Magnesium[1]

Magnesium (Mg^{2+}) is an essential nutrient that is involved in many key metabolic reactions such as energy production, glycolysis, and the synthesis of nucleic acids and proteins. It is also important for oxidative, immune, and neuromuscular functions and bone development. Magnesium assists in maintaining electrolyte balance and calcium, sodium, and potassium homeostasis, all of which are essential for stabilizing excitable membranes (1). It acts as a calcium channel antagonist, stimulates the production of vasodilator prostacyclins and nitric oxide, and alters vascular responses to vasoactive agonists (2). The adult human body contains ~25 g of magnesium, ~50–60% of which resides in the bones; most of what remains is present in soft tissues, and <1% resides outside of cells (1).

Body magnesium is regulated physiologically through 3 main mechanisms: absorption through the gut, renal excretion after filtration and reabsorption, and exchange from the large pool of bone magnesium. Magnesium is relatively well absorbed by the gut; oral bioavailability varies from 35% to 70% (3) and depends on a variety of factors such as the form of the magnesium salt (organic compared with inorganic), its rate and extent of uptake from the intestine into the blood, and its transfer into tissues because magnesium is primarily an intracellular cation. The absorption rate increases when dietary intake is low (4)

On a daily basis, ~2.4 g of magnesium is filtered by the kidney at a rate proportional to the plasma concentration, and any excess is rapidly excreted. Adequate kidney function generally prevents toxic systemic and circulatory levels (4). Urinary magnesium is a relatively good indicator of magnesium intake, and urinary excretion <80 mg/d indicates a risk for magnesium deficiency (5).

Deficiencies

Magnesium deficiency, as measured by serum magnesium levels, due to low dietary intake in otherwise healthy people is uncommon. Although age can negatively affect systemic magnesium levels as absorption from the gut decreases and renal magnesium excretion increases. Hypomagnesemia, typically defined as a serum magnesium concentration <0.75 mmol/L, may result from a number of conditions, including chronic inadequate intake of magnesium, chronic diarrhea, malabsorption, chronic stress, alcoholism, and the use of medications such as diuretics, antacids, proton pump inhibitors, or aminoglycoside antibiotics (1). The most common symptoms of hypomagnesemia are somewhat nonspecific and include muscle weakness, muscle cramps, and increased irritability of the nervous system with tremors or muscle spasms. Symptoms are usually mild or not present when hypomagnesemia is between 0.5 and 0.7 mmol/L but become more apparent and/or severe when serum magnesium falls below 0.5 mmol/L (4).

Although overt signs of clinical magnesium deficiency have not been routinely recognized in the healthy population, relatively low magnesium intake and/or magnesium status have been associated with chronic health issues, including cardiovascular disease, type 2 diabetes, osteoporosis, pulmonary disease, depression, migraine headaches, inflammation, and tumor development (2, 6). In most cases, these observations did not correlate with a deficiency in serum magnesium, raising the question of the prevalence of "subclinical" magnesium deficiencies. Individuals within the normal serum magnesium range can be low in tissue magnesium, and others with adequate tissue magnesium can be low in serum magnesium. Thus, the concept of chronic latent magnesium deficit has arisen to describe those with low tissue magnesium levels who show serum magnesium in the normal range (4).

Diet Recommendation

Approximately half of the US population has been shown to consume less than the daily requirement of magnesium from foods (7). The 2015 Dietary Guidelines Advisory Committee considered magnesium to be a shortfall nutrient that was underconsumed relative to the estimated average requirement (EAR) for many Americans. In the 2007–2010 NHANES, the percentage of teens aged 14–18 y who consumed less magnesium than their EAR was 75% for boys and 87% for girls. Among elderly persons aged ≥71 y, these values were 79% for men and 70% for women.

Food Sources

Magnesium is present in fruits, vegetables, whole grains, legumes, nuts, milk, meat, fish, and in fortified foods such as breakfast cereals (1). Magnesium is also present in tap, mineral, and bottled waters at varying concentrations; however, most deionized bottled waters sold in the United States contain zero magnesium (1). Dairy foods have been identified as a key source of magnesium, contributing 17% of the magnesium in the diet for individuals aged >2 y (7). Nuts, seeds, and soy foods are also good dietary sources of magnesium. The 2011–2012 NHANES reported that 19% of persons aged ≥2 y consumed supplements with magnesium that varied from 5% to 37% in the various age and gender groups. In the adult population of dietary supplement users, 6% (4% of men and 7% of women) exceeded the tolerable upper intake level of 350 mg/d for magnesium (8). Mild gastrointestinal effects may occur in a small percentage of individuals at intake levels of 360–380 mg/d, although most individuals do not show such effects even when receiving substantially more than the upper intake level of 350 mg/d.

Clinical Uses

Intravenous magnesium sulfate is a mainstay for treating preeclampsia and has been shown to be effective for treating stroke, myocardial infarction, and asthma in several large clinical trials (6). Decreased magnesium absorption is associated with a number of clinical disorders. Like most disorders of the bowel, including acute or chronic diarrhea, gastritis, colitis, malabsorption and steatorrhea, and small bowel bypass surgery, magnesium losses from both the upper and lower gastrointestinal tract can induce hypomagnesemia and are common when intestinal secretions are incompletely reabsorbed (4).

There are some genetic polymorphisms that negatively affect magnesium absorption. Patients who carry mutations in the transient receptor potential melastatin type 6 gene will have decreased intestinal magnesium absorption and inappropriate renal magnesium wasting (2).

In clinical practice, total serum magnesium is most commonly used to assess the magnesium status of patients; however, this parameter does not necessarily reflect the true total body magnesium content because normal serum magnesium levels may be present despite intracellular depletion. Serum magnesium levels should be determined alongside serum sodium, potassium, and calcium measurements in patients. A noninvasive method of determining magnesium levels is to analyze urinary magnesium excretion. Because renal magnesium excretion decreases in response to deficiency (i.e., the kidneys retain more magnesium when stores are low), this is an important parameter along with serum magnesium for assessing magnesium status (9).

Toxicity

Serum magnesium levels >1.1 mmol/L are generally considered hypermagnesemic. In individuals with either intestinal or renal disease, hypermagnesemia can occur with supplemental magnesium (3). Symptoms may include nausea, vomiting, lethargy, headaches, and/or flushing. Cardiac and electrocardiogram changes occur above 2.5 mmol/L, and extreme hypermagnesemia (>5 mmol/L) can result in coma, respiration depression, or cardiac arrest (4).

Aside from osmotic diarrhea related to unabsorbed magnesium, there is no evidence that large quantities of oral magnesium are harmful to persons with normal kidney function. However, very large doses of magnesium-containing laxatives and antacids (typically providing >5 g/d magnesium) have been associated with magnesium toxicity (serum magnesium levels from 5.2 to 9.7 mmol/L) because of excessive oral intake (1).

Recent Research

Dietary intake and chronic disease. A secondary data analysis of the NHANES 2001–2010 evaluated magnesium intakes and diabetes-related outcomes and the risk of metabolic syndrome in 14,338 adults aged >19 y. Sufficient (i.e., meeting the EAR) dietary intake of magnesium from foods or from foods plus supplements was associated with higher HDL cholesterol and lower C-reactive protein, insulin levels, BMI, blood pressure, and a reduced risk for metabolic syndrome (10).

Magnesium transporter proteins. Much has been learned about the molecular identities of the magnesium-transporting proteins in recent years through genetic screening and microarray-based expression studies. Of prime importance are several proteins critical to magnesium homeostasis. These include transporters such as transient receptor potential melastatin type 7, magnesium transporter 1, and solute carrier family 41 member 1. Tissue-specific transporters, transient receptor potential melastatin type 6 (kidney, colon), cyclin M2 (kidney), and cyclin M4 have also been identified (2, 6).

Genetic variations. Serum magnesium has been shown to have a heritable component, with heritability estimates of ~30%. The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium recently evaluated single-nucleotide polymorphisms across the genome in association with serum magnesium (along with serum potassium and sodium) levels in 15,366 participants of European descent. The Cohorts for Heart and Aging Research in Genomic Epidemiology study identified 6 different genomic regions that contained variants associated with serum magnesium concentrations in humans. The identified single-nucleotide polymorphisms were also found to be associated with clinically defined hypomagnesemia and some with traits linked to serum magnesium levels, including kidney function, fasting glucose, and bone mineral density (11).

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