DISTURBANCES OF MAGNESIUM METABOLISM: HYPOMAGNESEMIA

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SUMMARY – Hypomagnesemia is a relatively common entity occurring in up to 12% of hospitalized patients, however, the incidence may rise to as high as 60% to 65% in patients in intensive care setting in whom nutrition, diuretics, hypoalbuminemia and aminoglycosides may play important roles. Symptomatic magnesium depletion is often associated with multiple biochemical abnormalities such as hypokalemia, hypocalcemia, and alkalosis acidosis. As a result, it is often difficult to ascribe specific clinical manifestations solely to hypomagnesemia. The symptoms considered typical for magnesium depletion include generalized fatigue, tetany, positive Chvostek's and Trousseau's signs, and generalized convulsions. The route of magnesium repletion varies with the severity of clinical manifestations.

Key words: *Magnesium deficiency, diagnosis; Magnesium deficiency, therapy; Electrolyte, metabolism*

Magnesium is the fourth most abundant cation in the body and within the cell it is the second most abundant cation after potassium. Magnesium plays an essential role (Table 1), and this role is achieved through its ability to form chelates with important intracellular anionic ligands, especially ATP, and its ability to compete with calcium for binding sites, proteins and membranes[1]. Over 300 enzyme reactions are dependent on magnesium. Magnesium affects myocardial contractility and electrical activity of the myocardial cells, and the specialized conducting system of the heart by its ability to influence the movement of ions such as sodium, potassium and calcium across the sarcolemmal membrane. There is also evidence suggesting that magnesium may affect the vascular smooth muscle tone. Changes in intracellular magnesium concentration can induce changes in cell proliferation or maturation.

Magnesium is therefore essential for the synthesis of nucleic acids and proteins, for intermediary metabolism and energy producing/energy consuming reactions, and for specific actions in different organs such as the neuromuscular and cardiovascular systems.

The term hypomagnesemia and magnesium deficiency are commonly used interchangeably, although total body magnesium depletion can be present with normal serum magnesium concentrations and there can be significant hypomagnesemia without total body deficit. The normal concentration of magnesium in serum is between 0.65 and 1.05 mmol/L.

Hypomagnesemia is a relatively common entity occurring in up to 12% of hospitalized patients[1], but its incidence may rise to as high as 60% to 65% in patients in intensive care setting in whom nutrition, diuretics, hypoalbuminemia and aminoglycosides may play important roles[2-4].

Causes

Approximately one-third of dietary magnesium (5 mmol) is absorbed principally in the small bowel. In addition, approximately 1.6 mmol is secreted in intestinal secretions and absorption of another 0.8 mmol occurs in the

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Table 1. Physiologic functions of magnesium

- **Enzyme function**
  1. Enzyme substrate (ATPmg, GTPmg)
     – kinases B
       * hexokinase
       * creatine kinase
       * protein kinase
  2. ATPases or GTPases
       * Na^+, K^+, -ATPase
       * Ca^+, ATPase
     – cyclases
       * adenylate cyclase
       * guamylate cyclase
  3. Direct enzyme activation
     * phosphofructokinase
     * creatine kinase
     * 5-phosphoribosyl-pyrophosphate synthetase
     * adenylate cyclase
     * Na^+, K^+, -ATPase
- **Membrane function**
  1. Cell adhesion
  2. Transmembrane electrolyte flux
- **Calcium antagonist**
  1. Muscle contraction/relaxation
  2. Neurotransmitter release
  3. Action potential conduction in nodal tissue
- **Structural function:** protein, polyribosomes, nucleic acids, multiple enzyme complexes, mitochondria

large bowel. Balance is achieved by urinary excretion of approximately 4 mmol that is absorbed. There is no physiologic hormonal control of plasma magnesium and urinary magnesium excretion. Changes in its intake are balanced by changes in urinary magnesium reabsorption, principally in the loop of Henle and distal tubule in response to changes in plasma magnesium concentration. Magnesium deficiency may result from one or more of the following mechanisms: reduced magnesium intake, reduced intestinal magnesium absorption, increased gastrointestinal loss, increased loss through the kidneys, or redistribution of magnesium from extracellular or intracellular fluid. Causes of magnesium deficiency are listed in Table 2.

Gastrointestinal losses

Gastrointestinal secretory losses, which contain some magnesium, are continuous and not regulated. Although the obligatory losses are not large, marked dietary deprivation may lead to progressive magnesium depletion. Magnesium loss will also occur when the intestinal secretions are incompletely reabsorbed, as with most disorders of the small bowel including acute or chronic diarrhea, malabsorption, steatorrhea, and small bowel bypass surgery.

A much rarer disorder is an inborn error of metabolism characterized by a selective defect in magnesium absorption (primary intestinal hypomagnesemia). This disease presents in the neonatal period with hypocalcemia responsive to magnesium administration[5].

Hypomagnesemia can also be seen in acute pancreatitis. The mechanism is presumably similar to that responsible for at least part of the associated hypocalcemia: saponification of magnesium and calcium in necrotic fat. The degree of hypocalcemia may be exacerbated by hypomagnesemia, which can both lower parathyroid hormone (PTH) secretion and induce end-organ resistance to its effect.

Table 2. Causes of magnesium depletion

Poor Mg intake
Starvation
Anorexia
Protein calorie malnutrition
No Mg in intravenous fluids
Renal losses
Nasogastric suction
Vomiting
Intestinal bypass for obesity
Short-bowel syndrome
Inflammatory bowel disease
Pancreatitis
Diarrhea
Laxative abuse
Villous adenoma
Other
Lactation
Extensive burns
Exchange transfusions

Renal losses

Urinary magnesium losses can be inappropriately increased by inhibition of sodium reabsorption in those segments in which magnesium transport passively follows that of sodium, or by a primary defect in renal tubular magnesium reabsorption.

Loop and thiazide-type diuretics. Both loop and thiazide diuretics can inhibit net magnesium reabsorption, whereas the potassium-sparing diuretics may enhance magnesium transport and lower magnesium excretion. The degree of hypomagnesemia induced by the loop and thiazide diuretics is generally mild, in part because the associated volume contraction will tend to increase proximal sodium, water and magnesium reabsorption.

Volume expansion. Expansion of the extracellular fluid volume can decrease passive magnesium transport. If sustained, mild hypomagnesemia may ensue as in primary hyperaldosteronism.

Alcohol. Hypomagnesemia is common in alcoholic patients admitted to the hospital[6]. Excessive urinary excretion of magnesium occurred in 18 of 38 patients with hypomagnesemia. The defect in urinary excretion appears to reflect alcohol-induced tubular dysfunction that is reversible within 4 weeks of abstinence[7]. This effect is modest and other factors contribute to hypomagnesemia in these patients, including dietary deficiency, acute pancreatitis, and diarrhea.

Hypercalcemia. Calcium and magnesium seem to compete for transport in the thick ascending limb of the loop of Henle. The increased filtered calcium load in hypercalcemic states will deliver more calcium to the loop of Henle. The ensuing rise in calcium reabsorption will diminish that of magnesium.

Nephrotoxins. Many nephrotoxic drugs can produce urinary magnesium wasting[8]. Included in this group are aminoglycoside antibiotics, amphotericin B, cisplatin, pentamidine, and cyclosporine. Impairment in the loop and distal magnesium reabsorption may occur before the onset of and may persist after the resolution of overt tubular necrosis and acute renal failure. The magnesuria in this setting can be striking and the resulting hypomagnesemia may be sufficient to produce hypocalcemia. Carboplatin, an analog of cisplatin with less nonhematologic toxicity, produces significantly less hypomagenesemia than the parent compound[9].

Loop of Henle or distal tubular dysfunction. Magnesium wasting can occur as part of the tubular dysfunction seen in recovery from acute tubular necrosis, following renal transplantation, during postobstructive diuresis, or in patients with Bartter's syndrome.

Primary renal magnesium wasting. Primary renal magnesium wasting is an unusual disorder that may present sporadically or as a familial disease[10-14]. In some patients, magnesium wasting is also associated with abnormalities in calcium and potassium transport. Three types have been recognized.

- The first is associated with ***hypercalciuria,*** and affected patients usually present in childhood or adolescence with symptomatic hypocalcemia[10-14]. Recurrent nephrolithiasis and nephrocalcinosis are also seen, and progression to renal insufficiency and an acidification defect are common. The problem with acidification has been attributed to defective ammonia transfer to the deep nephrons and impaired medullary hydrogen ion secretion due to nephrocalcinosis[15]. Some patients present with hypokalemia presumably due to either secondary hyperaldosteronism and/or direct effects of hypomagnesemia on potassium transport. Some cohorts with familial hypomagnesemia and hypercalciuria have normal plasma potassium and bicarbonate concentrations[12].
- The second form is associated with ***hypocalciuria*** and ***hypokalemia,*** and is known as Gitelman's syndrome. It is associated with a defect in the gene coding for the

thiazide-sensitive sodium-chloride cotransporter. The hypokalemia is usually attributed to the decreased sodium chloride transport, but there is also evidence for direct effects of hypomagnesemia[16]. The hypomagnesemia has also been attributed to the reduction in sodium chloride transport, which presumably decreases the passive transport of magnesium. The hypomagnesemia in this syndrome is significantly more marked than that seen with thiazides. In a study in mice lacking the cotransporter after gene targeting, hypomagnesemia and hypocalciuria were present but there were only subtle changes in sodium homeostasis[17].

- The third form presents with ***isolated magnesium wasting*** with both an autosomal dominant and recessive mode of inheritance[10,11].

As routine measurement of the plasma magnesium concentration has been ever more widely used, it is likely that the acquired renal magnesium wasting due to aging and mild interstitial renal disease will become a more commonly recognized syndrome.

Miscellaneous. Hypomagnesemia may be seen following surgery, at least in part due to chelation by circulating free fatty acids[18] and after foscarnet therapy for cytomegalovirus chorioretinitis[19]. Chelation is involved again and the plasma calcium concentration is also typically reduced. Similarly, ionized hypomagnesemia has been seen during liver transplantation as the result of transfusion of citrate-rich blood products in the absence of adequate hepatic function[20].

Hypomagnesemia can also occur as part of the 'hungry bone' syndrome, in which there is an increased magnesium uptake by renewing bone after parathyroidectomy (for hyperparathyroidism) or thyroidectomy (for hyperthyroidism), or after correction of chronic systemic acidosis[21].

Several studies have demonstrated a higher than expected frequency of hypomagnesemia in patients with diabetes mellitus that seems to correlate with the degree of hyperglycemia[22]. It has been proposed, although not proven, that hypomagnesemia may impair glucose disposal and may play a role in the pathogenesis of some of the complications of diabetes. As a result, the American Diabetes Association has published a consensus statement suggesting that diabetic patients with hypomagnesemia should receive magnesium supplementation.

Signs and Symptoms

Many patients with magnesium deficiency and hypomagnesemia remain asymptomatic. As magnesium deficiency is usually secondary to other disease processes or drugs, the features of the primary disease may complicate or mask magnesium deficiency. The signs and symptoms of magnesium deficiency are usually not seen until the magnesium concentration declines to 0.5 mmol/L or lower.

Symptomatic magnesium depletion is often associated with multiple biochemical abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis. It is often difficult to ascribe specific clinical manifestations solely to hypomagnesemia. In 1960, five patients were reported with symptoms considered to be typical of mag-

Table 3. Signs and symptoms of hypomagnesemia

Cardiovascular
Electrocardiographic results
Prolonged P-R and Q-T intervals
U waves
Angina pectoris
Congestive heart failure
Atrial and ventricular arrhythmias
Hypertension
Digoxin toxicity
Atherogenesis
Central nervous system
Seizures
Obtundation
Depression
Psychosis
Coma
Ataxia
Nystagmus
Choreiform and athetoid movements
Muscular
Cramps
Weakness
Carpopedal spasm
Chvostek's sign
Trousseau's sign
Fasciculations
Tremulous
Hyperactive reflexes
Myoclonus
Dysphagia
Skeletal
Osteoporosis
Osteomalacia

nesium depletion, including tetany, positive Chvostek's and Trousseau's signs, and generalized convulsions[23]. Somewhat similar findings, i.e. generalized weakness, anorexia, hypokalemia, hypocalcemia, and positive Trousseau's and Chvostek's signs, were observed when magnesium depletion was induced in volunteers[24] (Table 3). Tetany can occur in the absence of hypocalcemia and alkalosis, and is presumably due to lowering of the threshold for nerve stimulation[25].

Hypokalemia

Hypokalemia is a common event in hypomagnesemic patients, occurring in 40% to 60% of cases[26]. This relationship is in part due to underlying disorders that cause both magnesium and potassium loss, such as diuretic therapy and diarrhea. There is also evidence for renal potassium wasting in hypomagnesemic patients[24], which is likely due to increased potassium secretion in the loop of Henle and perhaps in the cortical collecting tubule.

There are several mechanisms that may explain how this might occur. Potassium secretion from the cell into the lumen in the cells of the thick ascending limb and cortical collecting tubule is mediated by ATP-inhibitable luminal potassium channels[27]. Hypomagnesemia is associated with a reduction in the cell magnesium concentration, which may then lead to a decline in ATP activity and, due to removal of ATP inhibition, to an increase in the number of open potassium channels[27]. In addition, decreasing cytosolic magnesium has been shown to directly increase the activity of potassium channels of the ascending limb cells[10]. Given the very high cell potassium concentration, these changes would promote potassium secretion from the cell into the lumen and enhanced urinary losses. The hypokalemia in this setting is relatively refractory to potassium supplementation and requires correction of the magnesium deficit[28].

Bone and calcium metabolism

The most classical sign of severe hypomagnesemia (less than 0.5 mmol/L) is hypocalcemia. Early *in vitro* studies showed the reduction in extracellular magnesium concentration to stimulate the secretion of PTH in the absence of changes in calcium concentration. Immunoreactive PTH levels in most hypomagnesemic-hypocalcemic patients were either normal or low, indicating inappropriately low PTH secretion[29,30]. Further evidence for a suppressive effect of hypomagnesemia on PTH secretion is the observation that, in the majority of these patients, parenteral magnesium supplementation leads to a rapid rise in plasma PTH levels[29,30]. Several other factors play a role in the mechanism of hypocalcemia.

Parathyroid hormone resistance. Failure of the hormone secretion cannot explain all of the hypocalcemia, as bone resistance to PTH also plays a role[30]. Studies in isolated perfused bone have shown that magnesium depletion interferes with the generation of cyclic AMP in response to perfusion with PTH[31]. Why this occurs, is not clear. It is possible that severe hypomagnesemia may interfere with G protein activation in response to PTH, thereby minimizing the stimulation of adenylate cyclase.

Several findings suggest that PTH resistance may be of greater importance than diminished secretion in most patients. In general, PTH-induced release of calcium from bone is substantially impaired when the plasma magnesium concentration falls below 0.4 mmol/L. In comparison, diminished PTH secretion appears to require more severe hypomagnesemia. There may be a variable time course for the normalization of the different aspects of calcium and PTH metabolism in hypomagnesemic patients. In some patients, PTH secretion rises significantly earlier than the correction of hypocalcemia and restoration of PTH responsiveness[30]. This observation is compatible with the primary role of PTH resistance.

As noted above, symptomatic hypocalcemia is almost always associated with plasma magnesium levels below 0.5 mmol/L. Mild hypomagnesemia (plasma magnesium concentration between 1.1 and 1.3 mmol/L) can also lower plasma calcium concentration, but the change is quite small (0.05 mmol/L)[32].

Vitamin D deficiency. Low plasma levels of calcitriol (1,25-dihydroxyvitamin D) have been recorded in hypocalcemic, hypomagnesemic subjects and can contribute to the fall in plasma calcium concentration. Why this occurs, is not clear, since in one study, several days of magnesium replacement normalized plasma calcium and PTH levels but not the concentration of calcitriol[33].

Normomagnesemic magnesium depletion. A small number of patients have been reported with hypocalcemia responsive to magnesium administration in the absence of detectable hypomagnesemia[30-32]. In most of these patients, other tests suggested the presence of magnesium depletion, such as alcoholism or diarrhea. In a prospective study in 82 patients with alcohol related admission diagnoses, 30 of them had unexplained hypocalcemia of 2.0 mmol/L, 14 patients were hypomagnesemic, and 16 patients had normal plasma magnesium concentration[34]. However, both of the hypocalcemic groups had low mononuclear cell mag-

nesium levels, a finding also seen in normocalcemic patients, and both groups showed normalization of the plasma calcium concentration with the administration of 32 to 64 mmol of elemental magnesium *per* day for 3 to 5 days.

These findings do not conclusively demonstrate that intracellular magnesium depletion is the cause of unexplained hypocalcemia in patients with normal plasma magnesium concentration. Most patients with chronic alcoholism and diarrhea have tissue magnesium depletion that is independent of the presence or absence of hypocalcemia. Sepsis, hypoalbuminemia, stress, and vitamin D deficiency are among the many factors in these patients that can lower total and ionized calcium. There were no untreated time controls in this study, and it is possible that the resolution of hypocalcemia may have occurred without magnesium repletion as the clinical status of the patients improved upon admission. It seems reasonable to consider a trial of magnesium replacement in patients with normal renal function who have persistent, unexplained hypocalcemia and are at a risk of magnesium deficiency.

Heart and cardiovascular system

Magnesium depletion can induce changes in the electrocardiogram. Widening of the QRS complex and peaking of T waves have been described with modest magnesium loss, whereas more severe magnesium depletion can lead to prolongation of the PR interval, progressive widening of the QRS complex, and diminution of the T wave[35].

There are conflicting data as to whether hypomagnesemia is associated with arrhythmia in otherwise healthy subjects. A report on more than 3000 patients from the Framingham Heart Study suggests that the manner in which arrhythmia is defined is an important determinant[36]. No association with hypomagnesemia was noted for more than 10 ventricular premature complexes (VPC) *per* hour or for repetitive VPC. However, there was an increased risk of complex or frequent (more than 30/h) VPC with reductions in the plasma magnesium concentration of 0.08 mmol/L or more.

The clinical disturbance of greatest potential importance, however, is the association of mild hypomagnesemia with ventricular arrhythmias in patients with cardiac disease. A number of uncontrolled studies suggest that hypomagnesemia may be an important risk factor for arrhythmias in the setting of an acute ischemic event, congestive heart failure, *torsades de pointes*, after cardiopulmonary bypass, or in the acutely ill patient in the intensive care unit.

The mechanism underlying the possible association between hypomagnesemia and arrhythmias is at present unknown. Arrhythmias could be due to concurrent hypokalemia, hypomagnesemia itself, or both. Magnesium regulates several cardiac ion channels, including the calcium channel and outward potassium currents through the delayed rectifier[37]. Lowering the cytosolic magnesium concentration in magnesium depletion will markedly increase these outward currents, shortening the action potential and increasing the susceptibility to arrhythmias.

Acute ischemic heart disease. Patients with acute myocardial infarction who have mild hypomagnesemia appear to have a two- to threefold increase in the frequency of ventricular arrhythmias in the first 24 hours, when compared to those with normal plasma magnesium levels[21,22]. Uncontrolled studies suggest that the administration of intravenous magnesium at this time can reduce the frequency of potentially fatal ventricular arrhythmias[38,39].

Congestive heart failure. An increased incidence of hypomagnesemia has been repeatedly found in patients with congestive heart failure and is presumably in part due to diuretic therapy. A role for magnesium depletion in sudden death has been suggested but is not proven. In a prospective study including more than 1000 patients with class III or IV heart failure, for example, no correlation was found between hypomagnesemia at the beginning of the study and survival at a median follow-up of 6 months[40]. However, measurements were not made later in the study and all patients were receiving digoxin, diuretics and an angiotensin-converting enzyme inhibitor, any or all of which may have altered magnesium balance during the course of the study.

Torsades de pointes. The American Heart Association 1992 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care now include a recommendation that magnesium sulfate be added for the management of *torsades de pointes*, severe hypomagnesemia, or refractory ventricular fibrillation[41]. *Torsades de pointes* is a unique ventricular tachycardia most commonly precipitated by drugs that prolong the QT interval (*e.g.*, quinidine), electrolyte imbalance (hypokalemia and hypomagnesemia), or a slow heart rate. Treatment is aimed at accelerating the heart rate and/or shortening the QT interval. Intravenous magnesium is now regarded as the treatment of choice even when hypomagnesemia is not present.

Cardiopulmonary bypass. Hypomagnesemia may develop during cardiopulmonary bypass and predispose to arrhythmias. The cause of hypomagnesemia in this setting is unclear. The possible contributing factors include chelation by free fatty acids and/or citrate, and enhanced cellular uptake induced by increasing circulating levels of catecholamines.

Hypomagnesemic patients were found to have a significantly higher frequency of atrial dysrhythmias and an increased requirement of prolonged mechanical ventilatory support. A separate study suggested that 8 mmol of magnesium sulfate given after surgery reduced the level of ventricular ectopy[42].

These findings were corroborated in a prospective study of 100 patients who were randomized to either placebo or 8 mmol of magnesium chloride intravenously upon the completion of cardiopulmonary bypass[43]. Normomagnesemic patients had significantly fewer postoperative supraventricular and ventricular dysrhythmias, higher indices of cardiac performance, and a less frequent requirement of prolonged mechanical ventilatory support than patients with low plasma magnesium levels.

Intensive care unit. Hypomagnesemia is extremely common in patients in intensive care unit, and is frequently associated with hypokalemia and hypocalcemia[2,3]. In one study, for example, hypomagnesemia present on admission to the intensive care unit was associated with a mortality rate approximately twice that of comparably ill normomagnesemic patients[31]. It has not been shown, however, that magnesium supplementation would improve the outcome.

Coronary heart disease. Two large prospective epidemiologic studies investigated the relationship between serum magnesium concentration and subsequent development of coronary heart disease (CHD)[44,45]. Both suggest that a low serum magnesium is a risk factor for CHD, but it is not clear how a low serum magnesium might predispose to CHD.

Diagnosis

The plasma magnesium concentration is often not measured as part of the routine screening blood tests. The possible presence of hypomagnesemia should be suspected in the following situations: chronic diarrhea, hypocalcemia, refractory hypokalemia, and ventricular arrhythmias, particularly during an ischemic event. If the situation is life-threatening, blood should be drawn for the measurement of plasma magnesium concentration, and intravenous magnesium can be given immediately if renal function is relatively normal.

If hypomagnesemia is confirmed, the diagnosis can usually be obtained from the history. If no cause is apparent, the distinction between gastrointestinal and renal losses can be made by measuring 24-hour urinary magnesium excretion or fractional excretion of magnesium in a random urine specimen. The latter can be calculated from the following formula:

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7 \times P_{Mg}) \times U_{Cr}} \times 100$$

U and P refer to urine and plasma concentrations of magnesium (Mg) and creatinine (Cr). The plasma magnesium concentration is multiplied by 0.7, since only about 70% of the circulating magnesium is free (not bound to albumin) and therefore able to be filtered across the glomerulus.

The normal renal response to magnesium depletion is to lower magnesium excretion to very low levels. Daily excretion of more than 0.4 mmol to 1.2 mmol or a fractional excretion of magnesium above 2% in a subject with normal renal function indicates renal magnesium wasting due to drugs such as diuretics, aminoglycosides or cisplatin.

Normomagnesemic magnesium depletion

Normomagnesemic magnesium depletion should be considered as a possible cause of refractory hypokalemia or unexplained hypocalcemia in patients at a high risk of magnesium loss. It has been suggested that this syndrome can be detected by demonstrating low urinary magnesium excretion (as defined above). One study, for example, evaluated patients with chronic diarrhea due to small bowel resection or diffuse disease[44]. The 24-hour urine magnesium excretion was 0.76 mmol in these patients as compared with 5.08 mmol in matched control subjects. The plasma magnesium concentration was only slightly lower in the patients with small bowel disease (0.7 *versus* 0.8 mmol/L), 56% of whom had a normal level.

Another method to detect an underlying magnesium depletion is to demonstrate a reduced excretion (less than 80% over 24 hours) of the infused magnesium load (0.09 mmol/kg of lean body weight given over the initial 4 hours)[45,46]. The utility of this test is uncertain. Patients with malnutrition, cirrhosis, diarrhea, or longterm diuretic use typically have positive test results irrespective of whether they have signs or symptoms referable to magnesium depletion. It seems prudent to simply administer magnesium to these patients if they have unexplained hypocalcemia and/or hypokalemia.

Treatment

The route of magnesium repletion varies with the severity of the clinical manifestations (Table 4). As an exam-

ple, the hypocalcemic-hypomagnesemic patient with tetany or the patient suspected of having hypomagnesemic-hypokalemic ventricular arrhythmias should receive 50 mmol of intravenous magnesium given slowly over 8 to 24 hours. This dose can be repeated as necessary to maintain the plasma magnesium concentration above 0.4 mmol/L or 0.8 mmol/L. In the normomagnesemic patient with hypocalcemia, it has been suggested to repeat this dose daily for 3 to 5 days[34,46].

Table 4. Guidelines for magnesium replacement

Life-threatening event, *e.g.*, seizures and cardiac arrhythmia

1. 2-4 g $MgSO_4$ i.v. or i.m. (2-4 vials/2 mL each of 50% $MgSO_4$); provides 8.3-16.7 mmol Mg
2. i.v. drip over 24 h to provide no more than 50 mmol Mg/24 h

Closely monitor:
Deep tendon reflexes
Heart rate
Blood pressure
Respiratory rate
Serum Mg (>2.5 mmol/L/6 mg/dL)
Serum K

Subacute and chronic Mg replacement
16.7-25 mmol Mg daily for 2-5 days
i.v.: continuous infusion
i.m.: painful
oral: use divided doses to minimize diarrhea

Acute increases in the level of serum magnesium may cause nausea, vomiting, cutaneous flushing, muscular weakness, and hyporeflexia. Magnesium should be administered with caution in patients with renal failure.

It must be appreciated that the plasma magnesium concentration is the major regulator of magnesium reabsorption in the loop of Henle, the major site of active magnesium transport. An abrupt elevation in the plasma magnesium concentration will partially remove the stimulus to magnesium retention, and up to 50% of the infused magnesium will be excreted in the urine. Magnesium uptake by the cells is slow and repletion requires sustained correction of the hypomagnesemia.

For these reasons, oral replacement should be given in the asymptomatic patient, preferably with a sustained-release preparation. There are several such preparations currently available. These preparations provide 2.5 to 3.5 mmol or 60 to 84 mg of magnesium *per* tablet. Six to eight tablets should be taken daily in divided doses for severe magnesium depletion. Two to 4 tablets may be sufficient for mild, asymptomatic disease.

The underlying disease should also be corrected, if possible. Patients with hypomagnesemia induced by a thiazide or loop diuretic, who cannot discontinue diuretic therapy, may benefit from the addition of a potassium-sparing diuretic such as amiloride. These drugs may decrease magnesium excretion by increasing its reabsorption in the cortical collecting tubule. Amiloride may also be helpful in conditions associated with persistent urinary magnesium wasting such as Bartter's or Gitelman's syndrome or cisplatin nephrotoxicity. In these settings, magnesium repletion alone may be relatively ineffective, since raising the plasma magnesium concentration will, as mentioned above, lead to increased magnesium excretion.

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Sažetak

POREMEĆAJI METABOLIZMA MAGNEZIJA: HIPOMAGNEZEMIJA

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Hipomagnezemija je razmjerno čest poremećaj koji se javlja u oko 12% bolnički liječenih bolesnika. U jedinicama intenzivnog liječenja, gdje bolesnici dobivaju diuretike, aminoglikozide, a zbog bolesti mogu biti pothranjeni i imati hipoalbuminuriju, hipomagnezemija se javlja u 60% do 65% bolesnika. Simptomatska hipomagnezemija često je udružena s drugim biokemijskim poremećajima, kao što su hipokalemija, hipokalcemija i metabolična acidoza. Zbog toga je često vrlo teško opisati specifične simptome koji nastaju isključivo kao posljedica hipomagnezemije. Simptomi za koje se vjeruje da su znakoviti za manjak magnezija u organizmu su opća slabost, tetanija, pozitivan Chvostekov znak, Trousseauov znak i generalizirane konvulzije. Odluka o načinu liječenja ovisi o težini kliničke slike.

Ključne riječi: *Manjak magnezija, dijagnostika; Manjak magnezija, terapija; Elektrolit, metabolizam*