

12 Mg Magnesium	
20 Ca Calcium	21 Sc Scandium

Magnesium

Introduction

Although American diets generally do not contain adequate amounts of magnesium,¹ physiological magnesium deficiencies are more likely to occur in those on diuretics or high sodium diets,² with malabsorption syndromes,³ or with diabetes.⁴ Because magnesium plays such a diverse and essential role in human physiology, subclinical magnesium deficiency can manifest in symptoms such as fatigue and muscle weakness.³ Magnesium deficits can also exacerbate an already existing disease state or increase the risk of complications in specific conditions, including diabetes, cardiovascular conditions, renal stones, osteoporosis, hypertension, preeclampsia, and asthma.

Magnesium exists mostly as an intracellular cation with 99 percent of body stores in intracellular spaces. Approximately 66 percent is found in bone, and 33 percent in cardiac muscle, skeletal muscle, and liver.³

Pharmacokinetics

Absorption of magnesium is proportional to the amount ingested, with fractional absorption decreasing the larger the dosage. It is absorbed in both the small intestine and colon, with the distal jejunum and ileum the sites of most efficient absorption, via both active and passive transport. It is taken up in the cells by a carrier-mediated transport system and excreted via the kidneys.

Enteric-coated magnesium salts are less well absorbed than non-enteric-coated supplements.⁵ Salts with high solubility such as magnesium citrate appear to be better absorbed than less soluble forms such as magnesium oxide.⁶

Mechanisms of Action

Magnesium is involved in over 300 enzymatic reactions in the body, including ATP synthesis, protein synthesis, glycogen breakdown, fatty acid oxidation, and maintenance of membrane stability of the cardiovascular, neuromuscular, neuroendocrine, and immune systems.⁷ Magnesium plays a regulatory role in the sodium-potassium ATPase pump, with a magnesium deficiency impairing movement of potassium into the cell.⁴ This may explain the clinical phenomenon of hypokalemia that is remedied only when magnesium supplementation is used.⁸ Magnesium also acts as a calcium channel blocker, with magnesium deficiency resulting in increased intracellular calcium. Conversely, higher levels of magnesium inhibit

intra- and extracellular calcium flux.⁹ Magnesium affects parathormone (PTH) secretion; hypomagnesemia induces hypocalcemia as a chronic magnesium deficiency impairs PTH production.¹⁰ Magnesium deficiency also impairs the synthesis of 1,25(OH)₂ vitamin D and can lead to peripheral resistance to the effects of vitamin D as well as resistance to PTH.¹¹

Deficiency States and Symptoms

Magnesium deficiency may be precipitated by a multitude of factors, including acute renal tubular damage, diabetes,³ caffeine use,¹² cocaine use, alcohol abuse, malabsorption syndromes, short bowel syndrome, pancreatitis, diarrhea, laxative use, phosphorus depletion (found in eating disorders), parenteral feeding, hyperthyroidism, acute myocardial infarction, cardiac bypass surgery, major trauma, burns,³ and AIDS.¹³

The symptoms of magnesium deficiency are diverse and include cardiac arrhythmias,¹⁴ hypertension, vasospasm, electrocardiogram changes, and muscle fasciculations.¹⁵ Bronchospasm, muscle weakness, headache, hypokalemia, and insulin resistance also occur in non-critical patients with low magnesium.¹⁶

Clinical Indications

Asthma

Epidemiological evidence indicates a relationship between declining magnesium intake and increased prevalence of asthma.¹⁷ Children with asthma have lower leukocyte magnesium levels during bronchial obstruction and acute attacks compared to children without asthma.¹⁸ There is good evidence, in acute episodes, that intravenous magnesium acts as a large airway bronchodilator.¹⁹⁻²² Not only does magnesium have a relaxing effect on bronchial airways, it has a positive effect on reducing mast cell degranulation, pulmonary muscle contractility, and neuro-hormonal mediator release.²³ The majority of research has involved either intravenous or nebulized magnesium sulfate in acute asthma attacks and in chronic asthma.²⁴

A single-blind, placebo-controlled, cross-over study found significant reduction in airway resistance in stable asthmatics in response to 2.5 g intravenous magnesium sulfate.¹⁹ The effect lasted for 20 minutes post-infusion, which was the extent of the monitoring period. This work has been replicated by several researchers,^{25,26} and although no studies have looked at oral magnesium supplementation in asthma, there is a significant correlation between increased bronchial reactivity and lowered intracellular magnesium levels in asthmatics.²⁷

Several authors have suggested oral magnesium salts are beneficial in the treatment of asthma and other reactive airway diseases.^{17,23,24,28} Harari²⁴ studied 38 asthmatic patients who were treated at a clinic on the Dead Sea, an environment where both the water and the ambient air are high in magnesium and bromides. At the end of 28 days, all patients had experienced a significant decrease in their peak flow index, 36.8 percent had suspended their medications, and 43 percent had reduced the frequency of medication use.

Cardiovascular and Cerebrovascular Disease

Using a variety of assays for tissue magnesium stores, studies of patients with vasospastic angina, coronary artery disease, and cardiovascular mortality revealed low magnesium stores in the majority of those tested.²⁹

Ischemia-Reperfusion Injury

Magnesium has been shown to reduce ischemia-reperfusion injury in the myocardium.²⁹ When blood flow is re-established in ischemic tissue, free radicals and an influx of leukocytes can cause further damage to this tissue. Ischemia-reperfusion injury occurs in 23-27 percent of all patients receiving thrombolytic therapy during an acute myocardial infarction.³⁰ Magnesium can prevent and reverse free radical-mediated damage to the endothelium.^{30,31}

Stroke

Epidemiological evidence indicates risk for stroke and stroke-related mortality is reduced in populations that have magnesium-rich diets.³² A 1997 study found 98 of 105 stroke patients (many below age 55) had deficient levels of serum ionized magnesium.³³ The levels of magnesium in the study were found to cause rapid, prolonged, and often irreversible contraction and spasm of cultured, cerebral-vascular smooth muscle cells. Both animal and human studies have shown low magnesium levels correlate with greater cerebral infarct size.^{34,35}

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is particularly prevalent among women of childbearing age. A randomized study of 141 patients with echocardiogram-confirmed MVP found 60 percent had an abnormally low serum magnesium level (<0.7 mMol/L).³⁶ Seventy patients with low RBC magnesium levels received either oral magnesium supplementation or a placebo for a five-week period. The magnesium group received 1,800 mg/day of magnesium carbonate (510 mg of elemental magnesium) for the first week, then 1,200 mg/day of magnesium carbonate (340 mg of elemental magnesium) for the remaining four weeks. The average number of MVP symptoms in the patients treated with magnesium decreased from 10.4 to 5.6 after treatment. At the beginning of the study, anxiety was present in 54 percent of the supplemented patients and five weeks later was present in only 15 percent. The level of norepinephrine excreted in the urine also declined markedly after magnesium supplementation, and increased in the placebo group. The researchers concluded MVP symptoms were linked to magnesium deficiency in the study population and hypothesized the deficiency may be caused by an increased release of epinephrine and norepinephrine in MVP patients. The beneficial effect of magnesium was speculated to be a result of magnesium's ability to inhibit the toxic effects of an excessive release of catecholamines.

Hyperlipidemia

One uncontrolled, pilot study in 16 hyperlipidemic adults with abnormally low HDL (35.2 ± 8.7) found supplementation with magnesium chloride reduced total cholesterol an average of 40 points (from 297.6 ± 56.9 to 257.1 ± 39.1).³⁷

The author's proposed mechanism for magnesium's hypocholesterolemic effect is the ability of magnesium to partially inactivate the catecholaminergic response of the adrenal gland and sympathetic nervous system, diminishing lipolysis. Magnesium also increases lipoprotein lipase through a similar mechanism.

Hypertension

Magnesium has been effective in lowering elevated blood pressure in long-term diuretic users, those on high-sodium diets, in hypertension associated with diabetes, and those with high renin levels.^{38,39} Approximately 50 percent of magnesium-depleted subjects have hypertension that responds to restoration of normal serum magnesium levels.⁴⁰

Pregnancy

Magnesium is essential for the release of parathyroid hormone in pregnancy. Epidemiological studies show an inverse relationship between magnesium levels in drinking water and risk of stillbirth.⁴¹ Randomized studies are conflicting in their assessment of magnesium supplementation in pregnancy and its effects on preeclampsia, reduced risk of preterm labor, maternal hospitalization, and increasing birth weight.^{42,43} However, when given during pregnancy, magnesium sulfate reduces risk of eclampsia in women with pregnancy-induced hypertension.⁴⁴

Osteoporosis

Women with osteoporosis have demonstrated significantly low serum magnesium, evidence of magnesium depletion in magnesium loading test, and low levels of magnesium in bone tissue.⁴⁵⁻⁴⁷ Magnesium intake has been positively correlated with forearm bone mineral content in women aged 23-75.⁴⁸ Prospective studies of osteoporotic women given tolerance-dosed (up to 750 mg per day) magnesium hydroxide for two years resulted in significant increases in trabecular bone density in the wrist during the first year of the study. In the second year, the bone density measurements simply leveled off.⁴⁵

A trial in ovariectomized rats, shown to be a useful model for research relating to postmenopausal women, utilized a high-magnesium, high-calcium diet to evaluate the effect of magnesium on bone strength and bone resorption.⁴⁹ Magnesium supplementation at 0.15 percent of the total diet (the equivalent of 1,300 mg magnesium/day in an adult female) increased osteocalcin (a marker for osteoblastic activity), reduced parathyroid hormone and deoxypyridinoline (a bone resorption marker), and increased bone strength and fracture resistance of

the femur. Bone formation, prevention of bone resorption, and increase in dynamic strength of bone occurred even though intestinal calcium absorption was reduced in rats on the high-magnesium diet.

Magnesium supplementation also appears to have benefit in osteoporosis secondary to malabsorption in gluten-sensitive enteropathy (GSE).⁵⁰ In five patients with GSE and osteoporosis of the hip and spine, 500-575 mg magnesium hydroxide daily resulted in statistically significant increases in femoral neck and total proximal femoral bone density. This increase, which took place after two years, occurred along with an increase in erythrocyte magnesium levels.

Diabetes and Insulin Resistance

Diabetics, especially those with type 1 diabetes, are at risk for magnesium deficiency because glycosuria and insulin insensitivity increase renal loss of magnesium and decrease magnesium absorption from the intestine.⁵¹⁻⁵³ There is a positive correlation between elevations in glycosylated hemoglobin and the severity of magnesium deficiency in diabetes.⁴ Conversely, studies indicate magnesium supplementation improves glucose handling in nondiabetics and improves insulin sensitivity in type 1 and 2 diabetes.⁵⁴⁻⁵⁶

Magnesium deficiency appears to play a role in the development of diabetic retinopathy, as magnesium levels are lower in diabetics with retinopathy and magnesium deficiency states may contribute to circulatory damage that leads to microangiopathy.^{57,58}

Kidney Stones

Several studies have addressed the efficacy of both magnesium and citrate separately in the prevention of recurrent calcium oxalate stones.^{59,60} Citrate forms insoluble complexes with calcium, inhibiting the formation of calcium phosphate and oxalate stones.⁶¹ When citrate is given as a salt (in combination with sodium or potassium), it increases urinary pH, inhibiting uric acid stone formation.⁶² In idiopathic calcium-stone formers, low erythrocyte magnesium levels indicate possible magnesium deficiency as a factor in stone formation.⁶³

Magnesium supplementation alone has been shown to reduce oxalate levels in the urine and prevent recurrent stone formation. In a controlled study, 55 patients who had an average of 0.8 stones per year, were given 500 mg elemental magnesium daily.⁶⁴ After a period of 2-4 years, the rate of stone formation was reduced to 0.08 stones/person/year, a 90-percent reduction. Eighty-five percent of patients remained stone free during the trial. A control group of 43 patients experienced an increase in incidence of stone formation with 59 percent developing new stones in the four-year follow-up period. In another controlled trial, 45 out of 56 patients (80%) were stone free after 200 mg magnesium hydroxide twice daily for two years. In the control group, 44 percent experienced recurrences.⁶⁵

Magnesium and potassium, supplemented in combination as magnesium-potassium citrate, were able to produce a higher level of urinary citrate than either alone.⁶¹ An uncontrolled study in patients with calcium renal stones found magnesium-potassium citrate supplementation resulted in a significant decrease in the ability to form calcium oxalate stones in those with idiopathic calcium urolithiasis.⁶⁶ Patients were given magnesium-potassium citrate in doses that supplied 185 mg elemental magnesium with 22 mMol potassium daily. Uric acid levels in those patients decreased by 60 percent, urinary pH rose by 80 percent, and calcium oxalate formation declined significantly.

Headache

Migraine and cluster headaches have been associated with low free magnesium levels in the brain, with the lowest levels in those with the most severe migraine symptomology.⁶⁷ Multiple studies have also found low serum and erythrocyte magnesium levels in the majority of those with either migraine or cluster headaches.^{68,69} Magnesium has been used effectively intravenously for symptom relief, and oral supplementation of 360 mg elemental magnesium has shown relief in premenstrual migraine.^{70,71}

Physical Exertion/Altitude Sickness

Athletes are at risk for magnesium deficiency.⁷² An uncontrolled study of four mountain climbers reported significant improvement in altitude sickness symptom scores at 3,700-4,600 meter elevations after taking magnesium citrate at daily doses of 900-1,200 mg.⁷³ The climbers reported feeling less fatigue and muscular discomfort; no adverse effects were reported.

Chemical Toxicity

Magnesium is one of the most common nutrient deficiencies in those with environmentally-induced illness.⁷⁴ Patients found to retain chemical residues and heavy metals were also found to excrete high amounts of magnesium in their urine.⁷⁵ This deficiency leads to decreased cytochrome p450 and NADPH cytochrome reductase activity, both of which are essential for proper drug and chemical biotransformation. Magnesium deficiency, particularly in chemically toxic individuals, also limits metabolism of aniline and aminopyrene, both carcinogens. Supplementation with magnesium can reverse the effects of these deficits.⁷⁵

Premenstrual Syndrome

Some subpopulations of women with premenstrual syndrome (PMS) demonstrate low magnesium levels. In a double-blind, placebo-controlled study, women with PMS were given 360 mg magnesium three times daily or placebo from day 15 of their menstrual cycle until menses. Magnesium significantly improved some measurements of mood changes.⁷⁶

Fibromyalgia

Abnormalities in magnesium status have been noted in patients with fibromyalgia, including elevated hair magnesium,⁷⁷ high leukocyte magnesium, and low erythrocyte magnesium.⁷⁸ Supplementation of magnesium combined with malic acid has reduced severity of pain and tenderness associated with fibromyalgia.⁷⁹

Drug-Nutrient Interactions

Medications that cause magnesium deficiency include diuretics (especially loop diuretics), amphotericin-B, platinum-based chemotherapy, aminoglycosides, cyclosporine, and albuterol and other beta agonists.³

Digoxin causes increased urinary magnesium loss; this can be dangerous, as magnesium deficiency increases the toxicity of digoxin, which develops at significantly lower blood levels when the patient is magnesium deficient.⁸¹

Magnesium can interfere with the absorption of tetracyclines. It is advised to supplement with magnesium at a time of day other than when taking tetracyclines.

Side Effects and Toxicity

Dosages over 500 mg magnesium hydroxide or oxide have resulted in gastrointestinal disturbances and diarrhea (probably due to poor absorption), and may induce net phosphate loss.⁸⁰ Elevated blood levels of magnesium occur infrequently in renal insufficiency and in chronic use of magnesium-containing laxatives and antacids. Magnesium supplementation is contraindicated in renal insufficiency.³

Dosage

Therapeutic effects appear in oral dosages as low as 250 mg elemental magnesium in magnesium-deficient individuals but may need to be increased to 12 mg per kg body weight for therapeutic interventions.⁸² Both magnesium citrate and magnesium citrate-malate are significantly more soluble and absorbable than the oxide or hydroxide forms.^{6,83}

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