

REVIEW ARTICLE

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Magnesium Disorders

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CME



ALTHOUGH THE PAST SEVERAL YEARS HAVE SEEN SUBSTANTIAL ADVANCES in the understanding of molecular and cellular mechanisms regulating sodium, potassium, calcium, bicarbonate, and volume homeostasis in health and disease,¹⁻³ there has been a paucity of clinically relevant information about disorders of magnesium. Around 1980, magnesium was described as the “forgotten electrolyte,”⁴ even though it was and remains recognized as “nature’s ... calcium blocker.”⁵ Reasons for the apparent lack of appreciation for the clinical significance of magnesium may be due, at least in part, to the lack of information regarding the regulatory processes of this cation at the cellular, tissue, and systems levels.

Although Murphy suggested at the turn of the millennium that it was high time to “unravel ... the mysteries of magnesium,”⁶ her call was heeded only recently, with a growing appreciation of the role of magnesium in clinical medicine. This change has been facilitated by the discovery of magnesium-specific channels and transporters, as well as the characterization of physiological and hormonal processes that regulate magnesium homeostasis.⁷ This review focuses on recent discoveries in how magnesium functions in the body, concentrating on hypomagnesemia, the most common clinical magnesium disorder. Hypermagnesemia is rare and occurs primarily in patients with kidney disease who are receiving magnesium-retaining drugs.⁸

MAGNESIUM AS VITAL FOR CELL FUNCTION AND HEALTH

Typically, magnesium exists as the Mg^{2+} ion. It is present in all cells in all organisms from plants to higher mammals and is indispensable for health and life because it is an essential cofactor for ATP, the cellular source of energy.⁹ Magnesium is involved in major cellular and physiological processes, primarily through its nucleotide-binding properties and its regulation of enzymatic activity.¹⁰ All ATPase reactions require Mg^{2+} -ATP, including those involved in RNA and DNA functions. Magnesium is a cofactor for hundreds of enzymatic reactions in every cell type (Fig. 1).^{10,11} Furthermore, magnesium regulates glucose, lipid, and protein metabolism.¹² Magnesium is involved in the control of neuromuscular function, regulation of cardiac rhythm, modulation of vascular tone, hormone secretion, and N-methyl-D-aspartate (NMDA) release in the central nervous system.¹⁰ Magnesium is a second messenger involved in intracellular signaling and a regulator of circadian-clock genes, which control circadian rhythm in biologic systems.^{13,14}

MAGNESIUM TRANSPORTERS AND THEIR ROLES

Because of the fundamental nature of magnesium in the regulation of cell function and signaling, intracellular magnesium levels need to be tightly controlled.

KEY POINTS

MAGNESIUM DISORDERS

- The normal serum magnesium concentration in adults is 1.7 to 2.4 mg per deciliter (0.7 to 1.0 mmol per liter) and is tightly controlled through intestinal absorption, renal excretion, and storage in bone.
- Hypomagnesemia is present in 3 to 10% of the general population, but its prevalence is increased among persons with type 2 diabetes and hospitalized patients, especially those in the intensive care unit.
- Hypomagnesemia is usually associated with other electrolyte derangements, including hypocalcemia, hypokalemia, and metabolic alkalosis, and refractory hypokalemia is often responsive to treatment only after the magnesium concentration has been normalized.
- Patients with hypomagnesemia often present with nonspecific symptoms, such as lethargy, muscle cramps, or muscle weakness, and thus the diagnosis of magnesium deficiency may be overlooked.
- Many drug classes, such as antibiotics, diuretics, biologic agents, immunosuppressants, proton-pump inhibitors, and chemotherapies, cause renal magnesium loss and hypomagnesemia.
- In 80% of patients with familial hypomagnesemia, pathogenic variants in genes that encode for magnesium transport pathways have been identified.

Magnesium-specific carriers were originally identified in the 1950s in bacteria, fungi, and yeast.^{15,16} But it was some 50 years later that magnesium-selective transporters were identified as gatekeepers of human magnesium homeostasis.¹⁷⁻¹⁹

Among the first magnesium transporters characterized in humans were the transient receptor potential cation channel subfamily M members 6 and 7 (TRPM6 and TRPM7).¹⁷⁻²⁰ TRPM6 is expressed primarily in the colon and distal convoluted tubule of the kidney and is responsible for magnesium reabsorption in the intestine and kidney (Fig. 2).^{10,18} The clinical significance of TRPM6 was first realized when TRPM6 mutations were linked to hypomagnesemia and secondary hypocalcemia (HSH) as well as to other hypomagnesemia-associated syndromes.¹⁸ In mice, homozygous deletion of *Trpm6* is lethal to the embryo, whereas its heterozygous deletion leads to hypomagnesemia that is refractory to magnesium supplementation.^{21,22} Unlike TRPM6, TRPM7 is ubiquitously expressed and is essential for cell viability and life itself.^{21,22} Homozygous *Trpm7*-knockout mice do not survive the embryonic stage, whereas *Trmp7* heterozygotes have hypomagnesemia, blunted growth, and vascular dysfunction.²³ Numerous factors that influence TRPM6 and TRPM7 activity have been described as magnesiotropic (involving magnesium regulation), including epidermal growth factor (EGF), fibroblast growth factor 23 (FGF23), uromodulin, adenosine diphosphate (ADP) ribosylation factor-like protein 15, aldosterone, angiotensin II, bradykinin, and insulin.^{10,24-26}

Other magnesium transporters include solute carrier family 41 members 1, 2, and 3; cyclin and CBS domain divalent metal cation transport mediators 1 through 4 (CNNM1 through CNNM4); and the magnesium-selective mitochondrial RNA splicing protein 2 (MRS2).^{7,12} MAGT1, originally described as a magnesium transporter, is a facilitator of N-linked protein glycosylation that indirectly influences magnesium transport and homeostasis.²⁷

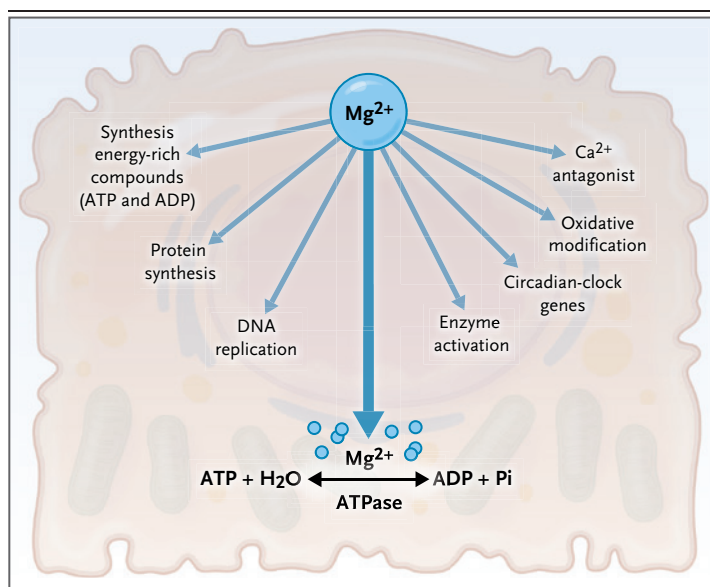
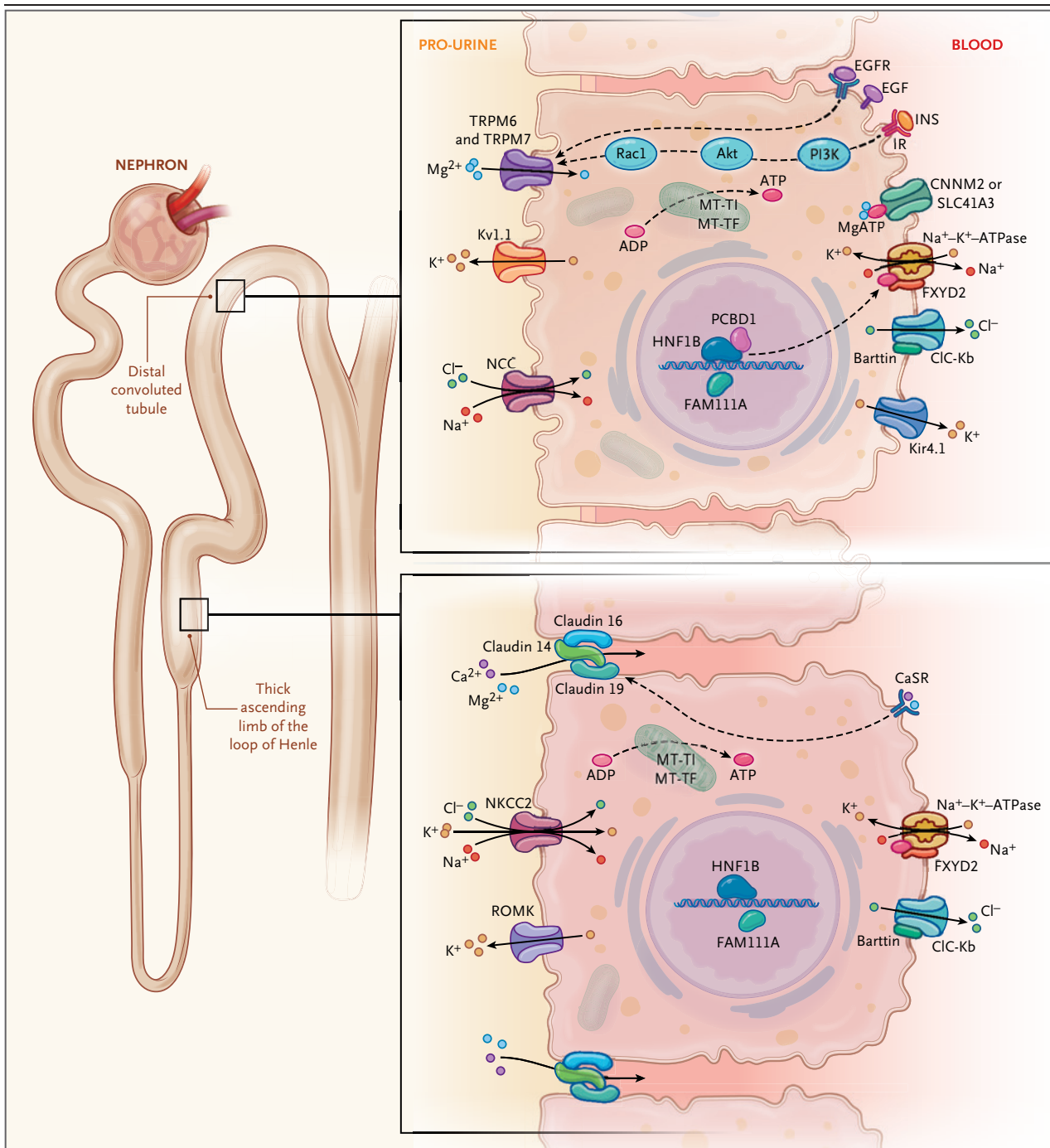


Figure 1. Magnesium and Cell Function.

Magnesium is an important cofactor for numerous enzymes. All ATPase reactions require Mg^{2+} -ATP, including those involved in RNA and DNA biologic functions. It opposes calcium actions and acts as a second messenger. Magnesium influences circadian-clock genes, which control circadian rhythm in biologic systems. ADP denotes adenosine diphosphate.



COORDINATED CONTROL OF MAGNESIUM BALANCE

The body contains approximately 25 g of magnesium, with the majority stored in bones and soft tissues (Fig. 3A). Magnesium is an intracellular ion and second only to potassium as the most abun-

dant intracellular cation.¹⁰ In cells, 90 to 95% of magnesium is bound to ligands (ATP, ADP, citrate, proteins, and nucleic acids). Only 1 to 5% of intracellular magnesium exists as free magnesium. The intracellular concentration of free magnesium is 1.2 to 2.9 mg per deciliter (0.5 to 1.2 mmol per liter), which is similar to the extracellular concen-

Figure 2 (facing page). Mechanisms of Magnesium Transport in the Kidney.

In the proximal tubule, Mg^{2+} reabsorption is dependent on paracellular permeability by claudins 2 and 12. In the thick ascending limb of the loop of Henle, the claudin 16–claudin 19 complex provides a cation-selective pore for paracellular Mg^{2+} reabsorption. The paracellular Mg^{2+} reabsorption in this segment is regulated by the calcium-sensing receptor, parathyroid hormone, and mechanistic target of rapamycin. Fine-tuning of Mg^{2+} reabsorption occurs in the distal convoluted tubule and involves transient receptor potential cation channel subfamily M members 6 and 7 (TRPM6 and TRPM7) divalent cation channels. Epidermal growth factor (EGF) and insulin (INS) could activate their receptors (EGFR and IR, respectively) to stimulate TRPM6 and TRPM7 activity. Basolateral Mg^{2+} extrusion is linked to the Na^+ gradient, with Cyclin M2 and solute carrier family 41 member 3 (SLC41A3) being major candidates as Na^+ – Mg^{2+} exchangers. Alterations in basolateral Na^+ – K^+ transport lead indirectly to impaired renal Mg^{2+} reabsorption in the distal convoluted tubule. Barttin denotes beta-subunit for chloride voltage-gated channel Kb, CaSR calcium-sensing receptor, ClC-Kb chloride voltage-gated channel Kb, CNNM2 cyclin and CBS domain divalent metal cation transport mediator 2, FAM111A FAM111 trypsinlike peptidase A, FXYD2 FXYD domain containing ion transport regulator 2, HNF1B hepatocyte nuclear factor 1 beta, Kir4.1 inward-rectifying potassium channel 4.1, Kv1.1 potassium voltage-gated channel subfamily A member 1, MT-TF mitochondrially encoded tRNA phenylalanine, MT-TI mitochondrially encoded tRNA isoleucine, NCC Na^+ – Cl^- cotransporter, NKCC2 Na^+ – K^+ – Cl^- cotransporter 2, PCBD1 pterin-4 alpha-carbinolamine dehydratase 1, PI3K phosphatidylinositol 3-kinase, and ROMK renal outer medullary potassium.

tration. In plasma, 30% of the circulating magnesium is bound to proteins, mostly through free fatty acids.²⁸ Therefore, patients with chronically high levels of free fatty acids generally have a lower blood magnesium concentration, and plasma magnesium levels are inversely proportional to the risk of cardiovascular and metabolic diseases.²⁸ Changes in free fatty acids and levels of EGF, insulin, and aldosterone may contribute to variability in blood magnesium levels.¹⁰ At a systems level, magnesium is regulated primarily by three organs: the intestine, where dietary magnesium absorption is regulated; the bone, which stores magnesium as hydroxylapatite; and the kidney, which regulates urinary magnesium excretion.¹⁰ These systems are integrated and highly coordinated and constitute the intestine–bone–kidney axis responsible for magnesium uptake, exchange, and excretion, respectively. Disturbances in this balance have pathophysiological consequences.

THE INTESTINE–BONE–KIDNEY AXIS AND MAGNESIUM HOMEOSTASIS

Dietary sources rich in magnesium include cereals, beans, nuts, and green vegetables (magnesium is the central core of chlorophyll). Of the total dietary magnesium consumed, 30 to 40% is absorbed in the intestine.¹⁰ Most absorption occurs in the small intestine through paracellular transport (passage of molecules between cells), which is a passive process and involves tight junctions (complexes that form the intercellular barrier between cells).²⁹ Fine-tuning of magnesium absorption occurs in the large intestine by transcellular mechanisms involving TRPM6 and TRPM7.^{21,30,31} Genetic inactivation of intestinal TRPM7 causes severe deficiency in magnesium, zinc, and calcium and is incompatible with early postnatal growth and survival.^{26,31} Intestinal magnesium absorption is influenced by factors such as dietary magnesium, intestinal lumen pH, hormones (estrogen, insulin, EGF, FGF23, and parathyroid hormone [PTH]), and gut microbiota.^{26,31–34}

In the kidney, magnesium reabsorption by the nephron is facilitated by paracellular and transcellular pathways.³³ Unlike most ions (e.g., sodium and calcium), only a small amount (20%) of magnesium is reabsorbed in the proximal tubule, whereas most magnesium (70%) is taken up by the thick ascending limb of the loop of Henle.¹⁰ In the proximal tubule and the thick ascending limb of the loop of Henle, magnesium reabsorption is paracellular, mainly driven by concentration gradients and membrane potential. Claudins 16 and 19 form the magnesium pores in the thick ascending limb of the loop of Henle, whereas claudin 10b contributes to the lumen-positive transepithelial voltage that drives paracellular transport.²⁹ Along the distal convoluted tubule, fine-tuning of transcellular reabsorption of magnesium (5 to 10%) is mediated through apical TRPM6 and TRPM7, which determines the final urinary magnesium excretion.^{33,35}

Magnesium is a key component of bone — 60% of the total magnesium in the body is stored in this compartment. Exchangeable magnesium in bone provides a dynamic reservoir to maintain physiologic plasma concentrations.¹⁰ It also contributes to the biologic process of bone formation by influencing activation of osteoblasts and osteoclasts.³⁶ High magnesium intake results in increased bone mineral content, which is important

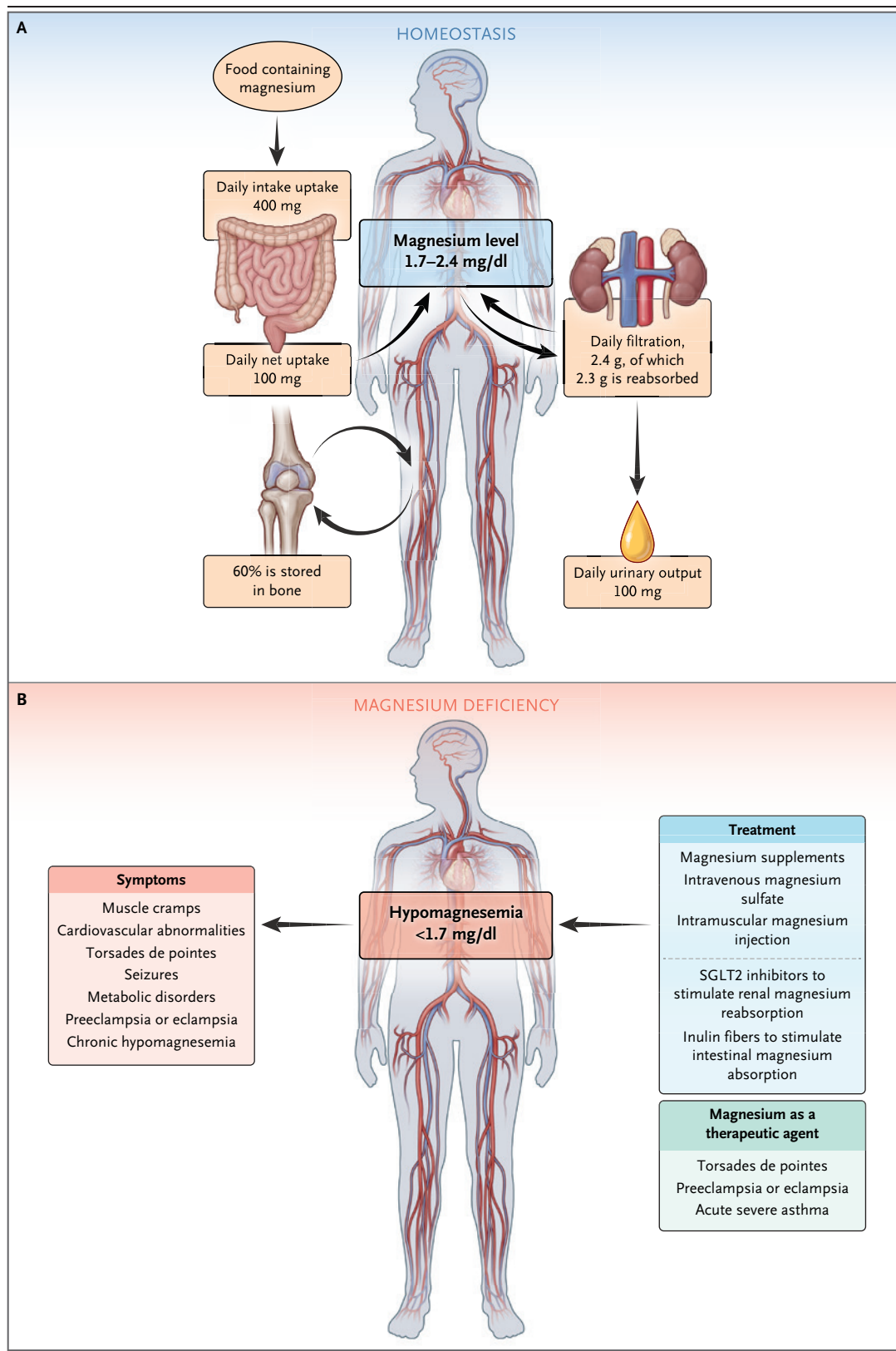


Figure 3 (facing page). Magnesium Homeostasis and Signs and Symptoms of Hypomagnesemia and Therapeutic Approaches.

Panel A shows that the total body content of magnesium is tightly regulated and involves multiple systems, especially the kidneys, gastrointestinal system, and bone. The diagram indicates the daily amount of magnesium intake and excretion. Each day, the intestines absorb approximately 120 mg and secrete 20 mg of magnesium, resulting in a net absorption of 100 mg. In the kidney each day, approximately 2400 mg of magnesium is filtered by the glomerulus, of which 2300 mg is reabsorbed along the kidney tubule, leading to a net excretion of 100 mg. Bone and muscle are major depots for magnesium storage. Panel B shows the causes and consequences of hypomagnesemia. It may result from inadequate dietary intake, increased gastrointestinal loss, reduced renal reabsorption, or redistribution of magnesium from the extracellular to the intracellular space. Severe hypomagnesemia is associated with neuromuscular irritability, cardiovascular abnormalities, and metabolic disorders. Magnesium sulfate is the agent of choice in preeclampsia or eclampsia, acute asthma, and torsades de pointes. Inulin and sodium–glucose cotransporter type 2 (SGLT2) inhibitors increase magnesium reabsorption.

in reducing the risk of bone fractures and osteoporosis during aging.³⁷ Magnesium has a biphasic effect in bone repair. During acute phases of inflammation, magnesium promotes increased expression of TRPM7 in macrophages, magnesium-dependent cytokine production, and a pro-osteogenic immune microenvironment.³⁸ In the later remodeling phases of bone healing, magnesium influences osteogenesis and suppresses hydroxyapatite precipitation. TRPM7 and magnesium are also involved in vascular calcification by influencing phenotypic switching of vascular smooth-muscle cells to an osteogenic phenotype.³⁹

HYPOMAGNESEMIA

The normal serum magnesium concentration in adults is 1.7 to 2.4 mg per deciliter (0.7 to 1.0 mmol per liter). Hypomagnesemia is defined as serum magnesium levels below 1.7 mg per deciliter.^{10,40} Most patients with borderline hypomagnesemia are asymptomatic.^{41,42} Because patients can present with chronic latent magnesium deficit at serum magnesium levels above 1.5 mg per deciliter (0.6 mmol per liter), it has been suggested to raise the low cutoff point that

defines hypomagnesemia.⁴¹ However, this level is controversial and awaits further clinical validation.⁴² Hypomagnesemia is present in 3 to 10% of the general population, but its prevalence is increased among persons with type 2 diabetes (10 to 30%) and hospitalized patients (10 to 60%), especially those in the intensive care unit (ICU) (>65%).⁴³ Data from several cohorts indicate that hypomagnesemia is associated with an elevated risk of death from any cause and death from cardiovascular causes.^{43,44}

THE CLINICAL SPECTRUM OF HYPOMAGNESEMIA

Hypomagnesemia may result from inadequate dietary intake, increased gastrointestinal loss, reduced renal reabsorption, or redistribution of magnesium from the extracellular to the intracellular space. Patients with hypomagnesemia often present with nonspecific symptoms, such as lethargy, muscle cramps, or muscle weakness (Fig. 3B).⁴² Hypomagnesemia is usually associated with other electrolyte derangements, including hypocalcemia, hypokalemia, and metabolic alkalosis. Consequently, the presence of hypomagnesemia may be overlooked, especially because the serum magnesium level is not routinely measured in most clinical settings. Only in severe cases of hypomagnesemia (serum magnesium level, <1.2 mg per deciliter [0.5 mmol per liter]) do symptoms such as neuromuscular irritability (carpopedal spasm, seizures, and tremors), cardiovascular abnormalities (arrhythmias and vasoconstriction), and metabolic disorders (insulin resistance and chondrocalcinosis) become evident.⁴⁵ The clinical importance of magnesium is highlighted by findings that low serum magnesium levels are associated with an increased incidence of hospitalization and increased mortality, especially when associated with concurrent hypokalemia.⁴⁶

Of clinical relevance, less than 1% of the magnesium in the body is in plasma, and hence plasma magnesium is not a reliable marker of the total content in tissues.⁴⁷ Controlled depletion–repletion studies in metabolic units have shown that even though serum magnesium concentration may be normal, intracellular stores can be depleted.⁴⁷ Therefore, the use of blood magnesium levels alone, without consideration

of dietary magnesium intake and urinary loss, probably underestimates magnesium deficiency in the clinic.⁴⁸

HYPOCALCEMIA, HYPOKALEMIA, AND HYPOMAGNESEMIA

Hypokalemia is common in patients with hypomagnesemia.⁴⁹ Refractory potassium repletion is often linked to magnesium depletion and is corrected only after the magnesium deficit has been normalized.⁵⁰ Magnesium deficiency amplifies renal potassium loss by promoting potassium secretion in the collecting duct. Decreased intracellular magnesium levels inhibit $\text{Na}^+\text{--K}^+\text{--ATPase}$ pump activity⁵¹ and increase the opening of renal outer medullary potassium (ROMK) channels,^{50,52} leading to renal potassium loss. The interplay between magnesium and potassium also involves activation of the $\text{Na}^+\text{--Cl}^-$ cotransporter (NCC), which promotes sodium reabsorption.^{52,53} Magnesium deficiency decreases the abundance of NCC through an E3 ubiquitin protein ligase called neuronal precursor cell developmentally down-regulated 4-2 (NEDD4-2) and prevents NCC activation by hypokalemia.⁵⁴ Sustained NCC down-regulation enhances distal Na^+ delivery during states of hypomagnesemia, promoting kaliuresis and hypokalemia.

Hypocalcemia is also frequently linked to hypomagnesemia.^{18,33} Magnesium deficiency suppresses the release of PTH and decreases renal sensitivity to PTH.⁵⁵ The decreased PTH level leads to reduced renal reabsorption of calcium, calciuria, and secondary hypocalcemia. Hypocalcemia resulting from hypomagnesemia-induced hypoparathyroidism is refractory to correction until the magnesium concentration is normalized.⁵⁵

DRUG-INDUCED HYPOMAGNESEMIA

Many drug classes, such as antibiotics, diuretics, biologic agents, immunosuppressants, proton-pump inhibitors (PPIs), and chemotherapies, may cause magnesium wasting and hypomagnesemia (Fig. 4).⁵⁶ Long-term use of PPIs causes magnesium deficiency in approximately 20% of patients receiving them, and these effects are dose-dependent.^{57,58} PPIs reduce intestinal magnesium uptake and are associated with changes in luminal pH

and the gut microbiome.⁵⁸ The reasons why only some patients are prone to PPI-induced hypomagnesemia may relate to the dose and duration of PPI therapy, dietary magnesium intake, cotreatment with other magnesium-losing drugs, and gut microbiome flora. Oral inulin has been reported to improve serum magnesium levels in patients with PPI-induced hypomagnesemia, through increased gastrointestinal absorption.⁵⁹

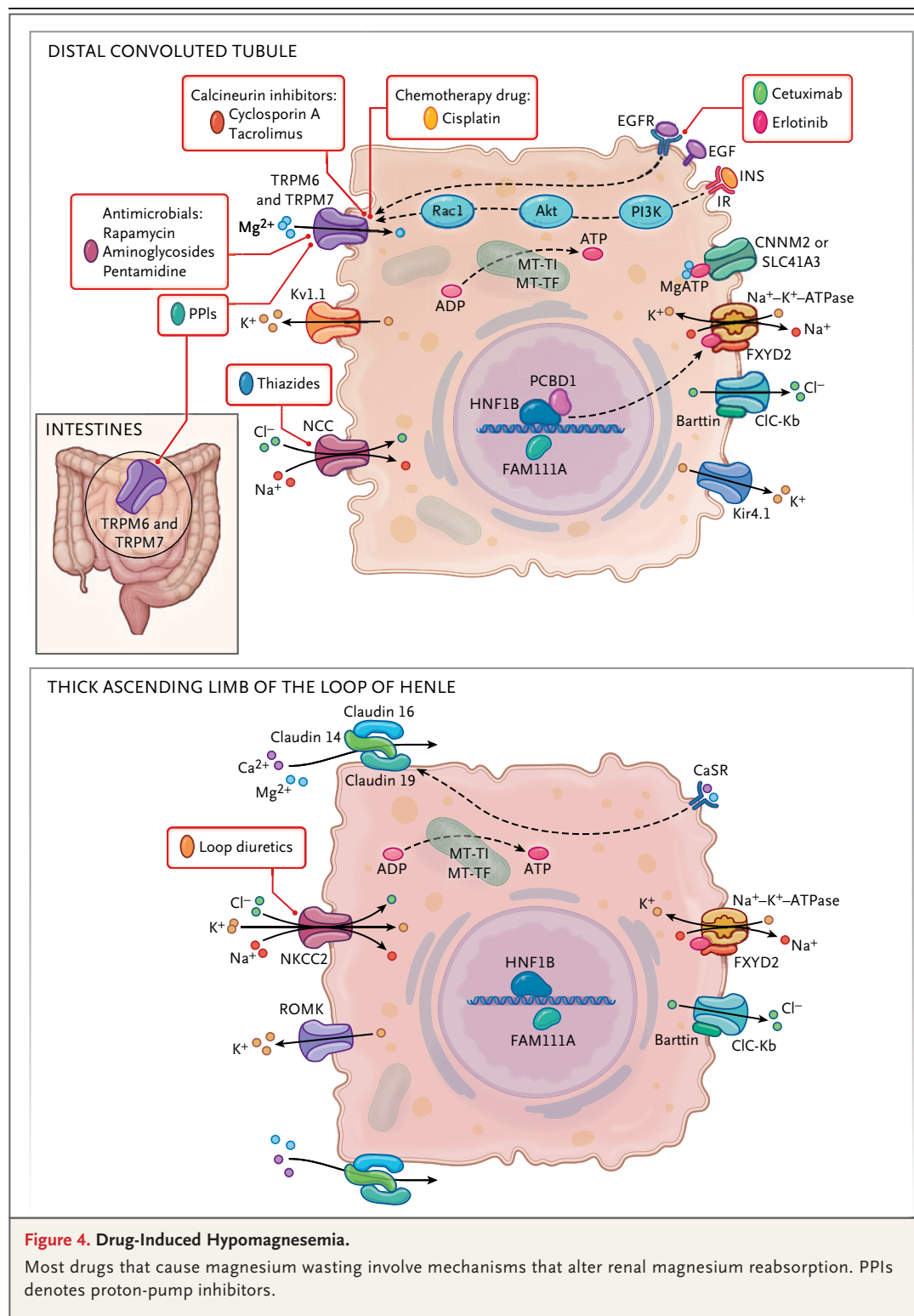
Most cases of drug-induced hypomagnesemia are explained by renal magnesium wasting. Calcineurin inhibitors, cisplatin, EGF receptor (EGFR) antagonists (e.g., cetuximab and erlotinib), and mammalian target of rapamycin inhibitors cause hypomagnesemia in 20 to 40% of patients receiving them, primarily through reduced TRPM6 and TRPM7 activity in the distal convoluted tubule.^{59,60}

NONDRUG CAUSES OF HYPOMAGNESEMIA

Hypomagnesemia is the most common electrolyte abnormality associated with chronic alcohol use disorder.⁶¹ Underlying mechanisms include decreased magnesium intake in malnourished persons, increased gastrointestinal loss, and magnesuria due to alcohol-induced renal tubular damage.⁶¹ The presence of hypomagnesemia in persons with alcohol use disorder is often associated with liver dysfunction and worse prognosis of their liver disease.

Hypomagnesemia is commonly observed in patients with type 2 diabetes mellitus.^{44,62} Renal magnesium wasting and increased albumin binding in the blood are probably the causes of hypomagnesemia. Insulin activates TRPM6 activity in the distal convoluted tubule.^{34,62} Consequently, insulin resistance results in decreased renal magnesium reabsorption and increased magnesuria.

Aberrant magnesium homeostasis is also associated with cardiovascular disease.^{44,63} In the heart, hypomagnesemia confers a predisposition to electrical irritability and arrhythmias, including atrial fibrillation, torsades de pointes, and long QT syndrome.¹⁰ In the vascular system, low magnesium levels are associated with endothelial dysfunction, vascular contraction, increased vascular tone, and vascular fibrosis — characteristic features of hypertension.^{63,64} These vascular



effects involve alterations in TRPM7 activity and impaired magnesium influx in vascular cells and are especially evident in hyperaldosteronism.⁶⁵

Preeclampsia and eclampsia are hypertensive diseases of pregnancy that are characterized by abnormal trophoblast invasion, endothelial dysfunction, and vascular inflammation. Serum magnesium levels may be normal or decreased in both conditions.⁶⁶ Although the causes of preeclampsia and eclampsia are unknown, intravenous magnesium treatment is beneficial and prevents or lessens complications. The protective effects of magnesium have been attributed to calcium-channel blockade and vasodilation.⁶⁷ However other factors have been implicated, including decreased levels of fms-like tyrosine kinase 1 and endoglin, reduced oxidative stress, inhibition of brain NMDA receptors, decreased production of proinflammatory mediators, and down-regulation of TRPM6 and TRPM7.⁶⁷

Autoantibodies against claudin 16 have been identified as a novel cause of hypomagnesemia, hypocalcemia, and tubulointerstitial nephropathy.⁶⁸ This finding suggests that autoimmunity could be a novel cause of hypomagnesemia.

HEREDITARY HYPOMAGNESEMIA

Identification of pathogenic variants in genes that encode for magnesium transport pathways and their regulators have led to a putative genetic cause of familial hypomagnesemia in approximately 80% of patients (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Most genetically based causes of hypomagnesemia affect magnesium reabsorption in the distal convoluted tubule.^{10,33} Mutations in *TRPM6* and *TRPM7* subunits lead to HSH.^{18,69} Hypocalcemia in such patients is explained by hypoparathyroidism, caused by low intracellular magnesium levels in the parathyroid gland, which impair PTH secretion.^{18,33} Pathogenic variants in *EGF* and *EGFR* result in hypomagnesemia and renal magnesium wasting, because of reduced TRPM6 activity.^{10,60} Pathogenic variants in *CNNM2* cause hypomagnesemia, seizures, and cognitive deficiency.⁷⁰ *CNNM2* is expressed in the distal convoluted tubule and regulates basolateral magnesium extrusion, although the molecular mechanism is unclear.^{17,33,70}

Gitelman's syndrome is primarily a sodium-wasting disorder caused by mutations in the

NCC.^{33,54,71} However, patients with Gitelman's syndrome present with hypomagnesemia, hypokalemia, and metabolic alkalosis. The cause of hypomagnesemia in this syndrome is elusive, but preclinical data indicate that atrophy of the distal convoluted tubule, which occurs when NCC is defective, may explain reduced magnesium reabsorption.^{54,71}

Pathogenic variants in the mitochondrial transfer RNAs for isoleucine and phenylalanine (*MT^{TI}* and *MT^{TF}*) are associated with a Gitelman's syndrome-like phenotype with hypomagnesemia.^{33,72} These mutations are associated with decreased activity of mitochondrial electron transport chain complex 4. Consequently, impaired cellular ATP production may reduce basolateral Na⁺-K⁺-ATPase activity and inhibit the NCC.

NCC activity is regulated by phosphorylation of its intracellular N-terminal domain. A mechanism called the potassium switch may explain how low extracellular potassium results in hyperpolarization of the basolateral membrane and activation of NCC.^{3,33} Mutations in potassium-switch genes encoding the basolateral potassium channel (*KCNJ10* and *KCNJ16*), chloride channel (*CLCNKB* and *BSND*), and the Na⁺-K⁺-ATPase complex (*ATP1A1* and *FXD2*) lead to a phenotype similar to Gitelman's syndrome, including hypomagnesemia.^{33,73,74} Patients with mutant *HNF1B* are prone to renal malformations, kidney cysts, and maturity-onset diabetes of the young (*MODY5*).⁷⁴

Mutations in *CLDN16* and *CLDN19*, which encode tight-junction proteins claudin 16 and claudin 19, result in familial hypomagnesemia, hypercalciuria, and nephrocalcinosis.^{29,75,76} Claudins 16 and 19 form a cation-selective pore that allows the paracellular reabsorption of calcium and magnesium in the thick ascending limb of the loop of Henle.^{10,29} Clinically, patients carrying pathogenic variants in *CLDN19* are distinguished from those with variants in *CLDN16* by the presence of ocular defects.⁷⁵ The main regulators of paracellular divalent cation transport in the thick ascending limb of the loop of Henle are PTH and calcium-sensing receptor. Pathogenic variants in RAS-related GTP binding D (*RRAGD*) have been identified as a cause of a kidney tubulopathy phenotype reminiscent of the familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) phenotype combined with dilated cardiomyopathy.⁷⁷

EVALUATING HYPOMAGNESEMIA IN THE CLINIC

Measurement of total serum magnesium is the standard approach to determine magnesium status in the clinic. It provides a rapid evaluation of short-term changes in magnesium status but may underestimate the total body content of magnesium.^{42,47,48} Endogenous factors (hypoalbuminemia) and exogenous factors (hemolyzed specimens and sample-tube anticoagulants [e.g., EDTA]) can influence magnesium measurements and need to be considered when blood results are interpreted. Serum ionized magnesium can also be measured, but the clinical usefulness is unclear.

When hypomagnesemia is diagnosed, the cause is usually apparent from the patient's history. However, if there is no clear underlying cause, it is important to distinguish between renal and gastrointestinal magnesium losses with the use of specific diagnostic approaches, such as 24-hour magnesium excretion, fractional excretion of magnesium, and the magnesium-loading test.^{42,47,48}

MAGNESIUM REPLACEMENT

The feasibility of magnesium replacement is the basis for managing hypomagnesemia. Yet, there are no clear treatment guidelines for hypomagnesemia; thus, approaches depend largely on the presence and severity of clinical manifestations. Mild hypomagnesemia is managed with oral supplements. Many magnesium preparations are available, and they have variable absorption rates. The most effectively absorbed forms are organic salts (magnesium citrate, aspartate, glycinate, gluconate, and lactate) rather than inorganic salts (magnesium chloride, carbonate, and oxide).⁷⁸ However, a common side effect of oral magnesium supplementation is diarrhea, which poses a challenge for oral replacement.

In resistant cases, adjuvant drug therapies may be necessary. Pharmacologic inhibition of the epithelial sodium channel with amiloride or triamterene in patients with normal renal function increases serum magnesium levels.^{10,42} Other potential strategies include inhibitors of sodium-glucose cotransporter type 2,⁷⁹ which increase serum magnesium levels, especially in patients with diabetes. Mechanisms that underlie these effects are unclear, but decreased glomerular filtration and increased renal tubular reabsorption

may be important. Parenteral therapy is indicated in patients whose hypomagnesemia is refractory to oral treatment, such as those with short-bowel syndrome, those with tetany or seizures, and those whose condition is hemodynamically unstable with arrhythmias or associated hypokalemia and hypocalcemia.⁴² PPI-induced hypomagnesemia responds favorably to oral inulin through mechanisms that might involve alterations in gut microbiota.^{58,59}

MAGNESIUM AS A THERAPEUTIC AGENT

Despite the many conditions in which magnesium has been implicated, there are only a few medical conditions in which magnesium is the therapeutic agent of choice. These include torsades de pointes, acute asthma exacerbations, and preeclampsia or eclampsia (clinical vignettes are provided in the Supplementary Appendix). Patients with torsades de pointes that is refractory to beta-blockers should be treated with magnesium. In severe asthma exacerbations with an inadequate response to intensive initial treatment and in patients with life-threatening asthma, clinical guidelines recommend intravenous magnesium sulfate.⁴² Nebulized magnesium sulfate when added to inhaled β_2 -agonists and ipratropium bromide may have additional benefit for lung function and may decrease or shorten hospital admissions. Beneficial effects of magnesium in asthma probably involve calcium-channel blockade in bronchial smooth muscle, resulting in bronchodilation.⁸⁰

According to international clinical guidelines on the treatment of hypertension in pregnancy, women with eclampsia should receive magnesium sulfate to prevent seizures.⁸¹ Women with preeclampsia who have proteinuria and severe hypertension or hypertension with neurologic signs and symptoms should be treated with magnesium sulfate to prevent eclampsia.⁸¹ Although these disorders are responsive to magnesium sulfate, the exact mechanisms whereby magnesium mediates clinical benefit are unclear.

CONCLUSIONS

Magnesium is a vital but often poorly understood electrolyte in clinical medicine. It is often not measured as part of routine electrolyte screening. Hy-

pomagnesemia is often asymptomatic. Although the exact mechanisms that regulate body magnesium homeostasis are still poorly defined, there have been advances in the understanding of renal magnesium handling. This understanding is attributable largely to gene screening panels and whole-exome sequencing that have identified new genes causing rare forms of inherited hypomagnesemia. Many drugs cause hypomagnesemia. Hypomagnesemia is common in hospitalized patients

and is a risk factor for a prolonged ICU stay. Hypomagnesemia should be corrected with magnesium replacement therapy in the form of the organic salt preparation. Although there is still much to be learned about magnesium and its regulation in health and disease, the field has advanced, and clinicians should be more attuned to the importance of magnesium in clinical medicine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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