Clinical Review

Magnesium Deficiency: A Cause of Heterogenous Disease in Humans

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INTRODUCTION

Magnesium is the most prevalent intracellular divalent cation and the second most prevalent cation in the body.\(^1,2\) The normal adult body content is \(\sim 25\) g and its distribution is approximately equally divided between the skeleton and soft tissues.\(^1\) A large proportion (about one-third) of skeletal magnesium (Mg) resides on the surface of bone. Because this fraction is surface exchangeable and because the skeletal Mg level falls during Mg depletion, it is hypothesized that this component serves as a reservoir to maintain the extracellular Mg concentration.\(^4\) Extracellular Mg accounts for only 1% of total body Mg. In the plasma, 55% of Mg is ionized, or free, 15% is complexed to anions, and the rest (\(\sim 30\))% is bound to protein (chiefly albumin).\(^2,5\) Mg is contained within all intracellular compartments. It is principally bound to ATP (80–90%) and other negatively charged molecules.\(^5\) Total cellular Mg ranges from 5–20 mM; the greater the metabolic activity of a cell, the greater the Mg content. Intracellular free Mg\(^{2+}\) accounts for about 1–5% of total cellular Mg (0.2–1.0 mM).\(^6\) Mg is actively transported into and out of cells and is influenced by various hormonal and pharmacological factors which perhaps regulate the intracellular Mg\(^{2+}\) concentration and hence activity of Mg-sensitive enzymes.\(^6–8\)

For example, insulin has been shown to increase intracellular Mg in a number of tissues including skeletal and cardiac muscle, uterine smooth muscle, red blood cells, platelets, and lymphocytes (for review see Refs. 9 and 10).

The physiological role of Mg is principally related to enzyme activity (Table 1); over 300 enzyme systems are dependent on the presence of this cation.\(^5,11\) All enzyme utilizing ATP requires Mg for substrate formation. Intracellular free Mg\(^{2+}\) also acts as an allosteric activator of enzyme action including critical enzyme systems such as adenylate cyclase, phospholipase C, and Na/K-ATPase.\(^12–15\) Transport of other ions such as potassium and calcium across the plasma membrane may also require the presence of Mg. Mg has been termed “nature’s physiologic calcium channel blocker.”\(^16,17\) During Mg depletion, intracellular potassium decreases while calcium and sodium increase.\(^15–18\) Mg is therefore critical for a number of cellular functions, including oxidative phosphorylation, glycolysis, DNA transcription, and protein synthesis. The clinical complications of Mg depletion no doubt are, at least in part, due to perturbation of Mg-requiring enzyme systems.

MAGNESIUM HOMEOSTASIS

Efficient mechanisms exist in both the gastrointestinal tract and the kidney that closely regulate Mg homeostasis. In the intestine, an active Mg-transport system accounts for greater fractional Mg absorption at low dietary intake.\(^19\) Mg absorption, however, continues at high dietary intakes, albeit at a lower fractional absorption rate, due to a passive absorption component.\(^20\) Mg is absorbed along the entire intestinal tract; however, it appears to be most efficiently absorbed in the distal small bowel. At a normal dietary Mg intake of approximately 300–350 mg/day, fractional absorption is 30–50%.\(^21\) This variation may be due to the presence of other nutrients that interact with Mg in the gut. High dietary fiber, phytate, oxalate, and phosphate intakes reduce Mg absorption by binding the cation.\(^22–24\) Dietary protein diets of \(< 30\) g/day hinder Mg absorption.\(^25\)

The kidney is the organ that most closely regulates Mg metabolism.\(^26\) There exists a threshold of filtered Mg in the kidney below which Mg is avidly conserved and above which Mg is totally excreted.\(^27\) This threshold is close to the normal plasma Mg concentration. Excessive Mg, either dietary or parenterally administered, is almost totally excreted. In contrast, at the time of Mg deprivation, the kidney avidly conserves Mg; less that 12–24 mg is excreted.
III. Influence membrane properties

Enhance Mg excretion. (32) The principal sites of Mg reabsorption are the proximal convoluted tubule and the thick ascending limb of Henle. (26) Reabsorption in the proximal tubule, 20–30% of filtered load, is linked to sodium and water as well as calcium transport. The major site of Mg reabsorption is the thick ascending limb of Henle, which handles about 65% of the filtered load. The mechanisms of Mg transport in the intestine and kidney are unclear. No hormone or factor principally involved in Mg metabolism has been described.

MAGNESIUM DEPLETION

Dietary deprivation

Recent deliberations by the Food Nutrition Board of the Institute of Medicine has resulted in an increase in the estimated average requirement (EAR) and recommended daily allowance (RDA) for Mg. (EAR = 265 mg for adult females and 350 mg for adult males per day; RDA = 320 mg for females and 420 mg for males per day). (33) The mean intake for females and males in the U.S.A., according to the United States Department of Agriculture is 228 and 323 mg, respectively, indicating that a substantial proportion of the population fall far short of the estimated requirements. (34) While low dietary Mg intake has not been unequivocally linked to chronic disease, epidemiological studies have suggested some associations. Several studies have demonstrated an increased relationship between dietary Mg intake and blood pressure, arteriosclerotic vascular disease, sudden death, and osteoporosis as discussed below. This may be particularly important in an aging population because gastrointestinal and renal mechanisms for Mg conservation may not be as efficient as in a younger population. (35–37) Nevertheless, low dietary Mg intake in subjects with concomitant disorders resulting in Mg loss will intensify the Mg-depleted state.

Disorders resulting in Mg depletion

Mg depletion, especially when moderate to severe, is almost always related to either gastrointestinal or renal Mg loss.

Gastrointestinal disorders: Disorders of the intestinal tract may result in profound Mg depletion as shown in Table 2. Because the content of Mg in diarrheal fluids may be quite high, any chronic and/or acute diarrheal syndrome or fistula drainage may result in Mg depletion. (38) Malabsorption syndromes resulting from intestinal mucosal disorders including gluten-sensitive enteropathy and regional enteritis will result in Mg malabsorption, presumably as a result of intestinal mucosal damage and/or steatorrhea through formation of nonabsorbable Mg-lipid salts. (39–43) Intestinal resection, infarction, and specific defects in Mg absorption will also result in Mg deficiency. (44–48) Acute pancreatitis is associated with low serum Mg levels in up to 20% of cases. (49–51) This may be due to a predisposing condition (e.g., alcoholism) or saponification of Mg in necrotic parapancreatic fat.

Renal Mg wasting: Renal Mg wasting underlies the basis for Mg depletion in many patients, as shown in Table 2. Conditions decreasing proximal tubule Mg reabsorption include osmotic diuresis (glycosuria accompanying poorly controlled diabetes mellitus), increased sodium excretion (sodium-containing parenteral fluids), and increased calcium excretion (most hypercalcemic states). (52–54) Hypercalcemia limits Mg reabsorption in the ascending limb of Henle as was demonstrated by micropuncture studies in the rat. (55) Loop diuretics (lasix) will also cause decreased Mg reabsorption in this segment of the nephron. (56)

A number of commonly used medications may result in renal Mg wasting by unclear mechanisms. Aminoglycosides have been reported to cause a reversible renal lesion, resulting in hypermagnesuria and hypomagnesemia within days of administration in from 4.5% to as high as 38% of treated patients. (57,58) Amphotericin B, viomycin, capreomycin, and pentamidine have been reported to result in renal Mg wasting (for review see Ref. 59). Cisplatin causes a dose-related renal Mg loss in up to 100% of patients that may persist for months to years after therapy. (60–62) Cyclosporine given for immunosuppression is also known to re-
A. Chronic parenteral fluid therapy
B. Osmotic diuresis
glucose (diabetes mellitus)
mannitol
urea
C. Hypercalcemia
D. Drugs
diuretics (furosemide, ethacrynic acid)
aminoglycosides
amphotericin B
viomycin
capreomycin
pentamidine
cisplatin
cyclosporin
E. Alcohol
F. Metabolic acidosis (starvation, ketoacidosis, alcoholism)
G. Primary renal hypomagnesemia
H. Renal diseases
chronic pyelonephritis, interstitial nephritis and glomerulonephritis
diuretic phase of acute tubular necrosis
postobstructive nephropathy
renal tubular acidosis
post renal transplantation
I. Bartter’s Syndrome and Gitelman’s Syndrome

result in tubular damage leading to renal Mg wasting. Alcohol, acidosis, and a variety of renal disorders may also impair the ability of the kidney to conserve Mg and contribute to Mg depletion.

**CLINICAL SEQUELAE OF Mg DEPLETION**

Mg depletion is often due to another disease process as discussed above. Clinical features of the primary disease may complicate or mask symptoms of Mg depletion. A high index of suspicion is therefore warranted. Known and/or putative manifestations of moderate to severe Mg deficiency are shown in Table 4.

**Bone and mineral metabolism**

**Hypocalcemia:** Under normal physiological circumstances, acute changes in Mg concentrations affect parathyroid hormone (PTH) secretion qualitatively similar to calcium. Mg depletion, however, markedly perturbs calcium homeostasis. Hypocalcemia is a common manifestation of moderate to severe Mg deficiency in humans as well as most other species. Mg therapy alone restores the serum calcium to normal; calcium and/or vitamin D therapy are not effective.

The major factor for the hypocalcemia appears to be impaired PTH secretion. The majority of Mg-deficient hypocalcemic patients have low or inappropriately normal (for the low serum calcium) PTH levels. Mg administration results in an immediate rise (within minutes) in the serum PTH concentration to levels well above normal in most cases. As the serum Ca rises with Mg therapy given over several days, the serum PTH falls to normal. Some Mg-deficient hypocalcemic patients, however, have elevated serum PTH levels. These heterogeneous serum PTH values may be explained by the severity of Mg depletion. When hypomagnesemia occurs, the parathyroid gland responds normally with an increase in PTH secretion. As intracellular Mg depletion develops, however, the ability to secrete PTH is progressively impaired. This concept is supported by the observation that changes in serum PTH in experimentally induced human Mg deficiency correlate with a fall in red blood cell free Mg$^{2+}$.

While hypocalcemia exists in the face of normal or high PTH concentrations, Mg-deficient hypocalcemic patients appear also to be resistant to the action of PTH. Renal resistance (impaired phosphaturia and cAMP generation) and skeletal resistance (decreased calcemic effects) in response to PTH have been observed in Mg-deficient humans and animals.

The mechanism for the defect in PTH secretion and action is unclear but may be related to decreased enzyme activity. Enzymes thought to mediate PTH secretion and the cellular response to PTH, adenylate cyclase (cAMP generation), and phospholipase C (inositol-1,4,5-triphosphate and diacylglycerol) are highly dependent on Mg.

Lastly, vitamin D metabolism and/or action may be perturbed in Mg depletion. Vitamin D resistance has been reported in Mg-depleted humans and animals. The serum concentration of 1,25-dihydroxyvitamin D in hypocalcemic Mg-depleted patients are generally low. This may be due to a decrease in PTH secretion and/or a direct effect of Mg depletion on the ability of the kidney to synthesize 1,25-dihydroxyvitamin D.

**Osteoporosis:** Experimental Mg deficiency in the rat has been reported to result in decreased bone growth, increased bone resorption, decreased bone volume, and an increase in skeletal fragility. Mg depletion may therefore be a risk factor for osteoporosis. Significant reduction in the serum Mg and bone Mg content has been described in some studies of postmenopausal women with osteoporosis. Epidemiologic studies relating Mg intake to bone mass or rate of change in bone mineral density (BMD) but not in postmenopausal women. In another study, no correlation was found between BMD in pre- and postmenopausal women; however, Mg intake was positively correlated with the rate of change in humerus and radius BMD in this same population. BMD of the radius in postmenopausal Japanese-American women was weakly positively correlated with Mg intake but not in males; dietary Mg supplements in the Japanese-American men, however, had a positive effect on BMD but not in women. Recently, elderly women who consumed less than 187 mg of Mg per day were found to have a significantly lower BMD compared with women whose average Mg intake from diet was more than 187...
Limited studies on the effect of Mg supplementation on osteoporosis are available. One study reported an increase in radial bone mass in 31 osteoporotic postmenopausal women after 1 year of dietary Mg supplements (750 mg/day for the first 6 months followed by 250 mg/day). Another study demonstrated an increase in bone mass in postmenopausal women who received estrogen replacement therapy, and a combination of 500 mg of calcium, 600 mg of Mg, and a multivitamin-multimineral tablet as compared with sex steroid therapy alone.

Osteoporosis occurs with greater frequency in certain populations in which Mg depletion is also common, such as diabetes mellitus, alcoholism, and malabsorption syndromes (for review see Ref. 92). In a study of patients with celiac sprue on a gluten-free diet, both BMD and red blood cell Mg$^{2+}$ were found to be decreased. Mg supplementation, given over a 2 year treatment period at approximately 576 mg of Mg/day, resulted in a significant increase in BMD. The change in BMD correlated positively with an increase in red blood cell Mg$^{2+}$. Further investigation as to the role of Mg in bone metabolism and osteoporosis is needed.

### TABLE 4. MANIFESTATIONS OF MAGNESIUM DEPLETION

<table>
<thead>
<tr>
<th>I. Bone and mineral metabolism</th>
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<tbody>
<tr>
<td>A. Hypocalcemia</td>
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<tr>
<td>impaired PTH secretion</td>
</tr>
<tr>
<td>renal and skeletal resistance to PTH</td>
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<tr>
<td>resistance to vitamin D</td>
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<tr>
<td>B. Osteoporosis (putative)</td>
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</tbody>
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<tr>
<th>II. Neuromuscular</th>
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</thead>
<tbody>
<tr>
<td>A. Positive Chvostek’s and Trousseau’s sign</td>
</tr>
<tr>
<td>B. Spontaneous carpal-pedal spasm</td>
</tr>
<tr>
<td>C. Seizures</td>
</tr>
<tr>
<td>D. Vertigo, ataxia, nystagmus, athetoid and chorioform movements</td>
</tr>
<tr>
<td>E. Muscular weakness, tremor, fasciculation and wasting</td>
</tr>
<tr>
<td>F. Psychiatric: depression, psychosis</td>
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<th>III. Potassium homeostasis</th>
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<tbody>
<tr>
<td>A. Hypokalemia</td>
</tr>
<tr>
<td>renal potassium wasting</td>
</tr>
<tr>
<td>decreased intracellular potassium</td>
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</tbody>
</table>

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<tr>
<th>IV. Cardiovascular</th>
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<tbody>
<tr>
<td>A. Cardiac arrhythmia</td>
</tr>
<tr>
<td>EKG: prolonged P-R interval and Q-T interval, U waves</td>
</tr>
<tr>
<td>atrial tachycardia, premature contractions and fibrillation</td>
</tr>
<tr>
<td>junctional arrhythmias</td>
</tr>
<tr>
<td>ventricular premature contractions, tachycardia, fibrillation</td>
</tr>
<tr>
<td>sensitivity to digitalis intoxication</td>
</tr>
<tr>
<td>torsades de pointes</td>
</tr>
<tr>
<td>B. Myocardial ischemia/infarction (putative)</td>
</tr>
<tr>
<td>C. Hypertension (putative)</td>
</tr>
<tr>
<td>D. Atherosclerotic vascular disease (putative)</td>
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### TABLE 5. SUGGESTED PROTOCOL FOR USE OF MAGNESIUM TOLERANCE TEST

I. Collect baseline 24-h urine for magnesium/creatinine ratio.*

II. Infuse 0.2 mEq (2.4 mg) elemental magnesium per kilogram of lean body weight in 50 ml of 5% dextrose over 4 h.

III. Collect urine (starting with infusion) for magnesium and creatinine for 24 h.

IV. Percentage magnesium retained is calculated by the following formula:

\[
\% \text{Mg retained} = 1 - \left( \frac{\text{Postinfusion 24 h urine Mg} - \text{Preinfusion urine Mg/creatinine} \times \text{Postinfusion urine creatinine}}{\text{Total elemental Mg infused}} \right) \times 100
\]

V. Criteria for Mg deficiency

- >50% retention at 24 h = definite deficiency
- >25% retention at 24 h = probable deficiency

* A fasting 2-h spot or shorter timed-urine may be used.
Neuromuscular

The presenting complaint of Mg deficiency may be due to neuromuscular hyperexcitability. While hypocalcemia may contribute to the neurological signs, hypomagnesemia without hypocalcemia has also been reported to result in neuromuscular hyperexcitability. On physical exam, a positive Chvostek’s and Trousseau’s sign or spontaneous carpal-pedal spasm may be seen. Generalized seizures may also occur. Other signs seen less frequently include vertigo, ataxia, nystagmus, athetoid, and choreiform movements. Muscular tremor, fasciculations, wasting, and weakness may also be present.

The mechanism by which Mg affects the neuromuscular system relates to the fact that Mg stabilizes the nerve axon as well as influences the release of neurotransmitters at the myoneural junction. In Mg deficiency, there is a lower threshold for axonal stimulation and increased nerve conduction velocity, as well as increased quantity of neurotransmitter released. Mg is also involved in calcium handling by the muscle cell. With low intracellular Mg, calcium is more readily released from the sarcoplasmic reticulum and is reaccumulated more slowly. This results in a muscle that is more readily contractible to a given stimulus and is less able to recover from contraction, i.e., tetany prone. Psychiatric disturbances associated with hypomagnesemia include apathy, depression, nervousness, delirium, hallucinations, and even psychosis.

Potassium metabolism

Mg depletion also profoundly affects potassium homeostasis. A frequently encountered laboratory feature of Mg deficiency is hypokalemia. During Mg depletion, the kidney does not conserve potassium adequately and hypokalemia develops. In addition, intracellular potassium falls, probably due to Mg requiring processes such as Na,K-ATPase activity in myocardial cells and potassium channels characterized by inward rectification (myocardial cells) as discussed below. Attempts to replete the potassium deficit with potassium therapy alone are not successful without simultaneous Mg therapy.

Cardiovascular

Cardiac arrhythmias: Cardiac manifestations of Mg depletion include electrocardiographic (EKG) changes, arrhythmias, and increased sensitivity to cardiac glycosides. On EKG, moderate Mg deficiency may result in flattening of the T wave, shortening of the ST segment, and possible prolongation of the PR and QRS intervals. In severe Mg deficiency, all of the above may occur. In addition, the T wave may invert and U waves may become pronounced with prolonged deficiencies. These EKG changes are similar to those observed in potassium depletion, and the changes may therefore be secondary to hypokalemia, which is commonly seen in Mg deficiency (see above).

The arrhythmias that occur in Mg deficiency may be either atrial or ventricular. Supraventricular arrhythmias such as premature atrial complexes, atrial tachycardia, atrial fibrillation, and junctional arrhythmias have been described. Ventricular dysrhythmias include premature contraction, ventricular tachycardia, and fibrillation. The frequency of ventricular arrhythmias occurring post–myocardial infarction also appears to be increased in hypomagnesemic patients, and may be decreased with magnesium therapy. Magnesium depletion also renders the heart more susceptible to the arrhythmogenic effects of cardiac glycosides. Hypomagnesemia may be associated with digitalis toxicity through a number of mechanisms. In the presence of intracellular potassium depletion, which is seen in Mg deficiency, the action of digitalis on the cardiac muscle is enhanced. Also, there may be reduced sodium-potassium Na,K-ATPase activity in myocardial cells with Mg deficiency.

The arrhythmogenic effect of Mg deficiency may be related to its effect on maintaining intracellular potassium. Magnesium is necessary for Na,K-ATPase, which is responsible for active transport of potassium intracellularly during phase 4 of the action potential. Mg also is involved in regulating the potassium influx through other potassium channels. These potassium channels normally allow potassium to pass more readily inward than outward (inward rectification). Mg appears to regulate the outward movement of potassium in myocardial cells. In the absence of Mg, potassium is transported equally well in both directions. Therefore, a deficiency in myocardial Mg can lead to a reduced amount of intracellular potassium due to a less efficient Na,K-ATPase system and the loss of inward rectification. Because the resting membrane potential is determined in part by the intracellular potassium concentration, decreased intracellular potassium results in a less negative resting membrane potential. The result is a prolongation of the QT interval and enhanced vulnerability for ventricular arrhythmias.

While Mg administration may be effective in the therapy of arrhythmias, it is unclear if the antiarrhythmic action is due to a pharmacological effect of Mg or to repletion of a Mg deficit. Mg administration to normal humans prolongs the PR interval and AV conduction times, which provides a rationale for treatment of atrial and junctional arrhythmias with Mg.

Mg therapy may also be indicated during acute myocardial infarction. Some studies have reported low serum Mg and myocardial Mg and abnormal Mg tolerance tests in patients with acute myocardial infarction. A meta-analysis of a number of small investigations in which Mg was given parenterally during an acute myocardial infarction as well as a larger study (LIMIT-2), demonstrated improved patient survival. These data have been challenged by another recent large study (ISIS-4) in which no efficacy for Mg was found. Differences in study design may have led to these conflicting findings. No consensus concerning the role of Mg administration during acute myocardial infarction has been reached. Further studies are warranted.

Hypertension: Epidemiologic and clinical evidence suggests that Mg influences vascular tone and may play an important role in regulating blood pressure. A number of studies have demonstrated an inverse relationship between populations that have low dietary intake of Mg and blood...
pressure. One study of hypertensive patients revealed low serum Mg concentrations but another did not. More recently, patients with essential hypertension were found to have reduced free Mg\(^{2+}\) concentrations in red blood cells. The Mg\(^{2+}\) levels were inversely related to both systolic and diastolic blood pressure. The possible relationship between hypertension and Mg deficiency is an important consideration because the two often coexist in high proportions in populations such as diabetics and alcoholics. However, intervention studies with Mg therapy in hypertension have led to conflicting results. Several studies have shown a positive blood pressure lowering effect of Mg supplements, while others have not. Other dietary factors may also play a role. Recently, a diet of fruits and vegetables that increased Mg intake from 176 mg/day to 423 mg/day (along with an increase in potassium) significantly lowered blood pressure. The addition of nonfat dairy products, which increased calcium intake, as well, further lowered blood pressure.

The mechanism by which Mg may affect blood pressure is not clear. Mg administration increases the production of the vasodilatory prostaglandin prostacyclin (PGI\(_2\)). In addition, Mg depletion heightens the vasoconstrictive effect of angiotensin II and norepinephrine in vitro and in vivo. In contrast, increasing the Mg concentration reduces the pressor responses to these agents. Mg deficiency is also associated with an increase in platelet aggregation and release of the potent vasoconstrictor thromboxane A\(_2\). This effect may be reversed with Mg supplementation. These events may be affected by the influence of Mg on calcium channel activity. A rise in intracellular Ca\(^{2+}\) in response to angiotensin II and in platelets is crucial for smooth muscle contraction and platelet aggregation. Mg will cause a reduction in intracellular Ca\(^{2+}\) in vascular smooth muscle and in platelets. Therefore, hypomagnesemia is likely to cause increased intracellular Ca\(^{2+}\), increased smooth muscle contraction, and platelet aggregation.

**Atherosclerotic vascular disease:*** Another potential cardiovascular complication of Mg deficiency is the development of atherosomatous disease. Epidemiological studies have related water hardness (calcium and Mg content) inversely to cardiovascular death rates. Mg depletion in animals results in arterial wall degeneration and calcification. Experimental Mg depletion in animals is characterized by hypertriglyceridemia and hypercholesterolemia as well as atherosclerosis. Serum concentrations of very low density lipoprotein and low density lipoprotein were elevated while high density lipoprotein is reduced. Reduced lipoprotein lipase activity as well as decreased lecithin-cholesterol acyltransferase activity may be responsible for the hyperlipidemia.

Platelet hyperactivity is a recognized risk factor in the development of cardiovascular diseases. Mg has been shown to inhibit platelet aggregation against a number of aggregation agents. Diabetic patients with Mg depletion have been shown to have increased platelet aggregations. Mg therapy in these subjects returned the response to normal. The antiplatelet effect of Mg may be related to the finding that Mg inhibits the synthesis of thromboxane A\(_2\) and 12-HETE, eicosanoids thought to be involved in platelet aggregation. Mg also inhibits the thrombin-induced Ca\(^{2+}\) influx in platelets and stimulates synthesis of PGI\(_2\), the potent antiaggregatory eicosanoid.

**Diagnosis of magnesium deficiency**

Magnesium is an abundant cation in the body, but over 90% is either intracellular or in the skeleton. The serum Mg concentration is the most clinically available test for assessing Mg status. The total serum Mg concentration, of which 65–75% is diffusible is usually 1.7–2.2 mg/dl (1.5–1.9 mEq/l) and appears to be tightly held within this range. A serum concentration of less than 1.7 mg/dl usually indicates some degree of Mg depletion. The measurement of Mg concentration, however, may not reflect the true total body Mg content. Low intracellular Mg has been documented in patients with serum levels above 1.7 mg/dl. Intracellular levels in muscle, red blood cells, lymphocyte, and bone Mg can be measured and appear to be a more accurate assessment of body Mg status, but are not readily available for clinical use. Recently, ion-specific electrodes have become available for determining ionized Mg in the plasma. Early results suggest that this may be a better index of Mg status than total serum Mg concentration. Further evaluation is necessary.

In patients at risk for Mg deficiency but with normal serum levels, it may be useful to evaluate the amount of Mg excreted in the urine following an intravenous infusion of Mg as shown in Table 5. Normal subjects excrete at least 80% of an intravenous Mg load within 24 h, and patients with Mg deficiency excrete much less. The Mg load test however requires normal renal handling of Mg. Urinary Mg loss (such as related to diabetes or drugs or alcohol use) may yield an inappropriate negative test. Impaired renal function may result in a false positive test. Age may also be a confounding variable since older subjects have been reported to retain more Mg than younger subjects despite comparable dietary Mg intake.

**Treatment of magnesium deficiency**

Patients who present with signs and symptoms of Mg depletion should be treated with Mg. These patients will usually be hypomagnesemic and/or have an abnormal Mg tolerance test. These circumstances usually indicate treatment by parenteral administration. An effective treatment regimen is the administration of 2 g of MgSO\(_4\).7H\(_2\)O (200 mg of elemental Mg) as a 50% solution every 8 h intramuscularly. These injections can be painful and a continuous intravenous infusion of 600 mg of elemental Mg over 24 h therefore may be preferred and is better tolerated. Either regimen will usually result in a normal or slightly elevated serum Mg concentration. The restoration of a normal serum Mg concentration does not indicate repletion of body Mg stores, however, and therapy should be continued for approximately 3–7 days. By this time symptoms should resolve, and biochemical abnormalities such as hypocalcaemia and hypokalemia should correct. Patients who are hypomagnesemic and have seizures...
or an acute arrhythmia may be given 100–200 mg of Mg as an intravenous injection over 5–10 minutes, followed by 600 mg/day.\(^{(167)}\) Ongoing Mg losses should be monitored during therapy. If the patient continues to lose Mg from the intestine or kidney, therapy may have to be continued for a longer duration. Once repletion has been accomplished, patients usually can maintain a normal Mg status on a regular diet, provided the reason for the Mg deficiency has been corrected. If repletion is accomplished and the patient cannot eat, a parenteral maintenance dose of 100 mg of Mg should be given daily.

Patients who have chronic Mg loss from the intestine or kidney may require continuous oral Mg supplementation. Magnesium salts in the form of sulphate, lactate, hydroxide, oxide, chloride, and glycerophosphate are available. An initial daily dose of 300 mg to as high as 600 mg of elemental Mg may be used. The Mg is given in divided doses three or four times a day to avoid its cathartic effect.

Caution should be used with Mg therapy in patients with any degree of renal failure because hypermagnesemia may develop.\(^{(97,99)}\) If a decrease in the glomerular filtration rate exists, the dose of Mg should be halved, and the serum Mg concentration must be monitored daily. If hypermagnesemia ensues, therapy must be stopped. If the patient has normal renal function, the excess Mg will be excreted into the urine. Patients with severe Mg intoxication may be treated with intravenous calcium.\(^{(97,99)}\) The usual dose is an infusion of 100–200 mg of elemental calcium over 5–10 minutes. Dialysis may be required if the patient is in renal failure.\(^{(169)}\)

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MAGNESIUM DEFICIENCY


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