

Hypomagnesemia: a clinical perspective

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Abstract: Although magnesium is involved in a wide spectrum of vital functions in normal human physiology, the significance of hypomagnesemia and necessity for its treatment are under-recognized and underappreciated in clinical practice. In the current review, we first present an overview of the clinical significance of hypomagnesemia and normal magnesium metabolism, with a focus on renal magnesium handling. Subsequently, we review the literature for both congenital and acquired hypomagnesemic conditions that affect the various steps in normal magnesium metabolism. Finally, we present an approach to the routine evaluation and suggested management of hypomagnesemia.

Keywords: hypomagnesemia, magnesium, diabetes mellitus, alcohol, TRPM6, cisplatin

Introduction

Despite being the second most abundant intracellular and fourth most abundant extracellular cation in the body, hypomagnesemia has received relatively poor attention in the medical literature compared with hyponatremia, hypokalemia, and hypocalcemia. As of November 14, 2013, there were 2,100 versus 10,298, 1,107, and 12,345 citations related to the respective electrolyte disorders, recorded on PubMed (Figure 1). The low interest in hypomagnesemia may have stemmed from its relative lack of symptoms until plasma concentrations reach severely low levels, our poor understanding of magnesium metabolism until recent years, or both. Nonetheless, magnesium is involved in a wide spectrum of vital functions in human physiology. Magnesium is required for all enzymatic reactions requiring adenosine triphosphate (ATP), various reactions requiring kinases, neuromuscular excitability and cell permeability, regulation of ion channels and mitochondrial function, cellular proliferation and apoptosis, as well as immunity, among others.^{1–3}

Clinical manifestations

Hypomagnesemia, while typically defined as having serum magnesium concentration below 0.66 mmol/L (1.6 mg/dL), with or without accompanying total body depletion, does not lead to clinically significant signs and symptoms until serum levels fall below 0.5 mmol/L (1.2 mg/dL).³ Nonetheless, as magnesium is involved in an array of structural and physiological functions, adverse effects associated with hypomagnesemia may occur in almost every organ system, whether they are clinically acute and overt, or chronic and subtle.

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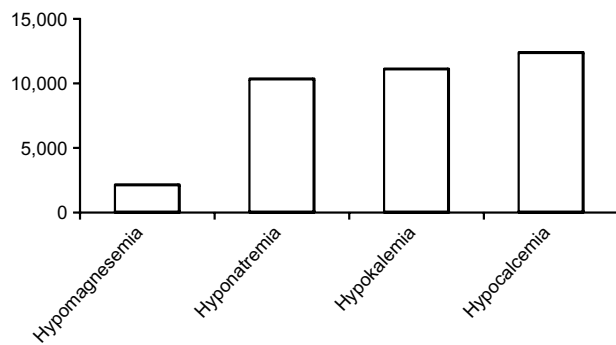


Figure 1 Number of PubMed citations (November 2013).

Clinical manifestations of hypomagnesemia that promptly lead to medical attention involve neuromuscular hyperexcitability that may range from tremors, fasciculation, tetany, to convulsions, and neuropsychiatric disturbances including apathy, delirium, and even coma. Other potentially life-threatening complications may arise not solely from hypomagnesemia, but also from the associated hypocalcemia and/or hypokalemia, and include atrial and ventricular arrhythmias, torsades de pointe, enhanced sensitivity to digoxin toxicity, and sudden death. In contrast, long-term adverse complications where the association with hypomagnesemia is not often recognized include altered glucose homeostasis, hypertension, atherosclerosis, osteoporosis, asthma, migraines, and other end-organ damage. Presumed mechanisms involved in various hypomagnesemia-associated signs/symptoms are listed in Table 1.²⁻⁵

The mechanisms of many, if not most, clinical signs and symptoms of hypomagnesemia are likely multifactorial and beyond the scope of discussion in the current review.

Magnesium metabolism

Gastrointestinal absorption

While the Institute of Medicine recommends a daily magnesium intake of 310–420 mg/day in adults, with the end of normal range for women and higher range for men, it has been estimated that 300–350 mg of magnesium is consumed daily in a typical American diet.⁶ Twenty percent to 80% of dietary magnesium is absorbed in the intestines, where absorption depends on both intake and body magnesium status, and occurs via both passive and active pathways.⁶⁻⁸ Passive Mg^{2+} absorption occurs paracellularly and predominantly in the small intestines, a process driven by a favorable electrochemical gradient and solvent drag with dietary intake. At low dietary magnesium intake, Mg^{2+} absorption relies heavily on active transcellular uptake via Mg^{2+} -specific transporters in the large intestines.^{7,9} Two Mg^{2+} -specific channels identified over recent years include the transient receptor potential melastatin (TRPM) 6 and TRPM7. TRPM7 is ubiquitously expressed among tissues, whereas TRPM6 is predominantly expressed along the full length of the intestine, the distal convoluted tubules (DCTs), the lungs, and the testis tissue. TRPM6 and TRPM7 can form heterodimers and may influence trafficking and activity of the TRPM6 Mg^{2+} channel. However, the extent and significance of the interactions between TRPM6 and 7 remain to be fully elucidated.⁸ Nonetheless, it

Table 1 Magnesium functions and hypomagnesemia related clinical manifestations

General functions	Specific involvement	Signs/symptoms and altered metabolisms associated with hypomagnesemia*
Enzymatic activities: functioning as substrate or direct enzyme activation	Kinases, ATPases or GTPases, cyclases, phosphofructokinase, creatine kinase, 5-phosphoribosyl-pyrophosphate synthetase, adenylate cyclase, $Na^+-K^+-ATPase$	Altered glucose metabolism, electrolyte imbalances (hypokalemia, hypocalcemia), osteoporosis, enhanced digoxin sensitivity, enhanced apoptosis, arrhythmias, atherosclerosis
Membrane function	Cell adhesion, transmembrane electrolyte flux	Arrhythmias: atrial tachycardia and fibrillation, supraventricular and ventricular arrhythmias, Torsade de pointes, rhabdomyolysis, hemolysis, myocardial infarction
Calcium antagonist	Neuromuscular function	Neuromuscular hyperexcitability: tremors, fasciculation, tetany, convulsions, neuropsychiatric changes, eg, apathy, depression, psychosis, vertigo, nystagmus, athetoid movements and choreiform movements, migraine, asthma (reactive airways), impaired exercise performance, electrolyte imbalances (hypokalemia, hypocalcemia), hypertension, atherosclerosis
Structural function, ion complex formation	Proteins, polyribosomes, nucleic acids, multiple enzyme complexes, mitochondria, ion complexes	Enhanced apoptosis, osteoporosis, kidney stones

Notes: Copyright © 2003. Australasian Association of Clinical Biochemists. Adapted from Swaminathan R. Magnesium metabolism and its disorders. *Clin Biochem Rev.* 2003;24(2):47–66.³ *Signs and symptoms are listed based on possible and/or presumed mechanisms of hypomagnesemia-induced defective structural or physiological functions. Many signs and symptoms are multifactorial, not fully understood, and beyond the scope of the current paper.

Abbreviations: ATPase, adenosine triphosphatase; GTPase, guanosine triphosphatase; $Na^+-K^+-ATPase$, sodium-potassium adenosine triphosphatase.

has been suggested that while TRPM6 plays an important role in epithelial Mg^{2+} transport, TRPM7 is involved in cellular Mg^{2+} homeostasis.¹⁰ Loss-of-function mutations of TRPM6 have been reported in patients with familial hypomagnesemia with secondary hypocalcemia.¹¹

Magnesium exists as protein bound (20% to 30%), complexed with organic anions such as sulfates, phosphates, or bicarbonates and citrates (5% to 15%), or free ionized cations (55% to 70%), where the proportion of each form is dependent on plasma pH, ionic strength, and protein/organic anion contents. Intracellular magnesium concentration has been estimated to range from 5 to 20 mmol/L (12–49 mg/dL), while extracellular magnesium concentration typically ranges from 0.70 to 1.05 mmol/L (1.7–2.6 mg/dL).⁵

Cellular shift

Unlike potassium, regulation of Mg^{2+} cellular uptake or release occurs slowly and likely does not occur in all cell types. Bone is the largest reservoir of magnesium but its role and regulation in maintaining plasma levels remain poorly understood.¹²

Kidney handling of magnesium

The kidneys are thought to play a key role in regulating and maintaining magnesium balance.

Approximately 70% to 80% of plasma magnesium in ionized or complexed forms is ultrafilterable in the kidneys. Once filtered, 15% to 25% is reabsorbed passively with sodium and water in the proximal tubules.¹³ Sixty-five percent to 75% of the filtered magnesium load is reabsorbed paracellularly in the thick ascending limb of the loop of Henle (TAL), a process facilitated by the tight junction protein claudin-16, also known as paracellin-1.^{14,15} Mutation of claudin-16 is associated with severe hypomagnesemia with hypercalciuria and nephrolithiasis.¹⁶ More recently,

mutations encoding the tight junction protein claudin-19 have also been reported to cause the inherited human renal disorder, familial hypomagnesemia with hypercalciuria and nephrocalcinosis.¹⁷ Although further studies are required, current evidence from both in vitro and in vivo studies suggests that claudin-16 and claudin-19 cogenerate a cation channel at the TAL tight junction necessary for normal Mg^{2+} reabsorption at this nephron segment.¹⁸

Five percent to 10% of the filtered magnesium, or 70% to 80% of magnesium delivered from the TAL, is reabsorbed at the DCT subsegment 1, the final nephron segment where Mg^{2+} can be reabsorbed, via an active and regulated transcellular pathway through the apical TRPM6 (Figure 2).^{19,20} Although the percentage of filtered magnesium reabsorbed in the DCT is lower than that at more proximal segments, regulated reabsorption at this segment is essential to magnesium balance because it determines the final urinary Mg^{2+} loss.²¹

DCT magnesium reabsorption Apical factors

In Gitelman syndrome, where there is a homozygous or compound heterozygous mutation or deletion in the *SLC12A3* gene encoding the apical thiazide-sensitive NaCl cotransporter (NCC), significant hypomagnesemia occurs in association with hypokalemic metabolic alkalosis and hypocalciuria.²² Although mechanistically unclear, Nijenhuis et al demonstrated reduced TRPM6 expression in mice chronically treated with thiazide, a Gitelman-equivalent condition.²³ Additionally, it has been suggested that the compensatory hyperaldosteronism associated with reduced NCC sodium reabsorption in Gitelman may lead to reduced TRPM6 activity, particularly in concert with low dietary magnesium intake.²⁴ It may also be speculated that reduced NCC sodium reabsorption could lead to sub-optimal basolateral $(3)Na^{+}-(2)K^{+}$ -ATPase activity, hence

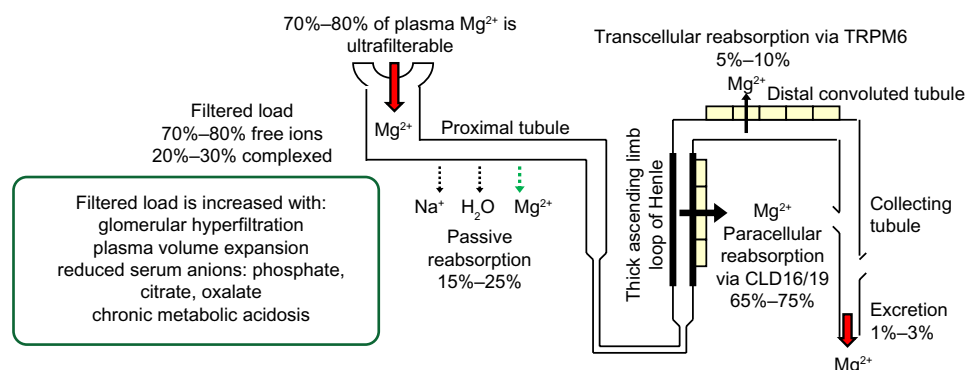


Figure 2 Kidney handling of magnesium.

Abbreviations: CLD, claudin; TRPM6, transient receptor potential channel 6.

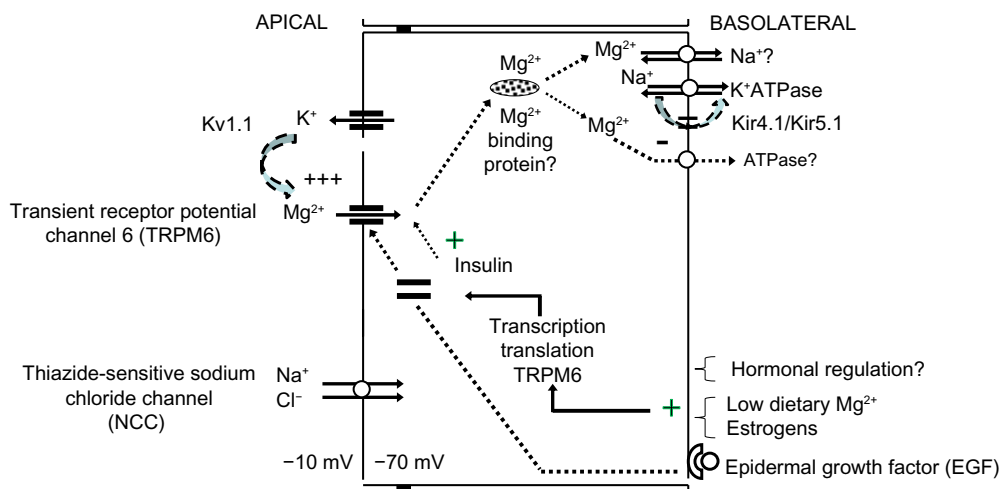


Figure 3 Magnesium reabsorption at the distal convoluted tubule.

reduced generation of the favorable potential difference (ie, more negative intracellular voltage) to facilitate apical Mg^{2+} reabsorption (Figure 3). Whatever the mechanism(s) is/are, normal NCC function is likely necessary for DCT Mg^{2+} reabsorption.

The apical voltage-gated potassium channel Kv1.1 has also been implicated to play a role in normal DCT Mg^{2+} reabsorption. A mutation involving substitution of asparagine for aspartic acid leading to nonfunctional Kv1.1 channels in the DCT has been reported in a family with isolated autosomal-dominant hypomagnesemia paired with signs and symptoms of neuromuscular dysfunction including recurrent muscle cramps and weakness, tremors, tetany, cerebellar atrophy, and myokymia.²⁵ It was suggested that the loss of Kv1.1 function reduces apical K^+ intraluminal secretion, hence the associated favorable intraluminal positive voltage to facilitate Mg^{2+} reabsorption via TRPM6.

Basolateral factors

Renal magnesium handling at the DCT occurs via the apical TRPM6, whose shuttling from intracellular vesicles toward apical membranes requires binding of epidermal growth factor (EGF) to its basolateral receptor. Mutations of the EGF gene have been shown to be the causative defect in recessive isolated renal hypomagnesemia, where apical TRPM6 expression is reduced.^{26,27}

It is speculated that following apical reabsorption, Mg^{2+} binds to Mg^{2+} -binding proteins for transport to the basolateral sides, where eventual reabsorption into the interstitium occurs via transporters such as Na^+/Mg^{2+} exchangers and/or Mg^{2+} -ATPase. While basolateral transport of Mg^{2+} has not been elucidated, mutations involving the γ -subunit of the basolateral $Na^+-K^+-ATPase$ or the regulatory protein of

$Na^+-K^+-ATPase$, the hepatocyte nuclear factor 1 homeobox B (*HNF1B*), are associated with renal Mg^{2+} wasting.^{28–30} Mutation in the *FXYD2* gene encoding the γ -subunit of $Na^+-K^+-ATPase$ is thought to affect normal routing, hence activity of the transporter. Suboptimal $Na^+-K^+-ATPase$ activity theoretically leads to depolarization of the DCT due to the $3Na^+$ -to- $2K^+$ exchange ratio (ie, reduced intracellular negative voltage that normally favors reabsorption of the divalent cation Mg^{2+}) thus reduced Mg^{2+} reabsorption via TRPM6. If basolateral Mg^{2+} reabsorption significantly relies on Na^+/Mg^{2+} exchangers, it may be also deduced that reduced $Na^+-K^+-ATPase$ activity, hence reduced basolateral Na^+ recycling, would also lead to reduced basolateral Mg^{2+} reabsorption. Heterozygous mutations of the *HNF1B* gene, either whole-gene deletion or point mutations, are linked to a dominant renal cysts and diabetes syndrome, where up to 50% of patients also present with renal magnesium wasting with hypocalciuria.³¹ *HNF1B* is thought to play a regulatory role in the transcription of the *FXYD2* gene, specifically at the promoter responsible for the transcription the γ -subunit of $Na^+-K^+-ATPase$.³⁰

The basolateral, heteromeric, inwardly rectifying Kir4.1/Kir5.1 K^+ channel has also been found to affect Mg^{2+} reabsorption, presumably via its K^+ recycling function necessary to maintain optimal $Na^+-K^+-ATPase$ activity. Mutations involving the *KCNJ10* gene encoding Kir4.1 have been reported to cause a clinical constellation involving hypomagnesemia with associated SEizures, Sensorineural deafness, Ataxia, Mental retardation, and Electrolyte imbalance Epilepsy, Ataxia, Sensorineural deafness, and renal Tubulopathy, known as (SeSAME/EAST) syndrome.^{32,33} It is possible that the associated suboptimal $Na^+-K^+-ATPase$ function leads to reduced sodium reabsorption at the DCT

thiazide-sensitive sodium chloride channel, a defect observed with Gitelman syndrome. Accordingly, with the exception of hypocalcemia, a Gitelman-like clinical syndrome including sodium wasting, hypokalemia, hypomagnesemia, and metabolic alkalosis may be observed with Kir4.1 loss-of-function mutation. Additionally, it has been reported that the Kir4.1/Kir5.1 K⁺ channel is extremely sensitive to inhibition by intracellular pH, a characteristic thought to be conferred by the intact Kir5.1 subunit.³⁴ Interestingly, activation or gain-of-function mutation of the calcium-sensing receptor (CaSR) has been shown to reduce basolateral Kir4.1 expression, presumably via altered caveolin-mediated trafficking of the channel, with resultant reduction in Mg²⁺ reabsorption and salt-wasting at the DCT.³⁵

Finally, although mechanistically unclear, both deletion and missense mutations involving cyclin M2, a protein localized to the basolateral side in both the TAL and the DCT, have been identified in two unrelated families with unexplained dominant hypomagnesemia.³⁶

Hormonal regulation

Regulatory hormones reported to influence magnesium homeostasis via TRPM6 and TRPM7 protein expression and activity include angiotensin II, aldosterone, bradykinin, thrombin, estrogen, and insulin. Parathyroid hormone and 1,25 vitamin D, however, do not appear to have any effect on TRPM6 expression.^{8,37-41} Of interest, the inability of insulin activation of TRPM6 in two single nucleotide TRPM6 polymorphisms, Ile1393Val and Lys1584Glu, has been linked to hypomagnesemia and presumed hypomagnesemia-induced glucose intolerance in women on low dietary magnesium intake.³⁷ Low dietary magnesium intake and estrogens have been shown to upregulate renal TRPM6 expression and reduce urinary magnesium excretion.³⁸

Aldosterone has been reported to induce renal Mg²⁺ wasting, an effect that may be ameliorated by aldosterone antagonists.^{39,40} Additionally, the use of aldosterone antagonists has also been shown to maintain plasma magnesium levels in patients receiving routine therapy for congestive heart failure, presumably via enhancing cellular Mg²⁺ efflux, thus implicating a role for aldosterone in cellular Mg²⁺ shift.⁴⁰ Sontia et al have suggested that aldosterone may influence urinary Mg²⁺ excretion through redistribution of Mg²⁺ (Mg²⁺ efflux) in muscle, bone, and the gastrointestinal tract via stimulation of the Na⁺/Mg²⁺ exchanger and downregulation of renal TRPM7.⁴¹

Congenital conditions associated with hypomagnesemia are summarized in Table 2.

Etiologies of acquired hypomagnesemia

Similar to congenital conditions, acquired etiologies of hypomagnesemia may be categorized based on the presumed defects in the various steps of magnesium metabolism and are summarized in Table 3.

Gastrointestinal causes

Common conditions include severely low dietary Mg²⁺ intake; prolonged nasogastric suction; and overall malabsorptive states including diarrhea, steatorrhea, celiac disease, regional enteritis, and short-gut syndrome. Gastrointestinal magnesium loss due to malabsorptive states may be due to rapid intestinal transit, Mg²⁺ binding to undigested free fatty acids, and/or reduction in both passive and active absorption.⁴²⁻⁴⁴ Of interest, diarrhea has been attributed as an important cause of hypomagnesemia in patients with chronic alcoholism. In a study involving 127 patients with chronic alcoholism, 20 out of 38 cases of hypomagnesemia were thought to be due to alcohol withdrawal syndrome and diarrhea. The remaining patients with hypomagnesemia had evidence of hypermagnesiuria, thought to be associated with hypophosphatemia and/or metabolic acidosis.⁴⁵

Cellular shift/tissue sequestration

Acute pancreatitis is known to be associated with hypocalcemia and hypomagnesemia, both presumably via saponification in necrotic fat. The accompanying hypocalcemia-induced hyperparathyroidism and resultant hypophosphatemia may also lead to concurrent renal Mg²⁺ loss.⁴³ Post-parathyroidectomized patients are thought to develop hypomagnesemia predominantly due to increased bone formation and mineralization, and in some cases, concurrent hypermagnesiuria.⁴⁶ Conditions associated with increased anabolic states and cellular magnesium uptake leading to reduced plasma magnesium concentration include refeeding syndrome, excessive parenteral alimentation, advanced pregnancy, and lactation.⁴⁷⁻⁴⁹ Hypomagnesemia associated with massive blood transfusions is not uncommon and presumed to be due to citrate toxicity, hemodilution, and/or associated comorbidities.⁵⁰ Cardiopulmonary bypass surgeries without magnesium supplementation may be associated with hypomagnesemia, thought to be due to increased cellular uptake with the high catecholamine state and chelation by free fatty acids and/or citrate.⁵¹ Hypomagnesemia associated with foscarnet has been proposed to occur via magnesium incorporation into bone matrix following complex formation with foscarnet.⁵²

Table 2 Congenital causes of hypomagnesemia

Sources of magnesium loss	Sites of defect in magnesium metabolism	Congenital
Gastro-intestinal absorption	Passive reabsorption	
	Active reabsorption	TRPM6
Cellular shift; tissue sequestration	–	–
Kidney handling	Glomerular filtration	–
	Proximal tubular reabsorption	Proximal renal tubular acidosis with or without associated Fanconi's syndrome
	Thick ascending limb of loop of Henle	Claudin-16
		Claudin-19
		NKCC2
		ROMK
		CIC-Kb
		CaSR
	Distal convoluted tubule:	TRPM6
		Kv1.1
		Kir4.1/Kir5.1
		NCCT
		Na ⁺ -K ⁺ -ATPase
		EGF
		CaSR
		CNNM2
		Insulin
Other sources of loss	Nonspecific tubular injury/ cellular leak	–
	Other	–

Abbreviations: NKCC2, sodium potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; CIC-Kb, chloride channel Kb; CaSR, calcium sensing receptor; Kv1.1, potassium voltage-gated channel subfamily A member 1; Kir4.1/Kir5.1, inward-rectifier type potassium channel 4.1/5.1 dimer; NCCT, sodium chloride cotransporter; Na⁺-K⁺-ATPase, sodium-potassium adenosine triphosphatase; *HNF1B*, hepatocyte nuclear factor 1 homeobox B; EGF, epidermal growth factor; CNNM2, cyclin M2; TRPM 6, transient receptor potential melastatin 6; SeSAME/EAST syndrome, SEizures, Sensorineural deafness, Ataxia, Mental retardation, and Electrolyte imbalance Epilepsy, Ataxia, Sensorineural deafness, and renal Tubulopathy.

Renal wasting

Hyperfiltration

Hyperfiltration associated with various conditions (including diabetes mellitus; post-obstructive, osmotic, or acute tubular necrosis diuresis; post-kidney transplantation; or excessive volume expansion) may lead to enhanced filterable magnesium load, thus overwhelming the kidneys' Mg²⁺ reabsorption capacity, and resultant hypermagnesiuria. Conditions favoring magnesium in its ionized form such as chronic metabolic acidosis or states with low organic anions may also contribute to a high filterable magnesium load and renal Mg²⁺ wasting.⁵³

Reduced proximal tubular reabsorption

As Mg²⁺ is reabsorbed passively at the proximal tubules, severe injury to this nephron segment in the presence of normal glomerular filtration can lead to hypermagnesiuria. Acquired Fanconi's syndrome and tubular toxicities induced by drugs such as cisplatin, aminoglycosides, and pentamidine, have all been reported to be associated with hypomagnesemia. Of note, pentamidine may also be associated with acute pancreatitis, which could be contributory to hypomagnesemia.⁵⁴ Dietary salt loading has been shown in rats to increase distal tubular Mg²⁺ delivery, presumably via reduced proximal passive reabsorption, and upregulation

Table 3 Acquired causes of hypomagnesemia

Sources of magnesium loss	Sites of defect in magnesium metabolism	Acquired	
Gastro-intestinal absorption	Passive reabsorption	Low dietary Mg ²⁺ intake; prolonged nasogastric suction; diarrhea; enteric fistulas; steatorrhea; short-gut syndrome; alcoholism	
	Active reabsorption	TRPM6 See DCT TRPM6 below	
Cellular shift; tissue sequestration	–	Acute pancreatitis (magnesium and calcium saponification in necrotic fat); hungry bone syndrome; refeeding syndrome; foscarnet (magnesium incorporation into bone matrix following complex formation with foscarnet); massive blood transfusions; third trimester pregnancy; lactation; excessive parenteral alimentation; cardiopulmonary bypass	
Kidney handling	Glomerular filtration	Hyperfiltration (diabetes mellitus, post-obstructive or acute tubular necrosis diuresis, osmotic diuresis, post-kidney transplantation); extracellular volume expansion; increased filterable Mg (metabolic acidosis, low organic anions)	
		Acquired Fanconi's syndrome, drug toxicity (cisplatin, gentamicin, pentamidine); high dietary salt intake	
	Proximal tubular reabsorption	–	
	Thick ascending limb of loop of Henle	Claudin-16	–
		Claudin-19	–
		NKCC2	Loop diuretics; hypokalemia
		ROMK	Hypokalemia
		CIC-Kb	–
		CaSR	Increase in serum calcium and magnesium; aminoglycosides
		TRPM6	Calcineurin inhibitors (cyclosporine and tacrolimus shown to reduce renal TRPM6 expression); rapamycin (reduced TRPM6 messenger (m)RNA stability); chronic metabolic acidosis
	Distal convoluted tubule:	–	Apical regulators/ effectors of TRPM6
		Kv1.1	Hypokalemia
		Kir4.1/Kir5.1	–
		NCCT	Thiazide diuretics; cyclosporine
		–	Basolateral regulators/ effectors of TRPM6
Na ⁺ -K ⁺ -ATPase		Hypophosphatemia; calcineurin inhibitors (cyclosporin shown to inhibit Na ⁺ -K ⁺ -ATPase); ethanol (inhibits Na ⁺ -K ⁺ -ATPase activity)	
EGF		Anti-EGF receptor antibodies (cetuximab, panitumumab); cisplatin (reduced EGF and TRPM6 mRNA); cyclosporine (reduce TRPM6, NCC, EGF mRNA)	
CaSR		Increase in serum calcium and magnesium; aminoglycoside (gentamicin, amikacin); ?cinacalcet	
Other sources of loss	Nonspecific tubular injury/cellular leak	CNNM2	–
		–	Hormonal regulators of TRPM6
		Insulin	Diabetes mellitus?
–	Other	Amphotericin; pentamidine	
–	Other	Severe burns (skin loss)	

Abbreviations: NKCC2, sodium potassium 2 chloride cotransporter; ROMK, renal outer medullary potassium channel; CIC-Kb, chloride channel Kb; CaSR, calcium sensing receptor; Kv1.1, potassium voltage-gated channel subfamily A member 1; Kir4.1/Kir5.1, inward-rectifier type potassium channel 4.1/5.1 dimer; NCCT, sodium chloride cotransporter; Na⁺-K⁺-ATPase, sodium-potassium adenosine triphosphatase; EGF, epidermal growth factor; CNNM2, cyclin M2; NCC, Thiazide-sensitive sodium chloride channel; TRPM6, transient receptor potential melastatin 6; DCT, distal convoluted tubule.

of TRPM6 in the DCT, but overall increases urinary Mg²⁺ excretion.⁵⁵

Reduced TAL reabsorption

Acquired causes of hypomagnesemia that target the TAL include loop diuretics, hypokalemia, hypercalcemia, and aminoglycosides. Effective reabsorption of Mg²⁺ at this nephron segment relies on luminal K⁺ recycling, which

requires the functional Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) for cellular K⁺ uptake, the renal outer medullary K⁺ channel (ROMK) for K⁺ recycling back into the lumen, and the CaSR for regulation of the ROMK. Potassium recycling into the lumen via the ROMK creates a more positively charged lumen, which facilitates divalent cation (Ca²⁺, Mg²⁺) reabsorption paracellularly. This process is facilitated by the tight junction proteins claudin-16 and claudin-19. Any

transporter defect leading to suboptimal K^+ recycling or claudin-16/claudin-19 function may induce Ca^{2+} and Mg^{2+} wasting. While loop diuretics specifically block NKCC2, hypokalemia may cause both suboptimal NKCC2 functioning as well as K^+ recycling. Activation of the CaSR with Ca^{2+} can inhibit ROMK, and hence cause ineffective K^+ tubular recycling. Reduction in K^+ recycling, hence favorable intraluminal positive voltage necessary to facilitate Ca^{2+} and Mg^{2+} paracellular reabsorption, leads to wasting of both divalent cations. Aminoglycosides have been suggested to directly inhibit tubular Mg^{2+} reabsorption via binding to and activation of the CaSR. Of interest, this class of antibiotics has been suggested to mimic type 5 Bartter syndrome where there is a gain-of-function mutation of the CaSR.⁵⁶⁻⁵⁸

Reduced DCT reabsorption

Drugs known to be associated with hypomagnesemia and likely exert their magnesiuric effect at the DCTs include calcineurin inhibitors and rapamycin. Both cyclosporine and tacrolimus have been shown to reduce TRPM6 expression in the DCT in animal studies.⁵⁹⁻⁶¹ Additionally, cyclosporine has been shown to induce reduced messenger (m)RNA expression of NCC.⁵⁹ Whether the latter effect affects TRPM6 expression or plays a contributory role in magnesiuria is not known. Clinically, tacrolimus has been observed to induce more significant magnesiuria compared with cyclosporine.⁶²

While rapamycin (sirolimus) has been reported to induce hypomagnesemia, the mechanism(s) whereby rapamycin causes magnesiuria is (are) not well defined. In an *in vitro* study using NRK-52E cells derived from normal rat renal tubules, Ikari et al revealed that sirolimus reduces mRNA expression TRPM6 at the DCT via inhibition of EGF-induced increase in TRPM6 expression, presumably by reducing the stability of TRPM6 mRNA.⁶³ In contrast, in a study using male Wistar rats treated with rapamycin, da Silva et al reported increased TRPM6 expression.⁶⁴ The magnesiuric effect of rapamycin in the latter study was thought to be due to the primary downregulation of NKCC2 protein expression leading to magnesiuria, followed by a secondary compensatory response with increased DCT TRPM6 protein expression. A direct rapamycin stimulatory effect on TRPM6 expression, however, could not be ruled out. Interestingly, rosiglitazone was shown to ameliorate the rapamycin-associated electrolyte disturbances including hypokalemia and downregulation of NKCC2.⁶⁴

Although both calcineurin and mammalian target of rapamycin (mTOR) inhibitors may induce renal Mg^{2+} wasting, mTOR inhibitors may have lower magnesiuric effect

compared with calcineurin inhibitors. In a retrospective review involving 138 renal transplant patients who were converted from calcineurin inhibitors to mTOR inhibitors over a 6-month period, magnesium levels significantly improved in association with reduced fractional excretion of Mg^{2+} .⁶⁵ In addition to drugs, acid-base status has also been shown to determine renal expression of TRPM6; whereas chronic metabolic acidosis reduces, chronic metabolic alkalosis enhances TRPM6 expression.⁶⁶

To our knowledge, acquired causes of hypomagnesemia associated with inhibition of basolateral Kir4.1/5.1 have not been reported. Although there is evidence of direct inhibition of basolateral Kir4.1/5.1 and Kir4.1 channels in the cortical collecting duct by dopamine and antibody production against the potassium channel Kir4.1 in patients with multiple sclerosis, hypomagnesemia is not associated with these conditions.^{67,68} Similarly, there are no known reported cases of acquired hypomagnesemia due to direct inhibition of Kv1.1.

As previously discussed, thiazide-, and to some extent, cyclosporine-induced hypomagnesemia may occur via downregulation of TRPM6 expression. Moreover, Loffing et al have shown that thiazide administration over three days in rats can provoke apoptosis of distal tubule cells and associated focal peritubular inflammation.⁶⁹ The direct effect of thiazides on the terminal nephron segment for magnesium reabsorption may explain the severe hypomagnesemia associated with Gitelman and not necessarily Bartter syndrome. As observed in animal studies where high-salt treatment was associated with increased distal delivery of Mg^{2+} and upregulation of TRPM6, the increased distal delivery of Mg^{2+} in patients with various types of Bartter syndromes may similarly upregulate DCT TRPM6, and hence reduce net Mg^{2+} wasting compared with Gitelman syndrome.⁵⁵

Factors known to be associated with hypomagnesemia that could act via inhibition of the DCT basolateral $Na^+-K^+-ATPase$ include hypophosphatemia, calcineurin inhibitors, and ethanol.^{70,71} As phosphate is required for all ATP-requiring cellular activities, it is conceivable that hypophosphatemia can lead to suboptimal $Na^+-K^+-ATPase$ activity and, if proven present and significant in the DCT, basolateral $Mg^{2+}-ATPase$.

While mutations involving EGF affect apical TRPM6 expression hence magnesium reabsorption, the use of anti-EGF receptor antibodies, particularly cetuximab and panitumumab, has accordingly been reported to be associated with hypomagnesemia. Other commonly used drugs associated

with hypomagnesemia that have been shown to reduce EGF expression include cisplatin and cyclosporine.^{59,72,73}

Clinical conditions and drugs that could potentially be equivalent to CaSR gain-of-function mutations to induce hypomagnesemia include hypercalcemia and aminoglycosides. Both may stimulate the CaSR and in turn reduce ROMK activity, hence reduce the favorable potential difference necessary for optimal paracellular Mg²⁺ reabsorption at the TAL. Moreover, CaSR activation at the DCT is also thought to induce renal Mg²⁺ wasting via inhibition of TRPM6 expression. Nonetheless, common conditions associated with hypercalcemia including primary hyperparathyroidism and granulomatous disease, however, have not been reported to be associated with significant hypomagnesemia. In contrast, aminoglycosides including amikacin and gentamicin are well known to induce hypomagnesemia, hypothesized to occur via binding to and activation of the CaSR.^{74,75} Whether the CaSR agonist cinacalcet can induce hypomagnesemia is not known. Incidentally, our research into this question led to the review of a case series with reported pre- and post-cinacalcet treatment serum magnesium levels in four patients with familial hypocalciuric hypercalcemia. Notably, all four patients' serum magnesium levels were lower at follow-up than at baseline. The serum magnesium levels before and at follow-up were 1.01±0.07 mmol/L and 0.95±0.01 mmol/L, respectively, *P*=0.11. Whether this observation is fortuitous, further investigation is warranted.⁷⁶

Diabetes mellitus is well known to be associated with hypomagnesemia, likely via a plethora of mechanisms.⁵³ Most recently, given reports of reduced insulin activation of TRPM6 in patients with TRPM6 polymorphisms, it may be speculated that the lack of insulin in the diabetic state may reduce TRPM6 activity and could thus contribute to hypomagnesemia.⁷⁷

Other drugs associated with hypomagnesemia include amphotericin and pentamidine. The former is thought to self-insert into renal tubular membranes and act as an ionophore for urinary magnesium leak, whereas the latter is thought to induce hypomagnesemia via nonspecific, yet to be determined, kidney injury.^{54,78}

Finally, hypomagnesemia has been reported in severe burn patients. The involved mechanisms are likely multifactorial and may involve the need for aminoglycoside administration, or associated hypokalemia, among others.⁷⁹

Diagnosis of hypomagnesemia

The clinical evaluation for the underlying cause of hypomagnesemia requires a thorough investigation for the presence

of diabetes mellitus, alcoholism, gastrointestinal conditions involving poor absorption and/or poor nutritional intake, or a family history of hypomagnesemia without or without other electrolyte abnormalities, and a complete list of medications used. The suspected underlying etiology may be confirmed with urinary studies based on its mechanism via renal wasting or extrarenal cause. Patients with hypomagnesemia due to renal Mg²⁺ wasting have been suggested to present with a fractional excretion of Mg²⁺ greater than 4%, whereas those with extrarenal causes present with a much lower percentage, typically 2% or less. The fractional excretion of Mg²⁺ is defined as:

$$\frac{(\text{Urine magnesium concentration} \times \text{Serum creatinine concentration})}{(0.7 \times \text{Serum magnesium concentration} \times \text{Urine creatinine concentration})} \times 100,$$

where the 0.7 factor indicates that in most circumstances, only 70% of serum magnesium is filterable.⁸⁰

Management of hypomagnesemia: authors' opinion

Magnesium metabolism and kidney handling of magnesium have been significantly elucidated over the last decade. A correlation between clinical conditions and specific mechanisms leading to hypomagnesemia will no doubt lead to better prevention and mechanism-specific therapy. Although mild-to-moderate hypomagnesemia is typically asymptomatic, long-term deficiencies have been reported to be associated with a spectrum of adverse micro- and macrovascular outcomes including increased risk of diabetes mellitus, various diabetic complications, arrhythmias particularly in association with congestive heart failure, hypertension, and more rapid progression of kidney disease, among others. Therefore, if safely tolerated, patients should receive therapy to correct the hypomagnesemic state.^{2-5,81,82} Currently, however, the management of hypomagnesemia still relies on relatively nonspecific management including avoidance or discontinuation of responsible agents if possible, corrections of underlying metabolic derangements, and/or magnesium supplementation.

Minimization of renal Mg²⁺ wasting

Routine corrections of the hyperfiltrative state, chronic metabolic acidosis, and low organic anion state (eg, hypophosphatemia and hypoproteinemia/hypoalbuminemia) should be done whenever applicable to minimize filtration of large amounts of free ionized Mg²⁺. Consultation with a dietitian may be necessary to

Table 4 Selected food sources of magnesium

Food	mg per serving	Percent daily value
Almonds, dry roasted, 1 ounce	80	20
Spinach, boiled, ½ cup	78	20
Cashews, dry roasted, 1 ounce	74	19
Peanuts, oil roasted, ¼ cup	63	16
Cereal, shredded wheat, 2 large biscuits	61	15
Soy milk, plain or vanilla, 1 cup	61	15
Black beans, cooked, ½ cup	60	15
Edamame, shelled, cooked, ½ cup	50	13
Peanut butter, smooth, 2 tablespoons	49	12
Bread, whole wheat, 2 slices	46	12
Avocado, cubed, 1 cup	44	15
Potato, baked with skin, 3.5 ounces	43	11
Rice, brown, cooked, ½ cup	42	11
Yogurt, plain, low fat, 8 ounces	42	11
Breakfast cereals, fortified with magnesium	40	10

Note: Adapted from US Department of Health and Human Services. National Institutes of Health. *Magnesium fact sheet for health professionals*. Available from ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#h3.⁸³

increase dietary magnesium intake as well as protein supplementation in malnourished patients. Reduction of glomerular hyperfiltration may be achieved with the addition of any renin-angiotensin inhibitors. The use of an aldosterone antagonist may be considered if safely tolerated. Diarrheal states should be evaluated by a gastrointestinal specialist and promptly treated.

Dietary intake of foods containing high levels of magnesium should be encouraged. In general, grains, and beans are good sources of magnesium. Selected food sources of magnesium may be found at ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#h3.⁸³ A few food sources containing at least 10% of the daily value of recommended total daily dietary

Table 5 Common oral magnesium formulations

Common formulations	Trade names	Elemental magnesium content (mg)
Magnesium oxide	Mag-Ox 400 tablets (400 mg)	241
	Uro-Mag capsules (140 mg)	84
Magnesium gluconate	Magnesium gluconate tablets (500 mg)	27
Magnesium chloride	Slow-Mag tablets (535 mg plus 212 mg calcium)	64
Magnesium oxide with soy protein	Mg Pro Plus tablets (133 mg plus 26 mg soy protein)	133
Magnesium L-lactate dihydrate	Mag Tab SR tablets (84 mg)	84
Magnesium-L-aspartate hydrochloride	Maginex tablets (615 mg)	61

Notes: Mag-Ox 400, Uro-Mag, Blaine Pharmaceuticals, Santa Fe Springs, CA, USA; Magnesium gluconate 500 mg, eg, Mag-G, Pernix Therapeutics, Houston, TX, USA; Slow-Mag, Purdue Pharma LP, Stamford, CT, USA; Mg Plus Protein, Miller Pharmacal Group, Inc., Carol Stream, IL, CA, USA; Mag Tab SR, Niche Pharmaceuticals, Southlake, TX, USA; Maginex 615 mg, Health Care Prod/Hi-Tech, Amityville, NY, USA.

Abbreviation: SR, slow release.

magnesium (400 mg for adults and children aged 4 and older) as developed by the US Food and Drug Administration are listed in Table 4. If all measures fail to achieve “normal” range or serum magnesium concentration >0.66 mmol/L (1.6 mg/dL), magnesium supplement should be added. Various magnesium formulations are available on the market and are listed in Table 5. In the authors’ experience, Mg Plus Protein (Miller Pharmacal Group, Inc., Carol Stream, IL, USA) appears to be best tolerated by patients in terms of magnesium supplement-induced diarrhea.

In conclusion, recent research has contributed a great deal to our understanding of various congenital and acquired hypomagnesemic states. Although no specific targeted therapy is currently available, routine corrections of underlying etiologies and electrolyte and metabolic derangements, increase in dietary magnesium intake, and/or magnesium supplementation are recommended, as chronic hypomagnesemic state has been reported to be associated with various micro- and macrovascular complications.

Disclosure

The authors report no conflicts of interest in this work.

References

- Sanders GT, Huijzen HJ, Sanders R. Magnesium in disease: a review with special emphasis on the serum ionized magnesium. *Clin Chem Lab Med*. 1999;37(11–12):1011–1033.
- Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium: an update on physiological, clinical and analytical aspects. *Clin Chim Acta*. 2000;294(1–2):1–26.
- Swaminathan R. Magnesium metabolism and its disorders. *Clin Biochem Rev*. 2003;24(2):47–66.
- Flink EB. Magnesium deficiency: etiology and clinical spectrum. *Acta Med Scand Suppl*. 1981;647:125–137.
- Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J*. 2012;5(Suppl 1):i3–i14.
- Schwartz R, Spencer H, Welsh JJ. Magnesium absorption in human subjects from leafy vegetables, intrinsically labeled with stable 26 Mg. *Am J Clin Nutr*. 1984;39(4):571–576.
- Fine KD, Santa Ana CA, Porter JL, Fordtran JS. Intestinal absorption of magnesium from food and supplements. *J Clin Invest*. 1991;88(2):396–402.
- Quamme GA. Recent developments in intestinal magnesium absorption. *Curr Opin Gastroenterol*. 2008;24(2):230–235.
- Schweigel M, Martens H. Magnesium transport in the gastrointestinal tract. *Front Biosci*. 2000;5:D666–D677.
- Schlingmann KP, Gudermann T. A critical role of TRPM channel-kinase for human magnesium transport. *J Physiol*. 2005;566(Pt 2):301–308.
- Schlingmann KP, Weber S, Peters M, et al. Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet*. 2002;31(2):166–170.
- [no authors listed]. Plasma and bone magnesium. *Nutrition Reviews*. 1960;18(7):214–216.
- Quamme GA, Dirks JH. The physiology of renal magnesium handling. *Ren Physiol*. 1986;9(5):257–269.
- Quamme GA. Control of magnesium transport in the thick ascending limb. *Am J Physiol*. 1989;256(2 Pt 2):F197–F210.

15. Blanchard A, Jeunemaitre X, Coudol P, et al. Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of Henle. *Kidney Int.* 2001;59(6):2206–2215.
16. Weber S, Schneider L, Peters M, et al. Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. *J Am Soc Nephrol.* 2001;12(9):1872–1881.
17. Konrad M, Schaller A, Seelow D, et al. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. *Am J Hum Genet.* 2006;79(5):949–957.
18. Hou J, Goodenough DA. Claudin-16 and claudin-19 function in the thick ascending limb. *Curr Opin Nephrol Hypertens.* 2010;19(5):483–488.
19. Voets T, Nilius B, Hoefs S, et al. TRPM6 forms the Mg²⁺ influx channel involved in intestinal and renal Mg²⁺ absorption. *J Biol Chem.* 2004;279(1):19–25.
20. Konrad M, Schlingmann KP, Guderman T. Insights into the molecular nature of magnesium homeostasis. *Am J Physiol Renal Physiol.* 2004;286(4):F599–F605.
21. Reily RF, Ellison DH. Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. *Physiol Rev.* 2000;80(1):277–313.
22. Lemmink HH, Knoers NV, Károlyi L, et al. Novel mutations in the thiazide-sensitive NaCl cotransporter gene in patients with Gitelman syndrome with predominant localization to the C-terminal domain. *Kidney Int.* 1998;54(3):720–730.
23. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca²⁺ reabsorption and reduced Mg²⁺ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. *J Clin Invest.* 2005;115(6):1651–1658.
24. Yogi A, Callera GE, O'Connor SE, et al. Dysregulation of renal transient receptor potential melastatin 6/7 but not paracellin-1 in aldosterone-induced hypertension and kidney damage in a model of hereditary hypomagnesemia. *J Hypertens.* 2011;29(7):1400–1410.
25. Glaudemans B, van der Wijst J, Scola RH, et al. A missense mutation in the Kv1.1 voltage-gated potassium channel-encoding gene KCNA1 is linked to human autosomal dominant hypomagnesemia. *J Clin Invest.* 2009;119(4):936–942.
26. Groenestege WM, Thébault 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.
27. 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.
28. Meij IC, Koenderink JB, van Bokhoven H, et al. Dominant isolated renal magnesium loss is caused by misrouting of the Na(+), (K+)-ATPase gamma-subunit. *Nat Genet.* 2000;26(3):265–266.
29. Arystarkhova E, Sweadner KJ. Splice variants of the gamma subunit (FXD2) and their significance in regulation of the Na, K-ATPase in kidney. *J Bioenerg Biomembr.* 2005;37(6):381–386.
30. Ferré S, Veenstra GJ, Bouwmeester R, Hoenderop JG, Bindels RJ. HNF-1B specifically regulates the transcription of the gamma a-subunit of the Na⁺/K⁺-ATPase. *Biochem Biophys Res Commun.* 2011;404(1):284–290.
31. Kolatsi-Joannou M, Bingham C, Ellard S, et al. Hepatocyte nuclear factor-1 beta: a new kindred with renal cysts and diabetes and gene expression in normal human development. *J Am Soc Nephrol.* 2001;12(10):2175–2180.
32. Scholl UI, Choi M, Liu T, et al. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. *Proc Natl Acad Sci U S A.* 2009;106(14):5842–5847.
33. Bockenhauer D, Feather S, Stanescu HC, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ 10 mutations. *N Engl J Med.* 2009;360(19):1960–1970.
34. Paulais M, Bloch-Faure M, Picard N, et al. Renal phenotype in mice lacking the Kir5.1 (Kcnj16) K⁺ channel subunit contrasts with that observed in SeSame/EAST syndrome. *Proc Natl Acad Sci U S A.* 2011;108(25):10361–10366.
35. Cha SK, Huang C, Ding Y, Qi X, Huang CL, Miller RT. Calcium-sensing receptor decreases cell surface expression of the inwardly rectifying K⁺ channel Kir4.1. *J Biol Chem.* 2011;286(3):1828–1835.
36. Stuiver M, Lainez S, Will C, et al. CNNM2, encoding a basolateral protein required for renal Mg²⁺ handling, is mutated in dominant hypomagnesemia. *Am J Hum Genet.* 2011;88(3):333–343.
37. Song Y, Hsu YH, Niu T, Manson JE, Buring JE, Liu S. Common genetic variants of the ion channel transient receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7), magnesium intake, and risk of type 2 diabetes in women. *BMC Med Genet.* 2009;10:4.
38. Groenestege WM, Hoenderop JG, van den Heuvel L, Knoers N, Bindels RJ. The epithelial Mg²⁺ channel transient receptor potential melastatin 6 is regulated by dietary Mg²⁺ content and estrogens. *J Am Soc Nephrol.* 2006;17(4):1035–1043.
39. Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1995;76(17):1259–1265.
40. Gao X, Peng L, Adhikari CM, Lin J, Zuo Z. Spironolactone reduced arrhythmia and maintained magnesium homeostasis in patients with congestive heart failure. *J Cardiac Fail.* 2007;13(3):170–177.
41. Sontia B, Montezano AC, Paravicini T, Tabet F, Touyz RM. Downregulation of renal TRMP7 and increased inflammation and fibrosis in aldosterone-infused mice: effects of magnesium. *Hypertension.* 2008;51(4):915–921.
42. MacIntyre I, Robinson CJ. Magnesium and the gut: experimental and clinical observations. *Ann NY Acad Sci.* 1969;162(2):865–873.
43. Hersh T, Siddiqui DA. Magnesium and the pancreas. *Am J of Clin Nutr.* 1973;26(3):362–366.
44. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol.* 1999;10(7):1616–1622.
45. Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC. Pathogenetic mechanisms of hypomagnesemia in alcoholic patients. *J Trace Elem Med Biol.* 1995;9(4):210–214.
46. Tambyah PA, Rauff A, Lee KO. Persistent hypomagnesaemia following parathyroid surgery, hypermagnesaemia as a possible cause. *Ann Acad Med Singapore.* 1990;19(4):536–539.
47. Weiselberg EC, Gonzalez M, Fisher M. Eating disorders in the twenty-first century. *Minerva Ginecol.* 2011;63(6):531–545.
48. Frazier TG, Mucha ME, Rush IH, Trull EJ, Carlson SA, O'Connor JA. Hypomagnesemia: higher risk using total parenteral nutrition in the treatment of patients with malignancies. *J Surg Oncol.* 1980;13(1):35–38.
49. Flink EB. Magnesium deficiency. Etiology and clinical spectrum. *Acta Med Scand Suppl.* 1981;647:125–137.
50. Ho KM, Leonard A. Risk factors and outcome associated with hypomagnesemia in massive transfusion. *Transfusion.* 2011;51(2):270–276.
51. Aglio LS, Stanford GG, Maddi R, Boyd JL 3rd, Nussbaum S, Chernow B. Hypomagnesemia is common following cardiac surgery. *J Cardiothorac Vasc Anesth.* 1991;5(3):201–208.
52. Gearhart MO, Sorg TB. Foscarnet-induced severe hypomagnesemia and other electrolyte disorders. *Ann Pharmacother.* 1993;27(3):285–289.
53. Pham PCT, Pham PMT, Pham SV, Miller JM, Pham PTT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol.* 2007;2(2):366–373.
54. Shah GM, Alvarado P, Kirschenbaum MA. Symptomatic hypocalcemia and hypomagnesemia with renal magnesium wasting associated with pentamidine therapy in a patient with AIDS. *Am J Med.* 1990;89(3):380–382.
55. Lee CT, Lien YHH, Lai LW, Ng HY, Chiou TT, Chen HC. Variations of dietary salt and fluid modulate calcium and magnesium transport in the renal distal tubule. *Nephron Physiol.* 2012;122(3–4):19–27.
56. Holmes AM, Hesling CM, Wilson TM. Drug-induced secondary hyperaldosteronism in patients with pulmonary tuberculosis. *Q J Med.* 1970;39(154):299–315.
57. Chou CL, Chen YH, Chau T, Lin SH. Acquired Bartter-like syndrome associated with gentamicin administration. *Am J Med Sci.* 2005;329(3):144–149.

58. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. *Nat Rev Nephrol.* 2009;5(4):193–202.
59. Ledeganck KJ, Boulet GA, Horvath CA, et al. Effects of renal distal tubule transporters TRPM6 and NCC in a rat model of cyclosporine nephrotoxicity and effect of EGF treatment. *Am J Physiol Renal Physiol.* 2011;301(3):F486–F493.
60. Nijenhuis T, Hoenderop JG, Bindels RJ. Downregulation 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.
61. Ikari A, Okude C, Sawada H, Takahashi T, Sugatani J, Miwa M. Down-regulation of TRPM6-mediated magnesium influx by cyclosporin A. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2008;377(4–6):333–343.
62. Aisa Y, Mori T, Nakazato T, et al. Effects of immunosuppressive agents on magnesium metabolism early after allogeneic hematopoietic stem cell transplantation. *Transplantation.* 2005;80(8):1046–1050.
63. Ikari A, Sanada A, Sawada H, Okude C, Tonegawa C, Sugatani J. Decrease in transient receptor potential melastatin 6 mRNA stability caused by rapamycin in renal tubular epithelial cells. *Biochim Biophys Acta.* 2011;1808(6):1502–1508.
64. da Silva CA, de Bragança AC, Shimizu MH, et al. Rosiglitazone prevents sirolimus-induced hypomagnesemia, hypokalemia, and downregulation of NKCC2 protein expression. *Am J Physiol Renal Physiol.* 2009;297(4):F916–F922.
65. Sánchez-Fructuoso AI, Santín Cantero JM, Pérez Flores I, Valero San Cecilio R, Calvo Romero N, Vilalta Casas R. Changes in magnesium and potassium homeostasis after conversion from a calcineurin inhibitor regimen to an mTOR inhibitor-based regimen. *Transplant Proc.* 2010;42(8):3047–3049.
66. Nijenhuis T, Renkema KY, Hoenderop JG, Bindels RJ. Acid-base status determines the renal expression of Ca²⁺ and Mg²⁺ transport proteins. *J Am Soc Nephrol.* 2006;17(3):617–626.
67. Zaika OL, Mamenko M, Palygin O, Boukelmoune N, Staruschenko A, Pochynyuk O. Direct inhibition of basolateral Kir4.1/5.1 and Kir4.1 channels in the cortical collecting duct by dopamine. *Am J Physiol Renal Physiol.* 2013;305(9):F1277–F1287.
68. Srivastava R, Aslam M, Kalluri SR, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. *N Engl J Med.* 2012;367(2):115–123.
69. Loffing J, Loffing-Cueni D, Hegyl I, et al. Thiazide treatment of rats provokes apoptosis in distal tubule cells. *Kidney Int.* 1996;50(4):1180–1190.
70. Younes-Ibrahim M, Barnese M, Burth P, Castro-Faria MV. Inhibition of purified human kidney Na⁺-K⁺-ATPase by cyclosporine A: a possible mechanism for drug human nephrotoxicity. *Ann NY Acad Sci.* 2003;986:633–635.
71. Rodrigo R, Thielemann L. Effects of chronic and acute ethanol exposure on renal (Na+K)-ATPase in the rat. *Gen Pharmacol.* 1997;29(5):719–723.
72. do Pazo-Oubiña F, Estefanell-Tejero A, Riu-Viladoms G, Anglada-Martínez H, Molas-Ferrer G, Creus-Baró N. Magnesium monitoring practice in monoclonal anti-epidermal growth factor receptor antibodies therapy. *J Clin Pharma Ther.* 2013;38(2):101–103.
73. Ledeganck KJ, Boulet GA, Bogers JJ, Verpooten GA, De Winter BY. The TRPM6/EGF pathway is downregulated in a rat model of cisplatin nephrotoxicity. *PLoS One.* 2013;8(2):e57016.
74. Chrispal A, Boorugu H, Prabhakar AT, Moses V. Amikacin-induced type 5 Bartter-like syndrome with severe hypocalcemia. *J Postgrad Med.* 2009;55(3):208–210.
75. Chou CL, Chen YH, Chau T, Lin SH. Acquired Bartter-like syndrome associated with gentamicin administration. *Am J Med Sci.* 2005;329(3):144–149.
76. Rasmussen AQ, Jørgensen NR, Schwarz P. Clinical and biochemical outcomes of cinacalcet treatment of familial hypocalciuric hypercalcemia: a case series. *J Med Case Rep.* 2011;5(1):564.
77. Nair AV, Hoche B, Verkaart S, et al. Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy. *Proc Natl Acad Sci U S A.* 2012;109(28):11324–11329.
78. Finkelstein A, Holz R. Aqueous pores created in thin lipid membranes by the polyene antibiotics nystatin and amphotericin B. *Membranes.* 1973;2:377–408.
79. Cunningham JJ, Anbar RD, Crawford JD. Hypomagnesemia: a multifactorial complication of treatment of patients with severe burn trauma. *JPEN J Parenter Enteral Nutr.* 1987;11(4):364–367.
80. 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.
81. Pham PC, Pham PM, Pham PA, et al. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. *Clin Nephrol.* 2005;63(6):429–436.
82. Van Laecke S, Van Biesen W, Vanholder R. Hypomagnesaemia, the kidney and the vessels. *Nephrol Dial Transplant.* 2012;27(11):4003–4010.
83. US Department of Health and Human Services. National Institutes of Health. *Magnesium fact sheet for health professionals.* Available from ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#h3. Accessed March 27, 2014.

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