
- Yamazaki D, Funato Y, Miura J, et al. Basolateral Mg^{2+} extrusion via CNNM4 mediates transcellular Mg^{2+} transport across epithelia: a mouse model. *PLoS Genet*. 2013;9(12):e1003983. doi:10.1371/journal.pgen.1003983

Magnesium Handling in the Kidney

The ultrafilterable magnesium (free fraction) constitutes 70% of the total plasma magnesium. In patients with renal failure, the ultrafilterable magnesium may be reduced even though the total magnesium might be elevated.

Proximal Tubule

The proximal tubule absorbs about 15%-20% of the filtered magnesium (Fig 1). This reabsorption is passive, paracellular, and dissociated from the reabsorption of sodium. Indirect evidence implicates a role for claudin-2 in magnesium transport in the proximal tubule. Claudin-10a mediates anion transport in the proximal tubule. Claudin-10a knockout mice compensate by overexpressing claudin-2, which is associated with the development of hypermagnesemia. This may in part explain hypermagnesemia which occurs in patients with loss of function mutations in *CLDN10*.

Thick Ascending Limb of Henle

The thick ascending limb of the loop of Henle (TAL), particularly the cortical segment, is the major site for tubular reabsorption of magnesium, accounting for 50%-65% of the filtered load (Fig 1). Magnesium transport in the TAL also occurs across the paracellular route (Fig 2) and depends on a lumen-positive electrical potential difference.

Sodium, potassium, and chloride enter the TAL via the luminal Na-K-2Cl (NKCC2) transporter, which is electroneutral. However, >80% of the potassium transported by NKCC2 is recycled back into the lumen through the apical potassium channel, ROMK. Basolateral transport of sodium is accomplished by the Na-K-ATPase, which generates the inwardly directed sodium gradient that drives entry through NKCC2. The chloride channels ClC-Ka and ClC-Kb mediate basolateral exit of chloride. Barttin is an accessory subunit required for function of these chloride channels. The net positive luminal potential difference is generated by the recycling of potassium through ROMK and the paracellular back-leak of sodium. Inactivating mutations in any of these transporters cause Bartter syndrome (see the section on inherited causes of hypomagnesemia).

The lumen-positive potential difference is important because it provides the driving force for passive reabsorption of sodium, calcium, and magnesium via the paracellular pathway. Calcium and magnesium reabsorption predominate in the cortical TAL, mediated by a paracellular channel composed of claudin-16 and claudin-19. Mutations in the genes coding for claudin-16 and -19 impair TAL reabsorption of both calcium and magnesium, leading to familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC).

Paracellular sodium reabsorption predominates in the medullary TAL and is mediated by claudin-10b. Genetic deletion of claudin-10b in the TAL decreases paracellular sodium transport while at the same time increasing magnesium and calcium transport, likely due to a compensatory increase in the expression of claudin-16 and -19. This explains most of the electrolyte disturbances in individuals with mutations in *CLDN10* or HELIX syndrome (hypohidrosis, electrolyte disturbances, lacrimal dysfunction,

ichthyosis, xerostomia), which include sodium wasting, hypermagnesemia, and hypocalciuria.

The calcium-sensing receptor (CASR) regulates TAL divalent cation transport (Fig 2). Activation of CASR, which occurs physiologically in response to hypercalcemia, inhibits transcellular sodium reabsorption while simultaneously up-regulating an inhibitory subunit, claudin-14, that interacts with claudin-16/19, thereby reducing paracellular calcium and magnesium reabsorption. Thus, activating mutations in CASR cause autosomal dominant hypocalcemia, which is associated with hypomagnesemia and sometimes with a Bartter-like syndrome. Parathyroid hormone (PTH) offers additional regulatory control in this segment by increasing reabsorption of magnesium.

Distal Convoluted Tubule

The distal convoluted tubule (DCT) reabsorbs about 5%-15% of the filtered load (Fig 1). Although the magnitude of reabsorbed magnesium is relatively small, it is critical in maintaining magnesium homeostasis. Magnesium reabsorption in the DCT is transcellular and mediated by TRPM6 and TRPM7, which form a heteromeric channel at the apical membrane for magnesium entry (Fig 3). Because there is not a large concentration gradient, apical entry depends on a hyperpolarized luminal membrane potential. As in the TAL, an outward potassium current is thought to be responsible for this, and Kv1.1 has been proposed to be the responsible potassium channel. Two patients who harbor 2 different mutations in *KCNA1*, the gene coding for Kv1.1, were found to have hypomagnesemia. However, most patients with the more than 30 mutations that have been described to date do not have or were not described to have hypomagnesemia, so the role of Kv1.1 in the DCT remains uncertain.

The energy for active transcellular magnesium transport derives from the sodium gradient generated by the Na-K-ATPase at the basolateral membrane. A basolateral potassium channel Kir4.1 is needed for the basolateral recycling of potassium that has been pumped into the cell. Kir4.1 forms heteromers with Kir 5.1, which serve as an extracellular fluid potassium sensor. This sensor regulates DCT sodium reabsorption through the thiazide-sensitive electroneutral sodium chloride transporter, NCC, via regulation of with-no-lysine kinase (WNK) and Ste20-related proline-alanine-rich kinase (SPAK). DCT magnesium reabsorption specifically is regulated by epidermal growth factor (EGF), which stimulates TRPM6 activity.

Whereas there is a fair degree of consensus on the identity of the transporters responsible for magnesium influx in the DCT, the candidate transporters that mediate basolateral efflux remain controversial. Based on variable evidence, 2 transporters have been proposed. *CNNM2* is localized to the basolateral DCT, and mutations in this gene cause severe hypomagnesemia and seizures. In a genomewide association study, common variants in *CNNM2*, as well as its homologs *CNNM3* and 4, were associated with serum magnesium levels. *In vitro* demonstration of transcellular magnesium transport, however, remains controversial. The transporter *SLC41A3* is the other candidate. Evidence for the role of this transporter includes an enriched expression in the DCT and the observation that murine knockout of *Slc41a3* results in hypomagnesemia.

Additional Readings

- De Baaij JHF. Magnesium reabsorption in the kidney. *Am J Physiol Renal Physiol*. 2023;324(3):F227-F244. doi:10.1152/ajprenal.00298.2022
- Ellison DH, Maeoka Y, McCormick JA. Molecular mechanisms of renal magnesium reabsorption. *J Am Soc Nephrol*. 2021;32(9):2125-2136. doi:10.1681/ASN.2021010042
- Franken GAC, Adella A, Bindels RJM, de Baaij JHF. Mechanisms coupling sodium and magnesium reabsorption in the distal convoluted tubule of the kidney. *Acta Physiol (Oxf)*. 2021;231(2):e13528. doi:10.1111/apha.13528
- Groenestege WM, Thebault S, van der Wijst J, et al. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. *J Clin Invest*. 2007;117(8):2260-2267. doi:10.1172/JCI31680
- Hou J, Renigunta A, Gomes AS, et al. Claudin-16 and claudin-19 interaction is required for their assembly into tight junctions and for renal reabsorption of magnesium. *Proc Natl Acad Sci U S A*. 2009;106(36):15350-15355. doi:10.1073/pnas.0907724106 ★ESSENTIAL READING
- Yu AS. Claudins and the kidney. *J Am Soc Nephrol*. 2015;26(1):11-19. doi:10.1681/ASN.2014030284

Pathogenesis of Hypomagnesemia

Case 1: *A 40-year-old man is referred for evaluation of hypomagnesemia. He has a history of iron deficiency, hypertension, and gastrointestinal reflux disease. Hypomagnesemia was incidentally diagnosed during his last admission for severe hypertension. His serum magnesium at the time was 0.8 mg/dL. He required intravenous magnesium. He has since been on oral magnesium oxide. He acknowledges he does not take this often because of diarrhea. His other medications include amlodipine, losartan, carvedilol, omeprazole, calcium carbonate, ferrous sulfate, and atorvastatin. His serum values are Mg, 1.0 mg/dL; K, 3.4 mmol/L; serum creatinine, 0.9 mg/dL; and serum urea nitrogen, 22 mg/dL.*

Question 1: Which of the following is the likely explanation for hypomagnesemia in this patient?

(a) Magnesium-deficient diet

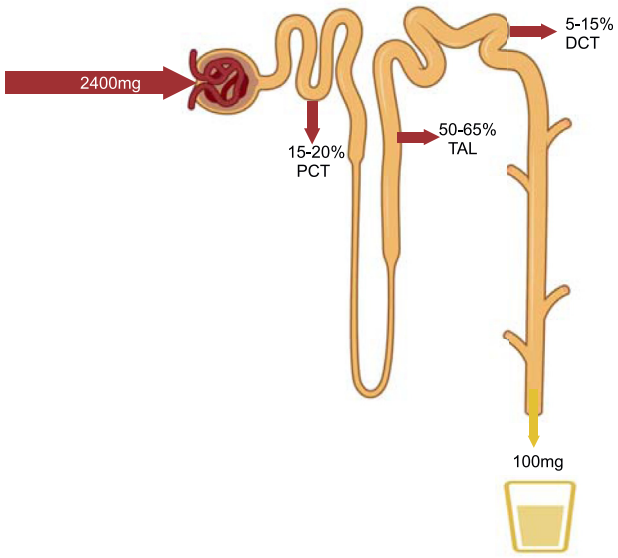

Figure 1. Magnesium reabsorption along the renal tubule. The kidney filters 2.4 g of magnesium daily. The bulk of reabsorption occurs along the paracellular route in the proximal tubule and the thick ascending limb of the loop of Henle. The distal convoluted tubule is responsible for the fine-tuning magnesium reabsorption with final fractional excretion of about 4%. Created with Biorender.com. Abbreviations: DCT, distal convoluted tubule; PCT, proximal convoluted tubule; TAL, thick ascending limb of the loop of Henle.

(b) Renal magnesium wasting
(c) Increased gastrointestinal secretion of magnesium
(d) Poor enteric absorption of magnesium
(e) Low gastric pH

For the answer to this question, see the following text.

Gastrointestinal Causes of Hypomagnesemia

The mechanisms involved in the gastrointestinal tract as a cause of hypomagnesemia involve poor oral intake, malabsorption of magnesium, and increased losses through gastrointestinal secretions. Multiple mechanisms often coexist in the same patient. Nutritional surveys suggest inadequate magnesium intake is widespread in the United States, particularly among adolescents and the elderly. Poor oral intake causing frank hypomagnesemia usually occurs as part of generalized micronutrient malnutrition. Patients with chronic diarrhea, surgical patients with short bowel syndrome, and high stomal output often present with difficult-to-treat hypomagnesemia. Hypomagnesemia may also be present as part of refeeding syndrome.

Hypomagnesemia is common in patients with pancreatitis. Similar to hypocalcemia, the mechanism involves saponification of magnesium in a milieu of pancreatic fat. Additionally, patients with pancreatitis often have preexisting negative magnesium balance. These patients often exhibit either hypoparathyroidism or resistance to PTH, which may further exacerbate hypocalcemia.

PPIs are widely available both as prescription and over-the-counter medications, and their use continues to increase. Hypomagnesemia in patients on PPIs may be severe and symptomatic. PPIs increase the gastrointestinal transluminal pH. This affects the intraluminal solubility of magnesium, increases the transepithelial electrical resistance, and down-regulates the function of TRPM6. Important factors associated with the risk of hypomagnesemia with PPI use include prolonged duration of exposure, dose, concomitant diuretic use, and genetic variants in *TRPM6*. In case 1, the finding of severe hypomagnesemia in a patient taking omeprazole strongly suggests the diagnosis of PPI-induced hypomagnesemia, so the answer is (d).

TRPM6 mutations cause hypomagnesemia with secondary hypocalcemia. This condition is inherited as an autosomal recessive disorder. Affected individuals have malabsorption of magnesium as well as renal magnesium wasting and present in infancy with tetany, seizures, hypomagnesemia, and hypocalcemia (see the section on inherited causes of renal magnesium wasting).

Renal Magnesium Wasting

Acquired renal magnesium wasting is common and is often because of medications; genetic causes are much rarer.

Medications

Drugs that cause renal magnesium wasting act by interfering with renal reabsorption mechanisms. Most of these medications act on either the TAL or the DCT.

Diuretics, among the most prescribed medications, are associated with hypomagnesemia, which is usually mild. Thiazide diuretics cause hypomagnesemia through the down-regulation of TRPM6 in the DCT. Other electrolyte manifestations including hypokalemia and hypocalciuria may be present as well. Although the TAL absorbs most of the filtered magnesium, the risk of hypomagnesemia with loop diuretics is less than with thiazide diuretics. Osmotic diuretics such as mannitol also increase the urinary magnesium, although it is not entirely clear whether this is solely due to interference with proximal tubular magnesium reabsorption or if interference with the TAL and DCT plays a role as well.

Antibiotics associated with hypomagnesemia include aminoglycosides, amphotericin B, foscarnet, and pentamidine. Aminoglycosides can cause a Bartter-like presentation with renal calcium, magnesium, and potassium wasting and metabolic alkalosis. This syndrome may present with or without clinical evidence of acute kidney injury. The mechanism has been postulated to be due to aminoglycoside activation of the calcium-sensing receptor (CASR). The potency of this activation may depend on the length of the amino acid side chain (neomycin > tobramycin > gentamicin > kanamycin) and

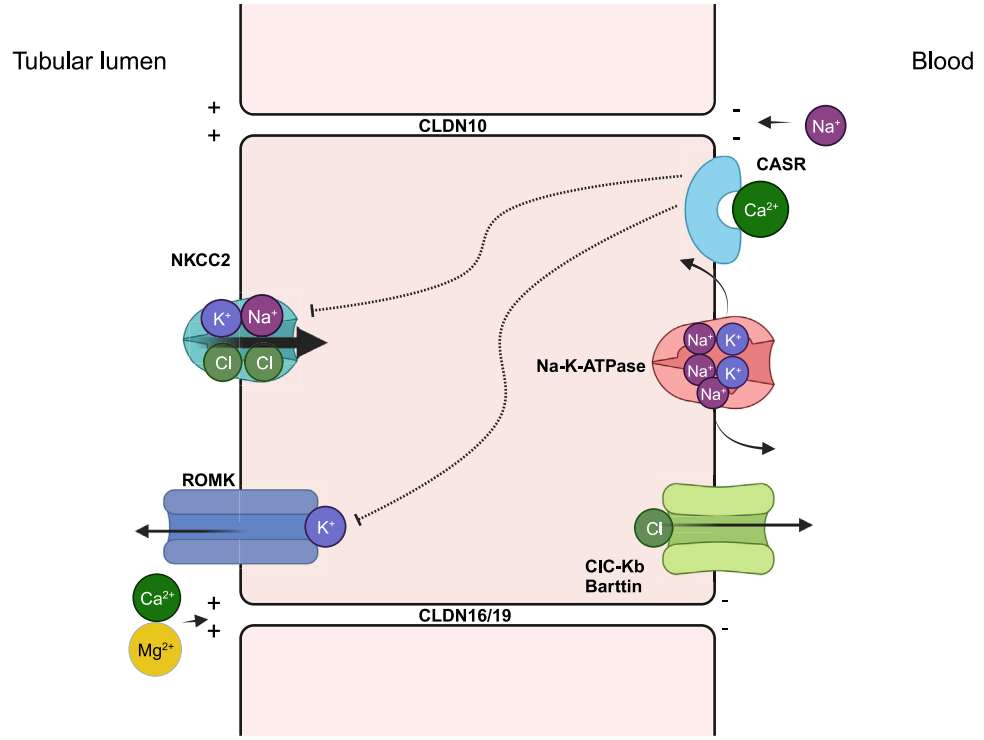

Figure 2. Mechanism of magnesium transport in the thick ascending limb of the loop of Henle. Magnesium reabsorption in this segment is paracellular, mediated by claudin-16/19. A positive luminal potential difference mediated by the recycling of potassium through ROMK and paracellular back-leak of sodium is critical for this to happen. Activation of CASR modulates paracellular cation permeability through claudin-14. Created with Biorender.com. Abbreviations: CASR, calcium-sensing receptor; CLDN10, Claudin-10; NKCC2, Na-K-2Cl; ROMK, renal outer medullary K^+.

the clinical syndrome can last for weeks even after discontinuing the antibiotic. A recent publication, however, has called into question the *in vitro* activation of CASR by aminoglycosides.

Hypomagnesemia occurs in more than two-thirds of patients exposed to amphotericin B and may persist beyond the duration of therapy. Amphotericin B binds to sterols in eukaryotic cells causing ion pores to form in the plasma membrane. The consequent inability to generate a gradient for magnesium efflux across the basolateral membrane and hence magnesium reabsorption may explain the development of renal magnesium wasting. Hypomagnesemia occurs more frequently in patients who receive the deoxycholate formulation compared with the liposomal formulation.

Foscarnet is associated with depletion of multiple cations including magnesium. The mechanism has not been fully elucidated. As a pyrophosphate, one plausible explanation is chelation of cations. Several case reports have reported hypomagnesemia together with hypocalcemia in patients who received intravenous pentamidine. This effect has not been reported with the inhaled formulation. Affected patients exhibit renal magnesium wasting, and the effect extends beyond the duration of therapy.

Multiple chemotherapeutic and immunosuppressive agents affect renal magnesium transport. Exposure to platinum-based chemotherapeutic agents, especially cisplatin, leaves most patients in negative magnesium balance, which may not be apparent from the assessment of plasma magnesium. Other platinum-based medications, including carboplatin, cause this problem less often. The mechanism involves direct tubular toxicity as well as down-regulation of TRPM6 and NCC in the DCT. Hypomagnesemia can persist up to 6 years after discontinuation of therapy. Patients on epidermal growth factor receptor (EGFR) inhibitors develop hypomagnesemia due to impaired stimulation of TRPM6 in the DCT. This is a pharmacologic correlate of the loss of function mutations in EGFR, which presents as autosomal recessive isolated hypomagnesemia. About a third of patients on EGFR inhibitors such as cetuximab present with hypomagnesemia. Compared with cetuximab, the risk of hypomagnesemia is higher with panitumumab, and zalutumumab has a lower risk. Calcineurin inhibitors (CNI) mediate hypomagnesemia through down-regulation of TRPM6 in the DCT. Hypomagnesemia occurs more often in patients on tacrolimus compared with patients on cyclosporine. Mammalian target of rapamycin (mTOR) inhibitors interfere with epidermal growth factor (EGF)-induced

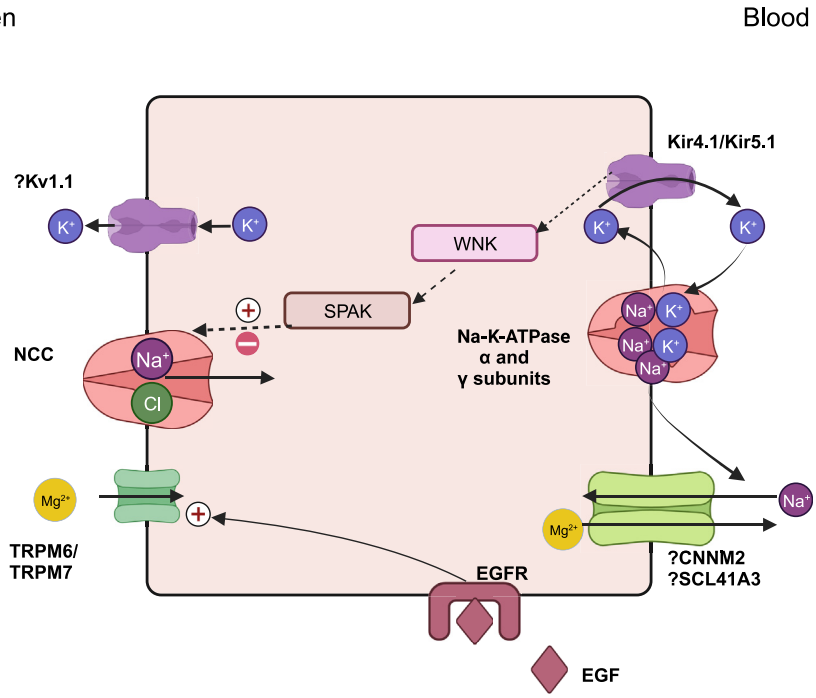

Figure 3. Mechanism of magnesium transport in the distal convoluted tubule. The large tubular epithelial resistance in this segment precludes paracellular transport. Magnesium reabsorption in this segment is transcellular through heteromers of TRPM6/TRPM7, and this determines the final urine output of magnesium. EGF has a paracrine influence on the activity of TRPM6. Phosphorylation of the NCC is a key regulatory mechanism. Under conditions of low extracellular potassium, potassium flux through the heteromeric Kir4.1/Kir5.1 channel hyperpolarizes the DCT, leading to efflux of intracellular chloride with sequential phosphorylation/activation of WNK, SPAK, and the NCC. Created with Biorender.com. Abbreviations: CNNM2, Cyclin M2; DCT, distal convoluted tubule; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; NCC, sodium chloride transport; SPAK, Ste20-related proline-alanine-rich kinase; TRPM6, transient receptor potential cation channel subfamily M member 6; WNK, with-no-lysine kinase.

expression of TRPM6. Hypomagnesemia, however, is less severe in patients on mTOR inhibitors compared with CNIs.

Additional Readings

- Alexander RT, Dimke H. Effect of diuretics on renal tubular transport of calcium and magnesium. *Am J Physiol Renal Physiol*. 2017;312(6):F998-F1015. doi:10.1152/ajprenal.00032.2017 ★ESSENTIAL READING
- Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int*. 2013;83(4):692-699. doi:10.1038/ki.2012.452 ★ESSENTIAL READING
- Gommers LMM, Hoenderop JGJ, de Baaij JHF. Mechanisms of proton pump inhibitor-induced hypomagnesemia. *Acta Physiol (Oxf)*. 2022;235(4):e13846. doi:10.1111/apha.13846
- McLarnon S, Holden D, Ward D, Jones M, Elliott A, Riccardi D. Aminoglycoside antibiotics induce pH-sensitive activation of the calcium-sensing receptor. *Biochem Biophys Res Commun*. 2002;297(1):71-77. doi:10.1016/s0006-291x(0202133-2)
- Nijenhuis T, Hoenderop JG, Bindels RJ. Down-regulation of Ca^{2+} and Mg^{2+} transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. *J Am Soc Nephrol*. 2004;15(3):549-557. doi:10.1097/01.asn.0000113318.56023.b6 ★ESSENTIAL READING
- Van Megen WH, Beggs MR, An SW, et al. Gentamicin inhibits Ca^{2+} channel TRPV5 and induces calciuresis independent of the calcium-sensing receptor-claudin-14 pathway. *J Am Soc Nephrol*. 2022;33(3):547-564. doi:10.1681/ASN.2021030392

Inherited Causes

Case 2: *An 18-year-old man presents to the renal clinic for evaluation of chronic kidney disease. He has not seen a physician for several years and was incidentally found to have elevated serum creatinine (3.8 mg/dL) during a health evaluation for Navy recruitment. His mother reports that in childhood he had failure to thrive and used to require magnesium supplements. There is no family history of electrolyte disorders. Laboratory results show serum K 5.2 mg/dL; HCO_3^-, 325 mmol/L; Mg, 1.6 mg/dL; and serum urea*

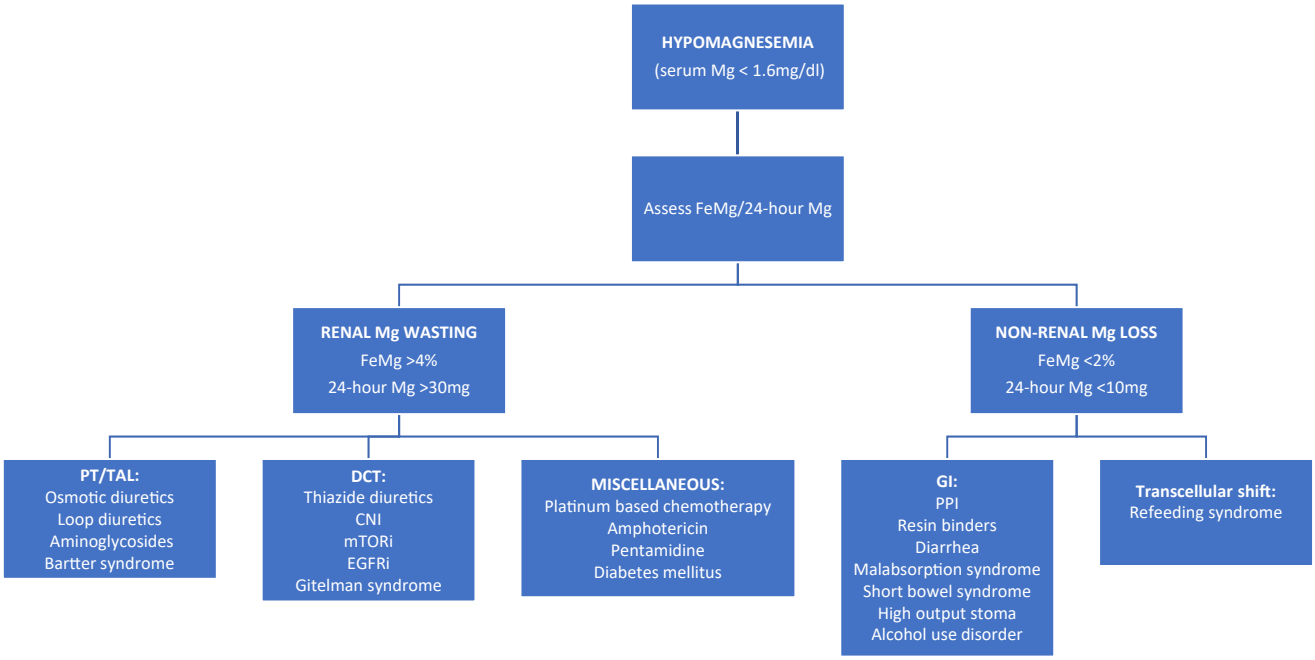

Figure 4. Algorithm for the evaluation of hypomagnesemia. Abbreviations: CNI, calcineurin inhibitor; DCT, distal convoluted tubule; EGFRi, epidermal growth factor receptor inhibitor; FeMg, fractional excretion of magnesium; GI, gastrointestinal; mTORi, mammalian target of rapamycin inhibitor; PPI, proton pump inhibitor; PT, proximal tubule; TAL, thick ascending limb of the loop of Henle.

nitrogen, 35 mg/dL. The 24-hour urine laboratory results were as follows: Mg, 151 mg; Ca, 450 mg; and FeMg, 19.4%. A renal ultrasound shows normal-sized kidneys with diffuse echogenicity of the medullary pyramids.

Question 2: Genetic testing is most likely to reveal which of the following?

(a) Inactivating mutation in the gene for the thiazide-sensitive electroneutral sodium chloride cotransporter (NCC)
(b) Inactivating mutation in the transcription factor, hepatocyte nuclear factor 1B
(c) Inactivating mutation in the gene for the magnesium entry channel, *TRPM6*
(d) Inactivating mutation in the gene for claudin 16

For the answer to this question, see the following text.

Inherited causes of hypomagnesemia are invariably rare. Their identification, however, has greatly advanced our understanding of the renal handling of magnesium. Most of these disorders have an autosomal recessive inheritance pattern, and they present in childhood with varied degrees of hypomagnesemia. Thus, as a cause of hypomagnesemia, they can be easily missed. In many cases, intrinsic to the clinical presentation is hypocalcemia, which manifests with neurologic signs and symptoms. Seizures frequently occur, which may be explained by the regulation of excitatory N-methyl-D-aspartate (NMDA) receptors in the brain by magnesium. In addition, syndromes that affect transporters found in both the brain and the kidney may present with refractory seizures unresponsive to magnesium due to the intrinsic dysfunction of the transporter in the brain. Another key difference with acquired causes of hypomagnesemia is that, because they are lifelong, individuals "accumulate" complications of hypomagnesemia. Thus, an infant with recurrent/intractable seizures may present in later childhood or adulthood with intellectual disability. Chondrocalcinosis is another long-term complication of chronic hypomagnesemia that presents in adults.

Hypomagnesemia With Salt Wasting

Gitelman Syndrome

Gitelman syndrome is an autosomal recessive inherited condition due to mutations in *SLC12A3* (which codes for NCC) and is the most common inherited cause of hypomagnesemia (1 in 40,000). Most patients have compound heterozygous mutations, with more than 350 inactivating mutations in the *SLC12A3* gene identified to date. In up to a third of patients with Gitelman syndrome, a genetic diagnosis may prove elusive using conventional sequencing techniques. Often in such cases only 1 pathogenic variant is identified, with the second variant revealed by more advanced techniques. So-called acquired Gitelman syndrome has been described in patients with autoimmune conditions, including systemic lupus erythematosus (SLE), systemic sclerosis, and scleroderma. The putative

Table 1. Oral Formulations of Magnesium Supplements, Magnesium Content, and Typical Starting Dose

Magnesium Formulation	Elemental Magnesium/ Dose, mg	Typical Dosing
Magnesium oxide, 400 mg	241.3	1 tablet 2-3 times daily
Magnesium carbonate	54 mg/5 mL	5-10 mL 3 times daily
Magnesium chloride, 520 mg	62.17	1-2 tablets 3 times daily
Magnesium glycinate, 665 mg	120	1 tablet 2-3 times daily
Magnesium glycerophosphate, 425 mg	50	2 tablets 2-3 times daily
Magnesium lactate, 84 mg elemental magnesium	84	1 tablet 3 times daily
Magnesium phosphate, 710 mg	27.73	1 tablet 3 times daily
Magnesium aspartate hydrochloride, 685 mg	133	1 tablet 3 times daily
Magnesium gluconate, 500 mg	28.5	2 tablets 3 times daily
Magnesium citrate, 625 mg	100	1 capsule 3 times daily

A reasonable target dose is to administer 300 mg of elemental magnesium in divided doses and titrate as tolerated. In general, although the amount absorbed increases, bioavailability decreases with increasing doses. However, the risk of diarrhea increases with increased amounts of elemental magnesium.

mechanism involves antibodies directed against the NCC. Hypomagnesemia in Gitelman syndrome results from the down-regulation of *TRPM6*. Most patients with Gitelman present in late childhood to early adulthood with varied degrees of hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and elevated plasma renin levels. The physical presentation is variable. Common symptoms include low blood pressure, salt craving, paresthesia, and muscle cramps. Severe symptoms, including ventricular arrhythmias and seizures, occur infrequently. In the long term, Gitelman syndrome may impact growth and stature.

Bartter Syndrome Type 3

Bartter syndrome type 3 (BS3) is due to inactivating mutations in *CLCNKB*, which codes for the basolateral chloride channel ClC-Kb, in the TAL. It is not clear why Bartter syndromes other than type 3 do not generally present with hypomagnesemia, considering the TAL is responsible for most of the magnesium reabsorption. It is possible that adaptive mechanisms in the DCT may be protective. ClC-Kb is also present in the DCT, and thus unsurprisingly BS3 exhibits phenotypic similarities to Gitelman syndrome. BS3 however occurs at a much lower frequency (1 in 100,000) and presents earlier in life. The condition is diagnosed in most patients in infancy and presents with polyuria, polydipsia, and failure to thrive. The electrolyte and acid-base presentations are similar to Gitelman syndrome although the hypomagnesemia and hypokalemia are usually less severe.

Autosomal Dominant Hypocalcemia

Hypomagnesemia occurs in patients with activating mutations affecting the basolateral CASR in the TAL. Because the CASR is constitutively activated, affected patients have a higher set point for PTH release and present with hypocalcemia and a poor PTH response. Activation of CASR leads to impaired paracellular reabsorption of calcium and magnesium, with hypomagnesemia occurring in more than 50% of patients. Phosphate may be normal or high. Symptoms are usually due to hypocalcemia and range from tetany, spasms, and fasciculations to severe presentations including arrhythmias and seizures. Because CASR also inhibits TAL sodium reabsorption, some patients present with a Bartter-like phenotype.

EAST/SeSAME Syndrome

EAST syndrome is an acronym for epilepsy, ataxia, sensorineural deafness, and tubulopathy; SeSAME stands for seizures, sensorineural deafness, ataxia, mental disorders, and electrolyte imbalance. Both refer to the same autosomal recessive condition due to inactivating mutations in *KCNJ10*, which codes for the basolateral potassium channel in Kir4.1. This channel is found in the brain, eye, inner ear, TAL, and DCT. Patients present with seizures in infancy, together with cerebellar dysfunction and hearing loss. The renal manifestations occur later in childhood and are similar to Gitelman syndrome.

Familial Hypomagnesemia With Hypercalciuria and Nephrocalcinosis (FHHNC)

FHHNC is an autosomal recessive condition affecting the TAL due to inactivating mutations in *CLDN16* and *CLDN19*. Affected patients present in childhood and adolescence with the triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis. Because of the nephrocalcinosis, affected patients develop progressive chronic kidney disease (CKD), and they present with end-stage renal disease (ESRD) by adolescence. Due to the progressive decline in glomerular filtration rate (GFR), by the time some patients are diagnosed they may already have spontaneous resolution of hypomagnesemia. Claudin-19 is present in the retina, and patients with *CLDN19* mutations additionally have ocular abnormalities, including myopia, coloboma, and nystagmus. Most patients who have been identified to date with *CLDN19* mutations are from Spain, which may be due to a founder effect.

Hypomagnesaemia With Secondary Hypocalcemia (HSH)

Autosomal recessive mutations in *TRPM6* cause hypomagnesaemia with secondary hypocalcemia (HSH). The affected patients present in childhood with profound

hypomagnesemia (often <0.2 mg/dL) and intractable seizures. Because magnesium is often very low, renal magnesium wasting may not be demonstrable on initial presentation. TRPM6/7 are responsible for the fine tuning of renal tubular magnesium reabsorption and are expressed in the intestine as well. Concurrent impaired intestinal absorption and increased renal excretion thus explain the severity of the hypomagnesemia. Hypocalcemia occurs because of impaired secretion of PTH. These patients present with tetany and seizures that do not respond to conventional anticonvulsants. If there is a delay in the diagnosis, permanent neurologic manifestation may ensue. The seizures promptly respond to treatment with magnesium, and the patients require lifelong magnesium replacement.

Isolated Dominant Hypomagnesemia

Isolated dominant hypomagnesemia is a heterogenous group of conditions due to mutations affecting different genes. *FXYD2* codes for a kidney-specific γ subunit, which regulates the Na-K-ATPase in the DCT. The described mutations to date are all inherited in an autosomal dominant pattern, and the affected patients develop seizures at a young age. An autosomal dominant mutation in the gene that codes for Kv1.1, *KCNA1*, has also been reported. These individuals present in infancy with muscle cramps, tetany, and weakness.

Isolated Recessive Hypomagnesemia

Isolated recessive hypomagnesemia is due to a mutation that affects the cytoplasmic domain of pro-EGF. This mutation prevents targeting of the EGF receptor to the basolateral domain, and thus prevents it from stimulating TRPM6, leading to hypomagnesemia in infancy.

HNF1B-related Diseases

Hepatocyte nuclear factor 1B (HNF1B) is a transcription factor important in renal development as well as in the pancreas and liver. Heterozygous mutations in *HNF1B* cause maturity-onset diabetes of the young, type 5, and are also associated with a broad range of renal phenotypes, including congenital anomalies of the kidney and urinary tract (CAKUT), polycystic kidney disease, and autosomal dominant tubulointerstitial kidney disease. Hypomagnesemia affects approximately half of the patients. The *FXYD2* gene has a binding site for HNF1B, which offers a mechanistic explanation for hypomagnesemia in these patients. Again, due to progressive CKD, hypomagnesemia may not be apparent by the time of presentation. A closely related disorder is due to mutation in *PCBD1*, the gene responsible for transient neonatal hyperphenylalaninemia and primapterinuria. PCBD1 dimerizes with HNF1B, and together they costimulate FXYD2.

Other Inherited Causes of Hypomagnesemia

Other inherited causes of hypomagnesemia are exceedingly rare. Patients with mutations in *CNNM2*, which encodes the basolateral magnesium transporter in the TAL and DCT, present with seizures beginning in the first 2 years of life, together with vertigo, headache, speech and intellectual impairment, and obesity. *ATP1A1* mutations in the α-1 subunit of Na-K-ATPase also present with hypomagnesemia. Whereas FXYD2 is kidney-specific, the α-1 subunit is ubiquitous, including expression in the brain. Therefore, unlike patients with mutations in *FXYD2*, seizures in individuals with the *ATP1A1* mutation do not respond to magnesium, and intellectual disability is a key feature.

With regards to case 2, the history of childhood hypomagnesemia without a family history suggests an inherited, likely recessive disorder, and the findings of urinary magnesium wasting, nephrocalcinosis, and progressive CKD together are most consistent with FHHNC. Plasma magnesium may be normal in patients with CKD because of the reduced filtered load of magnesium. The answer to question 2 is (d). Progressive CKD is not a feature of Gitelman syndrome and HSH. HNF1B mutations may present with CKD, but nephrocalcinosis is not a typical feature.

Special Populations

Patients with cancer and tissue/organ transplants commonly present with hypomagnesemia for a variety of reasons, including poor oral intake, diarrhea, redistribution, and renal magnesium wasting from chemotherapeutic agents (platinum-based drugs, EGFR inhibitors), immunosuppressants, and antimicrobial agents. The problem of hypomagnesemia in this patient population is heightened by the association with worse outcomes, including patient and allograft survival.

Individuals with alcohol use disorder are especially prone to hypomagnesemia due to poor nutritional intake, transcellular shift from respiratory alkalosis, and catecholamine stimulation during episodes of withdrawal. Acute alcohol intoxication also has a magnesuric effect.

Hypomagnesemia is common in patients with diabetes mellitus. In fact, hypomagnesemia and diabetes mellitus have a bidirectional relationship. Patients with diabetes mellitus develop hypomagnesemia, which has been attributed to the role of insulin in regulating TRPM6 activity and expression. Other mechanisms include hyperfiltration, increased urinary flow, and decreased intestinal absorption due to autonomic neuropathy. Conversely, hypomagnesemia is associated with development of insulin resistance and poor clinical outcomes among patients with diabetes mellitus. Single nucleotide polymorphisms (SNPs) of *TRPM6* have been associated with insulin resistance, suggesting a causal relationship.

Additional Readings

- Abdelhadi O, Iancu D, Stanescu H, Kleta R, Bockenhauer D. EAST syndrome: clinical, pathophysiological, and genetic aspects of mutations in KCNJ10. *Rare Dis.* 2016;4(1):e1195043. doi:10.1080/21675511.2016.1195043
- Adalat S, Woolf AS, Johnstone KA, et al. HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. *J Am Soc Nephrol.* 2009;20(5):1123-1131. doi:10.1681/ASN.2008060633 ★ESSENTIAL READING
- Blanchard A, Bockenhauer D, Bolignano D, et al. Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies conference. *Kidney Int.* 2017;91(1):24-33. doi:10.1016/j.kint.2016.09.046 ★ESSENTIAL READING
- Claverie-Martin F. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: clinical and molecular characteristics. *Clin Kidney J.* 2015;8(6):656-664. doi:10.1093/ckj/sfv081
- Konrad M, Nijenhuis T, Ariceta G, et al. Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders. *Kidney Int.* 2021;99(2):324-335. doi:10.1016/j.kint.2020.10.035
- Konrad M, Schlingmann KP. Inherited disorders of renal hypomagnesaemia. *Nephrol Dial Transplant.* 2014;29(suppl 4):iv63-71. doi:10.1093/ndt/gfu198 ★ESSENTIAL READING
- Oost LJ, Tack CJ, de Baaij JHF. Hypomagnesemia and cardiovascular risk in type 2 diabetes. *Endocr Rev.* 8 2023;44(3):357-378. doi:10.1210/endrev/bnac028
- Schlingmann KP, de Baaij JHF. The genetic spectrum of Gitelman(-like) syndromes. *Curr Opin Nephrol Hypertens.* 2022;31(5):508-515. doi:10.1097/MNH.0000000000000818
- Thebault S, Alexander RT, Tiel Groenestege WM, Hoenderop JG, Bindels RJ. EGF increases TRPM6 activity and surface expression. *J Am Soc Nephrol.* 2009;20(1):78-85. doi:10.1681/ASN.2008030327
- Van der Wijst J, Konrad M, Verkaart SAJ, et al. A de novo KCNA1 mutation in a patient with tetany and hypomagnesemia. *Nephron.* 2018;139(4):359-366. doi:10.1159/000488954

Presentation and Work-Up of Hypomagnesemia

Case 3: *A 60-year-old woman with a history of diabetes mellitus and recently diagnosed triple negative breast cancer presents for evaluation of hypomagnesemia. She is currently receiving neoadjuvant therapy comprising paclitaxel, cisplatin, and pembrolizumab. Her other medications include ibuprofen, insulin glargine, and metformin. A month after starting her cancer therapy she developed severe hypomagnesemia. Her serum magnesium level has since ranged between 0.6 mg/dL and 1 mg/dL. She receives 4 g of intravenous magnesium sulfate twice weekly. Her laboratory values are as follows.*

Laboratory Test	Value
Serum parameters	
Magnesium, mg/dL	0.8
Creatinine, mg/dL	0.5
Serum urea nitrogen, mg/dL	14
Potassium, mmol/L	3.0
Urine parameters	
Magnesium, mg/dL	10
Creatinine, mg/dL	60
Potassium, mmol/L	30

Question 3: What is the fractional excretion of magnesium?

(a) 2%
(b) 15%
(c) 50%
(d) 19%
(e) 10%

For the answer to the question, see the following text.

Plasma magnesium represents a very small fraction of the total body magnesium, and it may be normal even in individuals in negative magnesium balance. Most patients with hypomagnesemia are asymptomatic. Patients with severe hypomagnesemia, however, present with pleiotropic manifestations including cardiovascular, neuromuscular, and gastrointestinal symptoms. Secondary electrolyte abnormalities often occur. Hypomagnesemia impairs PTH release and causes end-organ PTH resistance, leading to hypocalcemia. Hypomagnesemia also leads to renal potassium wasting, postulated to be due to release of intracellular magnesium block of the ROMK channel, thereby leading to hypokalemia. In addition, many conditions associated with hypomagnesemia also cause concurrent hypokalemia, including diuretics, Bartter/Gitelman syndromes, and diarrhea. Neuromuscular manifestations include fasciculations, tetany, weakness, personality changes, and seizures. Electrocardiography may show prolonged PR interval, prolonged QRS interval, prolonged QT duration, R-on-T phenomenon, and ventricular arrhythmia including torsades de pointes.

The initial goal of testing in patients with hypomagnesemia is to determine whether the hypomagnesemia is due to a renal or an extrarenal cause (Fig 4). To identify other electrolyte abnormalities, initial plasma chemistries should include creatinine, potassium, calcium, phosphorus, and PTH. Spurious hypomagnesemia may result from ethylenediaminetetraacetic acid (EDTA) contamination of the

sample and from severe hypoalbuminemia. Hemolysis of the sample may mask hypomagnesemia or present as hypermagnesemia. Other tests, including whole blood ionized magnesium concentration, magnesium tolerance testing, red cell magnesium, and skeletal muscle magnesium, are either not done frequently in clinical practice or not readily available.

Fractional excretion of magnesium (FeMg) is calculated from blood and urine chemistries as follows: $\frac{(uMg \times pCr)}{(0.7 \times pMg \times uCr)} \times 100$, where u is urine, p is plasma, Mg is magnesium, Cr is creatinine, and 0.7 represents the average free fraction of plasma magnesium. In a patient with hypomagnesemia, FeMg > 3%-4% generally indicates renal magnesium wasting, and a value <2% suggests an alternative cause. If a 24-hour urine is collected, magnesium excretion of <10 mg or >30 mg is consistent with extrarenal and renal causes of hypomagnesemia, respectively.

HSH patients are unique in that they can have profound hypomagnesemia with a relatively mild renal magnesium transport defect. Thus, in HSH patients with very low serum magnesium levels (≤0.4 mg/dL), the filtered load may fall below the renal threshold, and the FeMg could be <2%. Renal magnesium wasting is unmasked when such patients are repleted with magnesium supplementation. If renal magnesium wasting is confirmed and the cause is not readily apparent, genetic testing informed by the clinical presentation should be pursued.

In case 3, the calculated FeMg is 15% (answer b), which is inappropriately high. This finding in the setting of severe hypomagnesemia suggests severe impairment of the ability of the kidney to reabsorb magnesium. The spot urine magnesium concentration can be misleading because it depends on the urine concentration. Hypokalemia and hypomagnesemia often occur together in renal wasting syndromes but can also be seen in gastrointestinal wasting such as with diarrhea.

Question 4: For the patient in case 3, which medication may explain the renal magnesium wasting?

(a) Pembrolizumab
(b) Cisplatin
(c) Metformin
(d) Paclitaxel
(e) Insulin glargine

For the answer to the question, see the following text.

Patients with cancer are prone to hypomagnesemia due to multiple interacting factors. Anorexia with poor oral intake is common in this population because of the disease and treatments. Gastrointestinal side effects of therapies including vomiting and diarrhea may increase extrarenal magnesium losses. Due to multiple comorbidities, polypharmacy is common. Lastly, specific medication side effects may predispose individuals to renal magnesium wasting. Platinum-based chemotherapeutic agents are a particularly common culprit and may cause hypomagnesemia in up to 90% of patients. The implicated mechanisms include direct renal tubular toxicity and downregulation of the EGFR-TRPM6 pathway. These factors result in renal magnesium wasting with an inappropriately normal or frankly elevated fractional excretion of magnesium. Thus, the answer to question 4 is (b). None of the other medications that this patient is taking are associated with hypomagnesemia.

Additional Readings

- Elisaf M, Panteli K, Theodorou J, Siamopoulos KC. Fractional excretion of magnesium in normal subjects and in patients with hypomagnesemia. *Magnes Res.* 1997;10(4):315-320. ★ESSENTIAL READING
- Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol.* 2007;18(10):2649-2652. doi:10.1681/ASN.2007070792
- Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. *Am J Nephrol.* 2013;38(1):50-57. doi:10.1159/000351804

Treatment of Hypomagnesemia

The treatment of hypomagnesemia begins with an assessment of the severity of symptoms and determination of the etiology, which informs the therapeutic approach. Most patients are asymptomatic unless the plasma magnesium is <1 mg/dL. There is a paucity of data to guide management in patients with hypomagnesemia and no organized consensus guidelines. In the presence of life-threatening symptoms like seizures and ventricular arrhythmias, rapid stabilization can be achieved by administering a bolus dose of intravenous magnesium sulfate of 1-2 g. This may be repeated if the clinical situation persists. The optimal rate of infusion has not been determined, but 1-2 g given over a few minutes in an emergent situation is reasonable. Pregnant women with eclampsia routinely tolerate loading doses of 4-6 g administered over 20-30 minutes.

The total body deficit in patients with hypomagnesemia ranges from 0.5 to 1.0 mmol/kg. Because the plasma magnesium equilibrates slowly with intracellular sources, the renal threshold is easily exceeded, and 90% of the intravenous magnesium may be excreted in the urine over the first 24 hours. For the same reason, plasma magnesium after administration of intravenous magnesium may give a spurious impression of correction. Magnesium sulfate is the most widely available intravenous form of magnesium; 1 g contains 4 mmol of magnesium, and this is administered as a 20% formulation. A 50% intramuscular formulation is also available for pregnant women with eclampsia. Close attention should be paid to the plasma magnesium, especially in patients with reduced renal function. In nonemergency situations, if an intravenous formulation is required, it may

be administered at a rate not exceeding 1 g/hour, with slower rates resulting in more magnesium retention.

Careful attention should be paid to factors that promote magnesium loss, such as concurrent drugs. For instance, PPI use is common, and in the absence of compelling indications, alternative gastric acid suppressants should be considered. Potassium binders, sodium polystyrene sulfonate, and patiromer may bind magnesium in the gut and lower the plasma magnesium. Similarly, medications associated with diarrhea and diuretics should be discontinued or substituted with alternatives. In certain patient populations (eg, transplant patients on calcineurin inhibitors or cancer patients on EGFR inhibitors) the culprit medication(s) cannot be stopped and must be continued concurrently with treatment for hypomagnesemia.

A variety of oral magnesium formulations are available, but they differ in their magnesium content (Table 1). There is a paucity of rigorous empiric evidence regarding the oral bioavailability of different magnesium salts. It is generally believed that organic salts are more bioavailable compared with inorganic salts. Several studies have suggested that magnesium citrate is more bioavailable compared with magnesium oxide, based on measurements of plasma and urine magnesium. Diarrhea is a major limiting factor to replacement with oral magnesium. Because of its poor absorption, magnesium is an effective osmotic laxative, and the severity of diarrhea increases linearly with the magnesium content of stool. Some formulations such as magnesium hydroxide are primarily laxatives and should not be used at all to treat hypomagnesemia. Although various magnesium formulations are touted as having better absorption or lower incidence of diarrhea, the evidence for most is very weak.

In cases of chronic hypomagnesemia where diarrhea limits oral treatment, patients may need intermittent dosing of intravenous magnesium. Subcutaneous delivery of magnesium sulfate has been used in intractable hypomagnesemia. Topical application of magnesium to increase plasma magnesium has also been described but requires further rigorous evaluation. Modulation of urinary magnesium may be a helpful adjunct in the treatment of hypomagnesemia. Blockers of the epithelial sodium channel, ENaC, such as amiloride and triamterene have been reported to decrease urine magnesium with a concurrent increase in the plasma magnesium. However, their efficacy is limited.

In randomized controlled trials of sodium/glucose cotransporter 2 (SGLT2) inhibitors, the treated patients had higher plasma magnesium compared with placebo. Several case reports have suggested that SGLT2 inhibitors may correct hypomagnesemia and potentially be more effective than magnesium repletion. They have been shown to decrease the fractional excretion of magnesium. The mechanism is unclear, but it has been proposed that SGLT2 inhibitors, by decreasing the electrogenic absorption of sodium, might create a favorable electrical gradient for magnesium reabsorption in the proximal convoluted tubule.

Patients should be counseled on increasing their intake of foods that are rich dietary sources of magnesium. Seeds, nuts, and legumes provide the highest source per serving of magnesium. The bioavailability of dietary magnesium may be adversely affected by other food components, including oxalate and phytates. Inulin supplementation has been suggested to increase gut absorption of magnesium.

Additional Readings

- Ayuk J, Gittoes NJ. Treatment of hypomagnesemia. *Am J Kidney Dis*. 2014;63(4):691-695. doi:10.1053/j.ajkd.2013.07.025
- Jiang DM, Dennis K, Steinmetz A, et al. Management of epidermal growth factor receptor inhibitor-induced hypomagnesemia: a systematic review. *Clin Colorectal Cancer*. 2016;15(3):e117-e123. doi:10.1016/j.clcc.2016.02.011
- Ranade VV, Somberg JC. Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. *Am J Ther*. 2001;8(5):345-357. doi:10.1097/00045391-200109000-00008
- Toto RD, Goldenberg R, Chertow GM, et al. Correction of hypomagnesemia by dapagliflozin in patients with type 2 diabetes: a post hoc analysis of 10 randomized, placebo-controlled trials. *J Diabetes Complications*. 2019;33(10):107402. doi:10.1016/j.jdiacomp.2019.06.007 ★ESSENTIAL READING

Hypermagnesemia

Case 4: *A 63-year-old man with a past medical history of hypertension, diabetes mellitus, and ESRD on hemodialysis presents to the emergency department with extreme lethargy. On examination, his blood pressure is 153/75 mm Hg and heart rate is 72 bpm. He has mild, nontender abdominal distention, global weakness, and depressed reflexes. He missed his last dialysis session because he felt too tired to go. His laboratory values are as follows.*

Serum Parameters	Value
Creatinine, mg/dL	9
Serum urea nitrogen, mg/dL	80
HCO_3^-, mEq/L	18
Potassium, mmol/L	6.1
Magnesium, mg/dL	5.6
Phosphate, mg/dL	10

Question 5: Which of the following factors may explain his presentation?

(a) Use of an over-the-counter laxative
(b) Inadequate dosing of dialysis
(c) Uremic encephalopathy
(d) Dysfunction of the carbon filters at the dialysis unit
(e) A diet rich in nuts and cereal

For the answer to the question, see the following text.

Pathogenesis of Hypermagnesemia

Hypermagnesemia is defined as serum magnesium > 2.7 mg/dL (2.2 mEq/L). Hypermagnesemia is uncommon in patients with preserved kidney function because the capacity of the kidneys to excrete magnesium is high. Thus, for hypermagnesemia to occur 2 conditions must be satisfied: impaired renal function and magnesium intake either as therapy or prophylaxis. Among hospitalized patients, the reported rates of hypermagnesemia range from <1% to 9.3%. Because magnesium is not routinely measured, most cases may be missed.

Patient groups at risk include patients with ESRD/CKD and pregnant women with eclampsia who receive high doses of magnesium sulfate. In patients with ESRD, plasma magnesium is largely determined by oral intake of magnesium and dialysis. The standard dialysate used for peritoneal dialysis and hemodialysis in the United States contains 0.25 mmol/L and 0.37-0.5 mmol/L of magnesium respectively. Thus, patients on dialysis are predisposed to hypomagnesemia in the postdialysis period. However, when patients with ESRD are exposed to high magnesium intake from medications, including laxatives, antacids, and nutritional supplements, they can then develop hypermagnesemia, which may be symptomatic. Hypermagnesemia in patients with ESRD occurs at a prevalence of 10%-15%.

In pregnant women, the risk for hypermagnesemia stems from the high doses of magnesium used for seizure prophylaxis in women with pre-eclampsia or eclampsia. Usually this is transient, but acute kidney injury may complicate hypertensive diseases of pregnancy and predispose such patients to persistent hypermagnesemia. Despite the capacity of the normal kidney to respond to hypermagnesemia, there have also been several case reports of hypermagnesemia in people with normal renal function who ingested high doses of magnesium in preparations like Epsom salt.

Some inherited conditions including familial hypocalciuric hypercalcemia (FHH) and HELIX syndrome are associated with mild hypermagnesemia. FHH is rare and caused by heterozygous loss of function mutation in *CASR* or its downstream signaling proteins encoded by *AP2S1* and *GNA11*. Affected individuals present with mild elevation in the plasma magnesium, essentially manifesting the opposite phenotype to autosomal dominant hypocalcemia. HELIX syndrome presents with hypermagnesemia that is more pronounced in children compared with adults.

Clinical Presentation and Management of Hypermagnesemia

The clinical presentation of patients with hypermagnesemia depends on its severity. Mild cases present with lethargy, drowsiness, nausea, and vomiting. More severe hypermagnesemia (>7.2 mg/dL; 3 mmol/L) leads to cardiorespiratory depression and loss of tendon reflexes; magnesium levels of >12 mg/dL (5 mmol/L) may lead to paralysis, cardiac arrest, coma, and even death. The appropriate treatment depends on the severity and renal function of the patient. With preserved renal function, mild to moderate cases can be managed conservatively with intravenous fluid hydration and loop diuretics. Administration of calcium counteracts neurologic/muscular manifestations. In severe cases or in patients with ESRD or severely impaired kidney function, renal replacement therapy is often necessary.

Returning to case 4, the correct answer to question 5 is (a). Patients often resort to over-the-counter laxatives like milk of magnesia to treat constipation. ESRD predisposes patients to retention of magnesium in these situations. In addition, he had missed his dialysis session, which exacerbated this. The patient was promptly dialyzed, with subsequent resolution in his symptoms, and he was counseled to avoid magnesium-containing supplements.

Additional Readings

- Bongers EMHF, Shelton LM, Milatz S, et al. A novel hypokalemic-alkalotic salt-losing tubulopathy in patients with CLDN10 mutations. *J Am Soc Nephrol*. 2017;28(10):3118-3128. doi:10.1681/ASN.2016080881 ★ESSENTIAL READING
- Ishida Y, Tabuchi A. Severe hypermagnesemia with normal renal function can improve with symptomatic treatment. *Case Rep Emerg Med*. 2020;2020:2918249. doi:10.1155/2020/2918249
- Leenders NHJ, van Ittersum FJ, Hoekstra T, Hoenderop JGJ, Vervloet MG. Routine hemodialysis induces a decline in plasma magnesium concentration in most patients: a prospective observational cohort study. *Sci Rep*. 2018;8(1):10256. doi:10.1038/s41598-018-28629-x
- Marx SJ, Spiegel AM, Brown EM, et al. Divalent cation metabolism: familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. *Am J Med*. 1978;65(2):235-242. doi:10.1016/0002-9343(7890814-8)
- Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia: requested vs routine. *JAMA*. 1990;263(22):3063-3064. doi:10.1001/jama.1990.03440220087036

Article Information

Authors' Full Names and Academic Degrees: Emmanuel A. Adomako, MB, ChB, and Alan S.L. Yu, MB, BChir.

Authors' Affiliations: Division of Nephrology and Hypertension, Department of Internal Medicine, Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas.

Address for Correspondence: Alan S.L. Yu, MB, BChir, 3901 Rainbow Blvd, 6018 WHE, Kansas City, KS 66160-3018. Email: ayu@kumc.edu

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received June 8, 2023 in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form October 25, 2023.