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Clinical Consequences and Management of Hypomagnesemia

Kevin J. Martin,* Esther A. González,* and Eduardo Slatopolsky†

*Division of Nephrology, Saint Louis University, and †Renal Division, Washington University, St. Louis, Missouri

ABSTRACT

Magnesium deficiency and hypomagnesemia remain quite prevalent, particularly in patients in intensive care units, and may have important clinical consequences. Magnesium should be measured directly in clinical circumstances in which a risk for magnesium deficiency exists and appropriately corrected when found. This commentary reviews the current knowledge of magnesium homeostasis and the risk factors and clinical consequences of magnesium deficiency and outlines approaches to therapy.

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Magnesium (Mg^{2+}) is the second most abundant intracellular cation after potassium and the fourth most abundant cation of the body after calcium, potassium, and sodium. Mg^{2+} is involved in hundreds of enzymatic reactions and is essential for life. Mg^{2+} is an important co-factor for many biologic processes, most of which use ATP. Mg^{2+} is an essential mineral that is important for bone mineralization, muscular relaxation, neurotransmission, and other cell functions.[1] Extracellular Mg^{2+} concentration is tightly regulated by the extent of intestinal absorption and renal excretion. Like calcium (Ca^{2+}), Mg^{2+} plays a role in the regulation of parathyroid hormone (PTH) secretion. Hypermagnesemia suppresses the release of PTH. Acute hypomagnesaemia has the opposite effect; however, profound Mg^{2+} depletion decreases the release of PTH and induces skeletal resistance to PTH and severe hypocalcemia.[2] Consequently, profound Mg^{2+} deficiency causes tetany, cardiac arrhythmia, and bone instability and encourages renal stone formation. Mg^{2+} deficiency has also been reported in 20 to 60% of patients in intensive care units (ICU).[3–5] These patients have higher mortality and more prolonged hospitalization compared with those who are not Mg^{2+} deficient.[6,7]

BODY STORES OF MG^{2+}

The total body Mg^{2+} concentration is approximately 2000 mEq, or 25 g. Only a small fraction (approximately 1%) of the body Mg^{2+} is present in the extracellular fluid compartment, and approximately 60 to 65% of the total body Mg^{2+} is found in bone. Most of the Mg^{2+} in bone is associated with apatite crystals. A significant amount of the Mg^{2+} in bone is present as a surface-limiting ion on bone crystals and is freely exchangeable. Approximately 20% of the total body Mg^{2+} is localized in the muscle. The remaining 20% is found in other tissues of the body. The concentration of Mg^{2+} in blood is maintained with narrow limits, ranging from 1.5 to 1.9 mEq/L; however, because serum contains only 0.3% of the total body Mg^{2+}, it is a poor reflection of total body Mg^{2+} content. Approximately 80% of the serum Mg^{2+} is ultrafiltrable, and the rest is bound to protein. Most of the ultrafiltrable Mg^{2+} is present in the ionized form. Red cell Mg^{2+} concentration is approximately 5 mEq/L.

MG^{2+} BALANCE

Approximately 300 mg, or 25 mEq, of Mg^{2+} (1 mEq = 12 mg) is ingested daily in the diet. Of the total amount of Mg^{2+} ingested in the diet, approximately one third is eliminated in the urine and the remainder in feces. A small amount of Mg^{2+}, on the order of 15 to 30 mg/d, is secreted in the gastrointestinal tract.

Mg^{2+} homeostasis involves the kidney, small bowel, and bone. In the gastrointestinal tract, Mg^{2+} absorption occurs primarily in the jejunum and ileum by both a passive paracellular mechanism and an active transport process[8,9]; however, most evidence suggests that Mg^{2+} is absorbed mainly by ionic diffusion and "solvent drag" resulting from the bulk flow of water. At low intraluminal concentrations, Mg^{2+} is absorbed primarily through the active cellular route and, with increasing concentrations, through the paracellular pathway. Although there is some evidence to suggest that vitamin D may influence the absorption of Mg^{2+}, this role seems to be less important for Mg^{2+} than for the ab-

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Correspondence: Dr. Eduardo Slatopolsky, Washington University School of Medicine, Renal Division, 660 S. Euclid, Box 8126, St. Louis, MO 63110. Phone: 314-362-7208; Fax: 314-362-7875; E-mail: eslatopo@im.wustl.edu

sorption of calcium. The sigmoid colon has the capability of absorbing Mg^{2+}, and there are several reports in the literature of patients who developed Mg^{2+} toxicity after receiving enemas containing Mg^{2+}; however, most of those patients had renal insufficiency.

The kidney plays a crucial role in the maintenance of Mg^{2+} balance, and approximately 2 g of Mg^{2+} is filtered daily by the human kidney and approximately 100 mg appears in the urine. Thus, approximately 95% of the filtered Mg^{2+} is reabsorbed and 5% is excreted in the urine. At the glomerular membrane, Mg^{2+} is filtered at the rate of 80% of the total Mg^{2+} present in the serum. Microperfusion studies by Quamme and Dirks[10] revealed that the proximal tubule is relatively impermeable to Mg^{2+}. In the adult, the absorption of Mg^{2+} in this segment is approximately 10 to 15% of the filtered Mg^{2+}, considerably less than the reabsorption of sodium and Ca. The majority of Mg^{2+} is reabsorbed in the thick ascending limb of the Henle's loop through paracellular pathways. Approximately 70% of all filtered Mg^{2+} is reabsorbed in the thick ascending limb. The driving force for Mg^{2+} reabsorption in this segment of the nephron is the positive transluminal epithelial voltage generated by potassium recycling across the apical membrane.[11]

A member of the claudin family of tight junction proteins, paracellin-1, was detected in the thick ascending limb and in the distal tubule. Paracellin-1 is a highly negative charged protein. This negative charge contributes to the cationic selectivity of the reabsorptive paracellular pathway for Ca^{2+} and Mg^{2+}. Mutations in the paracellin-1 gene induces Mg^{2+} wasting, hypercalciuria, nephrocalcinosis, and renal failure.[12,13]

Recently, mouse studies by Hou *et al.*[14] suggested a reduction in paracellin-1 leads to magnesuria, hypercalciuria, loss of bone mass, and subsequent nephrocalcinosis. PTH stimulates Ca^{2+} and Mg^{2+} reabsorption within the thick ascending limb and distal tubule. The calcium-sensing receptor in the loop of Henle and distal tubule provide a negative feedback mechanism to mitigate overexuberant responses to PTH.

The distal convoluted tubule does the fine-tuning regulation of Mg^{2+} excretion. Mg^{2+} transport within the distal convoluted tubule is transcellular and secondary to an active process.[15] Mg^{2+} enters the cell through selective channels across the apical membrane. This process is driven by a transmembrane negative potential, and it seems that the Ca^{2+}/Mg^{2+} TRPM6 channel plays a major role.[16] There is little evidence for significant reabsorption of Mg^{2+} beyond the distal tubule. Recent work by Groenestege *et al.*[17] demonstrated that EGF stimulated the TRPM6 channel with a consequent increase in Mg^{2+} reabsorption. Mutations in the pro-EGF gene affects basolateral sorting and secretion of EGF with consequent decreases in the activity of TRPM6 and the development of magnesuria. The same investigators demonstrated that cetuximab, a mAb used in patients with carcinoma of the colon, inhibited EGF and blocked *in vitro* EGF-dependent stimulation of TRPM6 channel activity, causing hypomagnesemia and renal Mg^{2+} wasting in patients.

ETIOLOGY OF HYPOMAGNESEMIA

Because serum Mg^{2+} concentration is not often measured in routine blood tests, it needs to be measured directly in clinical situations that are likely to be associated with disturbed Mg^{2+} homeostasis, such as chronic diarrhea, hypokalemia, cardiac arrhythmias, and hypocalcemia (Table 1). Hypomagnesemia has been noted in up to 12% of hospitalized patients, and the incidence may rise above 60% in patients in ICU.[18,19] Mg^{2+} deficiency produces in a variety of clinical manifestations, including positive Chvostek's and Trousseau's sign, seizures, muscle cramps, vertigo, nystagmus, and psychiatric manifestations. In addition, cardiac arrhythmias such as supraventricular tachycardia and torsade de pointes may occur. In addition, Mg^{2+} deficiency may be associated with hypokalemia and hypocalcemia.

Table 1. Clinical consequences of hypomagnesemia

Electrolyte abnormalities
hypokalemia
hypocalcemia
Neuromuscular
carpopedal spasm
tetany
muscle cramps
muscle fasciculations
Neurologic
vertigo
nystagmus
aphasia
hemiparesis
depression
delirium
choreoathetosis
Cardiovascular
ventricular arrhythmias
torsade de points
supraventricular tachycardia
enhanced sensitivity to digoxin

In general, Mg^{2+} deficiency is the result of either gastrointestinal or renal Mg^{2+} losses (Table 2). If no cause is readily apparent, then one can distinguish between gastrointestinal and renal losses by measuring the 24-h urinary Mg^{2+} excretion or fractional excretion of Mg^{2+}. The normal response of the kidney to Mg^{2+} depletion is to reduce Mg^{2+} excretion to low levels. The measurement of 24-h urinary Mg^{2+} excretion of >30 mg in a person with normal renal function and hypomagnesemia indicates renal Mg^{2+} wasting. If Mg^{2+} deficiency is suspected in the absence of hypomagnesemia, then one might consider evaluating the renal excretion of Mg^{2+} in response to an intravenous Mg^{2+} load.[20,21] This, however, is rarely done in clinical practice. In the presence of unexplained hypocalcemia or hypokalemia, a trial of Mg^{2+} administration is more commonly performed.

Common gastrointestinal causes of Mg^{2+} deficiency include any chronic diarrheal illness, intestinal malabsorption, and steatorrhea or as a consequence of intestinal bypass surgery. Rare gastrointestinal causes include either X-linked

Table 2. Causes of magnesium deficiency[a]

Gastrointestinal
malnutrition
malabsorption
chronic diarrhea
primary infantile hypomagnesemia
nasogastric suction
intestinal fistula
Renal
congenital magnesium wasting
Bartter syndrome
Gitelman syndrome
postobstructive diuresis
diuretic phase of ATN
loop and thiazide diuretics
cisplatin
aminoglycosides
pentamidine
foscarnet
cyclosporin A
tacrolimus
Endocrine
hyperparathyroidism
hyperthyroidism
SIADH
hyperaldosteronism
Redistribution
hungry bone syndrome
acute pancreatitis
blood transfusions
insulin treatment
Miscellaneous
diabetes
chronic alcoholism

[a]SIADH, syndrome of inappropriate antidiuretic hormone secretion.

recessive or autosomal recessive decreases in intestinal Mg^{2+} absorption, which seem to be associated with mutations in the TRPM6 gene. Acute pancreatitis can also be associated with hypomagnesemia, similar to the observations of the association between pancreatitis and hypocalcemia.[22] Renal causes of hypomagnesemia are either a primary defect in the tubular reabsorption of Mg^{2+} or disorders in which tubular sodium reabsorption is impaired. Thus, both loop and thiazide diuretics can inhibit Mg^{2+} reabsorption, although this effect is usually mild in clinical practice.

Renal Mg^{2+} wasting is also found in alcoholic patients and seems to be due to alcohol-induced impairment of Mg^{2+} reabsorption.[23–25] This effect may augment other potential contributing factors in this clinical setting, including dietary deficiency, pancreatitis, or diarrhea. Several drugs have been associated with urinary Mg^{2+} wasting, including aminoglycosides, amphotericin B, cisplatin, cyclosporin A, and pentamidine.[26] Renal Mg^{2+} wasting has also been associated with Gitelman syndrome and in some cases of Bartter syndrome.[27,28] Renal Mg^{2+} wasting has also been noted as a result of antibody therapy targeting the EGF receptor.[17,29]

Gitelman syndrome is a form of Mg^{2+} wasting that is caused by a defect in the gene encoding the thiazide-sensitive sodium chloride transporter, whereas Bartter syndrome is a group of disorders caused by impaired function of the components of the transporter of sodium chloride in the loop of Henle. Hypocalciuria and hypokalemia are commonly seen. Other forms of renal Mg^{2+} wasting are associated with hypercalciuria, nephrolithiasis, and nephrocalcinosis. This last syndrome is due to mutations in the paracellin-1 gene, which encodes for a tight junction protein that facilitates the paracellular transport of Ca^{2+} and Mg^{2+} in the thick ascending limb. Additional inherited causes of Mg^{2+} wasting have been identified to be due to mutations in the gene encoding the γ subunit of Na,K-ATPase. Hypomagnesemia is also common in patients with diabetes and seems to be the result of renal Mg^{2+} wasting.

TREATMENT OF HYPOMAGNESEMIA

It is well accepted that in cases of severe ($<$1 mEq/L in the serum) and symptomatic hypomagnesemia with neuromuscular or neurologic manifestations or cardiac arrhythmias, Mg^{2+} repletion should be achieved by intravenous administration of 2 g of Mg^{2+} sulfate in 100 ml of D5W over 5 to 10 min and followed by a continuous infusion of 4 to 6 g/d for 3 to 5 d if renal function is relatively normal. It is important that the cause of the Mg^{2+} deficiency also be addressed to prevent future recurrences. Maintenance therapy may require oral administration of Mg^{2+} oxide (400 mg twice daily or three times daily) for as long as the risk factors for Mg^{2+} deficiency exist. Oral Mg^{2+} gluconate (500 mg twice daily or three times daily) can also be used. In addition, there are several slow-release Mg^{2+} preparations. As noted, is also important to address the underlying cause, and if diuretic therapy is being used, consideration should be given to the use of potassium-sparing diuretics such as amiloride, which can increase Mg^{2+} reabsorption in the cortical collecting duct. Amiloride can also be useful in Gitelman or Bartter syndrome, as well as renal Mg^{2+} wasting associated with cisplatin.

The treatment of patients who have mild hypomagnesemia and are asymptomatic is more problematic. In asymptomatic hospitalized patients with relatively mild reductions in serum Mg^{2+} (between 1.0 and 1.5 mEq/L)—as often occurs in patients in the ICU setting—the significance of hypomagnesemia is not clear, and it is often associated with other abnormalities such as hypoalbuminemia, hypophosphatemia, and hypokalemia. In such patients, aggressive treatment does not need to be undertaken, and the treatment should be considered in conjunction with the treatment of the associated electrolyte abnormalities and the general management of the patient with attention to his or her nutritional therapy. Measurements of ionized Mg^{2+} have not helped to define the importance of this issue. It is reasonable, however, to consider the provision of Mg^{2+} in enteral or parenteral feedings in this patient group as long as they are not eating a normal diet. Although Mg^{2+} deficiency is associated with worse outcomes in these patients, no controlled trials have assessed whether supplementation would improve clinical outcomes.

Another area in which there is considerable controversy relates to asymptomatic hypomagnesemia, which has been reported to occur in between 13 and 48% of patients with type 2 diabetes.[30–35] Although it has been suggested that Mg^{2+} deficiency contributes to the induction of diabetes and its associated complica-

tions by altering glucose transport and impairing insulin secretion, insulin receptor binding, and postreceptor signaling, it is more likely that hypomagnesemia is a consequence of diabetes and its complications or treatment.[36] Although it would seem reasonable to measure Mg^{2+} in patients with diabetes and try to correct hypomagnesemia if it is detected, clinical trials have not been consistent in demonstrating improved clinical outcomes. Issues of sugar control, duration and dosage of Mg^{2+}, and variations in study population complicate these trials.[30,37–39]

CONCLUSIONS

Mg^{2+} deficiency continues to be underrecognized and may lead to serious consequences. It should be routinely measured in critically ill patients and in those with conditions that are known to be associated with Mg^{2+} deficiency.

DISCLOSURES

None.

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