

# Clinical Consequences and Management of Hypomagnesemia

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## 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.<sup>1</sup> 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. Hypomagnesemia 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.<sup>2</sup> 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).<sup>3–5</sup> These patients have

higher mortality and more prolonged hospitalization compared with those who are not  $Mg^{2+}$  deficient.<sup>6,7</sup>

## 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 ion-

ized 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<sup>8,9</sup>; 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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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<sup>10</sup> 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.<sup>11</sup>

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.<sup>12,13</sup>

Recently, mouse studies by Hou *et al.*<sup>14</sup> 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 nega-

tive 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.<sup>15</sup>  $Mg^{2+}$  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.<sup>16</sup> There is little evidence for significant reabsorption of  $Mg^{2+}$  beyond the distal tubule. Recent work by Groenestege *et al.*<sup>17</sup> 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.<sup>18,19</sup>  $Mg^{2+}$  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,  $Mg^{2+}$

**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

deficiency may be associated with hypokalemia and hypocalcemia.

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.<sup>20,21</sup> 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<sup>a</sup>**

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

<sup>a</sup>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.<sup>22</sup> 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.<sup>23–25</sup> This effect may aug-

ment 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.<sup>26</sup> Renal  $Mg^{2+}$  wasting has also been associated with Gitelman syndrome and in some cases of Bartter syndrome.<sup>27,28</sup> Renal  $Mg^{2+}$  wasting has also been noted as a result of antibody therapy targeting the EGF receptor.<sup>17,29</sup>

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  $\gamma$  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.<sup>30–35</sup> 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.<sup>36</sup> 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.<sup>30,37–39</sup>

## CONCLUSIONS

$Mg^{2+}$  deficiency continues to be under-recognized 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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