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Magnesium is an essential ion in the human body, playing an important role in practically every major metabolic and biochemical process, supporting and maintaining cellular processes critical for human life. Magnesium plays an important physiological role, particularly in the brain, heart, and skeletal muscles. As the second most abundant intracellular cation after potassium, it is involved in over 600 enzymatic reactions including energy metabolism and protein synthesis. Magnesium has been implicated in and used as treatment of several diseases. Although the importance of magnesium is widely acknowledged, routine serum magnesium levels are not routinely evaluated in clinical medicine. This review provides a discussion as to where magnesium is stored, handled, absorbed, and excreted. We discuss approaches for the assessment of magnesium status.

Key Words: Magnesium balance, Measurement, Homeostasis

INTRODUCTION

Magnesium (Mg^{2+}) is one of the most abundant ions in the earth's crust and has been recognized since ancient times. The name is derived from the Magnesia district in Thessaly (part of ancient Greece) where it was discovered. To this day, magnesium remains abundant in this region. In plants, magnesium is the central element in chlorophyll, similar to the role of iron in hemoglobin. Magnesium is an essential cation for health. Dr. Nehemiah Grew in 1697 identified magnesium sulfate ($MgSO_4$) as the major ingredient in Epsom salt.[1] Epsom salt was being extracted from a well in Epsom, England and used to treat abdominal pain, muscle strains, and cerebral edema. In 1755, Joseph Black recognized magnesium as an element. The role of magnesium in the human body emerged once it was first described in blood plasma by Willey Glover Dennis in the early 1900s. Magnesium deficiency was first described by Hirschfielder and Haury in 1934.[2]

Magnesium has been implicated in and used for the treatment of several diseases. Although the importance of magnesium is widely acknowledged, serum magnesium concentrations (sMg) are not routinely determined in clinical medicine. Hence, magnesium is frequently referred to as the "forgotten" cation. Unlike hormonal regulation of calcium by parathyroid hormone, there is minimal hormonal regulation of magnesium. Despite its importance, magnesium is referred to by some as the "orphan" cation. Increasing the awareness and understanding of magnesium homeostasis may focus greater clinical attention to its important role in health and disease.

MAINTENANCE OF MAGNESIUM HOMEOSTASIS

The human body is estimated to contain approximately 24 g (1 mol) of magnesium compared to 1000 g of calcium. The overwhelming majority of magnesium resides in the intracellular space. Magnesium is the second most common intracellular cation after potassium where a rather large concentration exists within the cell relative to serum such that small exchanges can lead to major repercussions on circulating levels. Bone accounts for 50-60% of the total body magnesium. However, only about one-third of the skeletal magnesium is exchangeable. The tightly bound proportion in bone may serve as a buffer supply.[3]

Extracellular magnesium accounts for only 1% of total body magnesium, and does not reflect total body stores. In plasma, 60% of magnesium exists in the ionized, free, active form, which is important for its physiologic functions; 30% is albumin-bound and 10% is complexed to serum anions such as phosphate and citrate.[3-7] US laboratories usually report magnesium concentrations in milligrams per deciliter (mg/dL). However, it may be reported in other units such as milliequivalents per liter (mEq/L) or millimole per liter (mmol/L).[8] The conversion factors are shown in Figure 1. The normal sMg concentration is 0.75 to 0.95 mmol/L (1.8-2.3 mg/dL), and a magnesium concentration of less than 0.75 mmol/L (1.8 mg/dL) is considered magnesium depletion.[8]

Serum magnesium concentration is regulated by the dynamic balance and interplay between intestinal and renal transport and bone exchange. To maintain constant plasma magnesium levels, the United States Food and Nutrition Board recommends a daily magnesium intake of 420 mg for men and 320 mg for women.[9] Dietary intake of magnesium-containing foods, such as peas, beans, spinach, nuts, seafood, vegetables, and seeds, is generally sufficient to meet the recommended daily allowance. Conversely, diets high in protein, fat, calcium, phosphorus, phytates, or alcohol decrease available magnesium and absorption.[10] Magnesium homeostasis depends on the collaborative actions of the intestine, responsible for magnesium absorption, bone that stores magnesium, and kidneys that regulate urinary magnesium excretion. Given a daily magnesium intake of 300 mg, the intestines absorb about 120 mg and secrete 20 mg resulting in a net absorption of approximately 100 mg. Intestinal absorption depends on 2 separate pathways: paracellular transport through a favorable electrochemical gradient and solvent-driven cellular uptake. The former is responsible for bulk magnesium absorption,

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and takes place primarily in the distal small intestine, whereas fine-tuning occurs in the cecum and colon via transcellular transport where transient receptor potential melastatin (TRPM) cationic channels 6 and TRPM7 magnesium channels facilitate luminal magnesium uptake by the enterocyte. TRPM6 is expressed along the entire length of the large intestine, whereas TRPM7 is more ubiquitously expressed and likely involved in cellular magnesium homeostasis.[11]

Despite this process, the intestine seems to have a limited role in regulating magnesium balance. In contrast to other minerals, intestinal magnesium absorption is poorly regulated and depends mainly on magnesium intake.[12,13] Gut absorption can range from 25% with ingestion of magnesium-rich diets to 75% when ingesting magnesium-poor diets. In contrast to calcium, magnesium transport in the colon is independent of 1,25-dihydroxyvitamin D_3 signaling.

As previously described, 50-60% of total body magnesium is stored in bone. Serum magnesium concentrations are closely related to bone metabolism. It has been hypothesized that the bone surface magnesium is continuously exchanged with blood magnesium.[14] In bone, magnesium ions bind at the surface of the hydroxyapatite crystals. Magnesium increases the solubility of phosphate and calcium in hydroxyapatite and thereby influences crystal size and formation.[15] Following prolonged magnesium deficiency, the mobilization of magnesium from bone also represents a potential homeostatic mechanism.[16] Magnesium plays a role in osteoblast proliferation; therefore, deficiency results in decreased bone formation. With a normal sMg concentration of 1.8 to 2.3 mg/dL and normal glomerular filtration rate, 70% of circulating magnesium (2400 mg) is filtered by glomeruli. About 2300 mg is reabsorbed along the kidney tubules by several coordinated transport processes and magnesium transporters. Only 30% of the filtered Mg is reabsorbed by the proximal tubule. The bulk of magnesium reabsorption, nearly 60%, occurs in the thick ascending limb of the loop of Henle. The distal convoluted tubule reabsorbs a relatively small proportion of filtered magnesium, but has an important role in the regulation of magnesium. The result is a net magnesium excretion of 100 mg. Thus, the kidneys primarily regulate magnesium homeostasis (See Fig. 2).

CLINICAL SUMMARY

- Understanding magnesium homeostasis may focus more clinical attention to its role in health and disease.
- Serum magnesium concentration is regulated by a dynamic balance between intestinal and renal transport and bone exchange.
- Serum magnesium measurement is the most available and commonly employed test to access magnesium status.

ROLE OF MAGNESIUM IN CELLULAR PHYSIOLOGY

Within the periodic table of elements, magnesium has the atomic number 12 and is classed as an alkaline earth element (group 2). It occurs in 3 stable isotopes: $^{24}Mg^{2+}$, $^{25}Mg^{2+}$, and $^{26}Mg^{2+}$. The former is the most common isotope (78.99%) and has a relative atomic mass of 24.305 daltons, a melting point of 648.8°C, and boiling point of 1090°C.[17]

Magnesium is highly water-soluble and the second most abundant cation in seawater.[18] In the dissolved state, it has 2 hydration shells, making its hydrated radius ~400 times larger than its non-hydrated radius. Magnesium is larger than that of other cations like sodium, potassium, and even calcium, perhaps explaining the difficulty of magnesium to pass through narrow biological channels that are readily traversed by calcium.[18] Consequently, magnesium must be dehydrated before passing through channels and transporters, a process that requires much energy.

Magnesium is the second most abundant intracellular cation after potassium, with typical concentrations of 10–30 mmol/L. However, since most of the intracellular magnesium is bound to ribosomes, polynucleotides, and ATP, the concentration of freely available magnesium falls within the low millimolar range (0.5-1.2 mmol).[19] In contrast to other abundant ions, for which cells maintain considerable transmembrane gradients, the free magnesium concentrations in the cell and extracellular fluid are comparable. Magnesium is a versatile ion that is involved in nearly every major metabolic and biochemical process within the cell. In general, the higher the metabolic activity of a cell, the greater its magnesium content.[11] Although a comprehensive review of all biochemical reactions and structural processes involving magnesium extends beyond the scope of this manuscript some of the fundamental homeostatic mechanisms are discussed.

Greater than 95% of intracellular magnesium is bound to proteins, negatively charged molecules, and ATP. Currently, enzymatic databases list over 600 enzymes for which magnesium serves as cofactor and an additional 200 enzymes in which it may act as an activator.[14,20] Cellular magnesium homeostasis is regulated by the combined action of several transporters. Mitochondrial RNA splicing 2 are considered to be the primary magnesium channels on the mitochondrial membrane. Knockdown of these genes has been proposed to reduce magnesium uptake in the mitochondria and cell death. In the nucleus, magnesium is involved in DNA stability and DNA repair and regulates the activity of the DNA and RNA polymerases. Overall, magnesium is a key factor in the maintenance of genomic and genetic stability.[21] Activation of growth factor receptors will increase magnesium uptake and release of membrane-bound magnesium, resulting in enhanced calcium release from the endoplasmic reticulum, an essential for cell growth and proliferation. In addition, the electrical properties of cell membranes are affected by any reduction of extracellular magnesium concentrations. Magnesium is a critical cofactor of Na^+-K^+-ATPase; therefore, hypomagnesemia can decrease the activity of

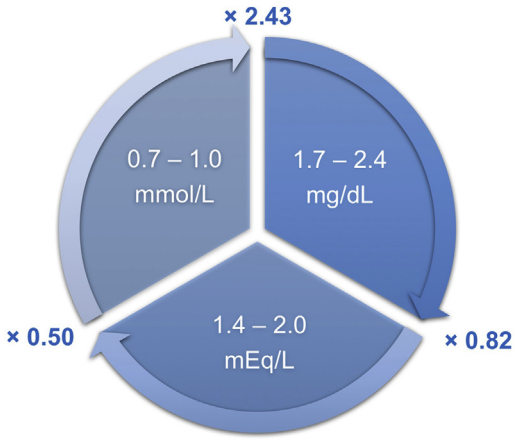

Figure 1. The atomic weight of elemental magnesium is 24.305 mg per millimole. To convert conventional units (US) in milligrams per deciliter (mg/dL) to milliequivalents per L (mEq/L), multiply by 0.82. Because magnesium is divalent, subsequent multiplication by 0.50 yields the magnesium concentration in International System of Units, millimoles per liter (mmol/L). Multiplication of the product yields the magnesium concentration in mg/dL.

this electrogenic membrane pump. Magnesium also regulates specific potassium channels that open in the absence of magnesium. Both properties decrease intracellular potassium, which depolarizes the cardiac myocyte membrane potential, increasing the probability for the generation of an action potential. Decreased intracellular potassium also decreases the speed of potassium efflux, resulting in a prolonged repolarization interval that may induce arrhythmias.[5] Magnesium availability is of prime importance in glucose metabolism, which may explain a pathogenetic role in diabetes mellitus type 2. Since kinases, ATPases, guanyl cyclases, and adenyl cyclases all depend on Mg-ATP for optimal cellular function, the role of magnesium extends farther than DNA and protein synthesis to virtually every process in the cell.

ASSESSMENT OF MAGNESIUM STATUS

It is difficult to evaluate the status of magnesium because of its intracellular nature. Consequently, the sMg concentration may not reflect intracellular magnesium availability. Knowledge of the state and distribution of magnesium within body compartments and the cell is fundamental to our understanding of magnesium metabolism and assessment of magnesium status. About 1% of the total body magnesium is present in serum and interstitial compartment. The intracellular magnesium is distributed among the soft tissues and skeleton in about a 1:1 ratio. It is not precisely known whether this intracellular magnesium is readily exchangeable with the serum or extracellular fluid, but it is evident that these reservoirs may be important in maintaining sMg levels. Similar to the distribution of potassium where a rather large concentration gradient exists within the cell relative to serum concentrations, small exchanges can have major repercussions on circulating levels. By contrast, intracellular calcium is relatively low, at least in soft tissues, so that serum calcium is not markedly affected by cellular redistribution. Current evidence indicates that the cellular free magnesium is highly mobile and controlled by various mechanisms within the cell. The fraction of the free form is a very small percentage of the total magnesium within the cell, but magnesium ion readily traverses the cell membrane.

Serum Magnesium

Measurement of sMg is the most available and commonly employed test to evaluate magnesium status. Magnesium levels have been measured by various techniques including photometry, fluorometry, flame emission spectroscopy, and the reference method, atomic absorption spectrometry. Photometric methods are most commonly used by clinical laboratories.[11,22-24] Serum is preferable to plasma as the anticoagulant constituents could be contaminated with magnesium or affect its assay. For instance, citrate binds not only calcium but magnesium and affects fluorometric and colorimetric procedures.[25] In addition, hemolysis, bilirubin, lipemia, high phosphate levels and delays in serum separation may influence magnesium measurements. sMg may be influenced by changes in serum albumin, other anionic ligands, and pH; however, correction for changes due to these factors is seldom done.[26] Clinical studies in patients with diabetes mellitus, alcoholism, or malabsorption syndromes have demonstrated low intracellular magnesium concentrations; however, sMg values have been reported to be within the normal range.[27,28] Accordingly, sMg concentration has not been validated as a reliable indicator of body magnesium status.[3]

Free (Ionized) Magnesium

In the last several years, ion-specific electrodes have become available for determining ionized magnesium in plasma. Some early evidence suggested that this may be a better index of magnesium status than total sMg. However, results from different instruments are not always in agreement as the electrodes are not entirely selective for ionized magnesium concentration, and a correction factor is required based on the ionized calcium concentration.[25,29] Only a few studies have been conducted to assess the validity of this approach.[30,31]

Intracellular Magnesium

Magnesium content in red blood cells, skeletal muscle, bone, and peripheral lymphocytes have been investigated as an index of magnesium status. Intracellular magnesium plays a critical role in enzyme activation within the cell, and measurement of intracellular magnesium has been considered more relevant physiologically. Several studies have shown poor correlation between sMg and intracellular levels.[32-34] Nuclear magnetic resonance techniques and fluorescence probes have been used to determine free magnesium in red blood cells, lymphocytes, and platelets.[27,28,35] As muscle contains nearly 30% of the total body magnesium content, this tissue may be appropriate to assess

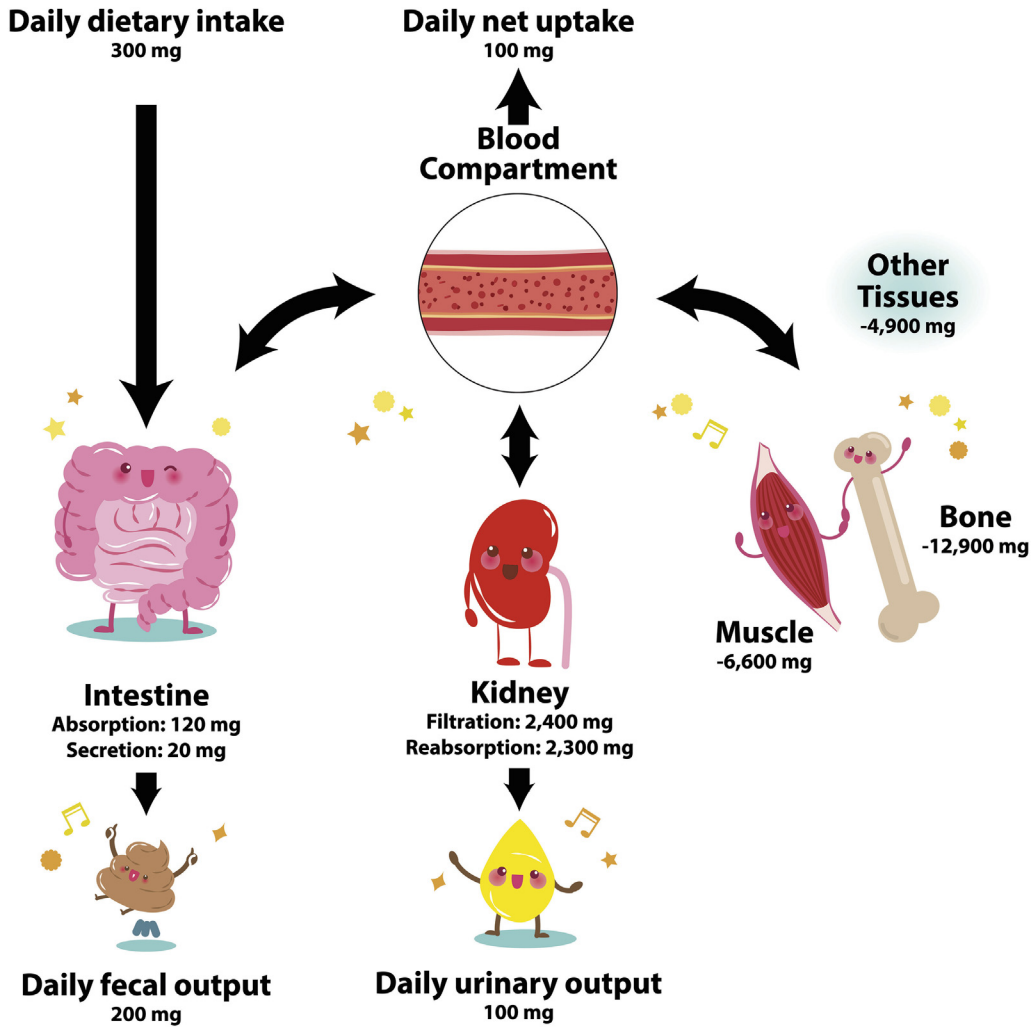

Figure 2. Magnesium homeostasis. Representative daily amounts of magnesium intake and excretion are shown. Dynamic magnesium fluxes among various tissue compartments are depicted. Overall, a daily net gut influx of ~100 mg magnesium is balanced by a renal magnesium excretion of 100 mg to maintain magnesium balance. During magnesium deficiency, other tissues such as bone and muscle provide magnesium to restore homeostatic concentrations.

magnesium status. Studies carried out in patients undergoing heart surgery showed that skeletal muscle magnesium was a better predictor of cardiac magnesium than lymphocyte or serum levels. However, this is an invasive and expensive procedure requiring special expertise. Current evidence is not sufficient to use intracellular magnesium levels as an indicator of status. Hair and teeth have also been used to assess magnesium status. The currently available evidence does not support the use of intracellular magnesium levels as an indicator of overall bodily magnesium status.[36]

Magnesium Tolerance Test and Magnesium Balance

The magnesium tolerance test has been used for many years, and represents an accurate means of evaluating magnesium status. The recommended dose is 2.4 mg per kg lean body weight. This test determines the percentage of magnesium retained after parenteral administration of magnesium. Magnesium-deficient persons demonstrate reduced excretion with less than 80% excretion of the administered magnesium load after 24 hours. In a study of 23 healthy subjects, 13 hypomagnesemic patients and 24 normomagnesemic patients at high risk of magnesium deficiency, the percentage of retention was 14% ± 4% (mean ± standard error of mean) in normal controls, 85% ± 3% in hypomagnesemic subjects, and 51% ± 5% in subjects at risk for development of magnesium deficiency. These data suggest that this test is a sensitive method for the detection of magnesium deficiency.[27,28,36,37] The test, however, depends on normal renal function, and is of limited value during renal magnesium loss. In the steady state, a 24-hour urine excretion of magnesium reflects intestinal absorption. The magnesium tolerance test is also of value in determining whether renal magnesium excretion is appropriate. Magnesium balance studies and studies using isotopes of magnesium are principally used in

research. In summary, no single method is satisfactory to assess magnesium status. The simplest, most useful, and readily available tests are the measurement of serum total magnesium and the magnesium tolerance test.

DISTURBANCES IN MAGNESIUM HOMEOSTASIS

Clinical interest in magnesium has grown over the last decade. Magnesium deficiency has been associated with a wide range of diseases including diabetes mellitus type 2, hypertension, and depression. Its therapeutic use has also been effective in conditions such as preeclampsia, ventricular arrhythmias, migraine headaches, asthma, and refractory status epilepticus.[21]

Hypomagnesemia

Hypomagnesemia is generally defined as sMg below 0.75 mmol/L. Patients may incur nonspecific symptoms such as depression, fatigue, muscle spasms, and muscle weakness. Consequently, specific diagnosis may be delayed. Widening of the QRS complex and peaking of T waves have been described with moderate magnesium depletion (0.4-0.7 mmol/L), while more severe magnesium depletion (<0.4 mmol/L) can lead to prolongation of the PR interval, progressive widening of the QRS complex, and diminution of the T wave. The normal renal response to magnesium depletion is to lower magnesium excretion to very low levels. Thus, daily excretion of more than 10 to 30 mg or a fractional excretion of magnesium above 2% in a subject with normal renal function signifies renal magnesium wasting due, for example, to drugs such as diuretics, aminoglycosides, or cisplatin. Severe magnesium depletion (<0.4 mmol/L) may lead to ventricular arrhythmias, tetany, and seizures.[38] It is beyond the scope of this review to discuss disturbances in potassium and calcium handling due to hypomagnesemia.

Hypermagnesemia

Hypermagnesemia is generally defined as serum magnesium levels above 1.1 mmol/L. Hypermagnesemia may cause nausea, vomiting, lethargy, headaches, or flushing. When magnesium levels exceed 3.0 mmol/L, severe electrocardiographic abnormalities that are characterized by bradycardia, hypotension, and prolongation of the QRS, PR, and QT intervals may be encountered.[5] Extreme hypermagnesemia may therefore result in coma, asystole, and cardiac arrest. To date, no congenital or genetic disorders of hypermagnesemia have been identified. Table 1 lists common causes of hypomagnesemia and hypermagnesemia.

Table 1. Causes of Hypomagnesemia and Hypermagnesemia

Hypomagnesemia	
Gastrointestinal Losses	Renal Losses
Marked dietary deprivation	**Medications**
Diarrhea, malabsorption, and steatorrhea	Loop and thiazide-type diuretics
Small bowel bypass surgery	Aminoglycoside antibiotics
Medications	Amphotericin B
Proton-pump inhibitors	Cisplatin
Genetic disorders	Pentamidine
Primary intestinal hypomagnesemia with secondary hypocalcemia	Cyclosporine
Acute pancreatitis	**Alcohol-induced tubular dysfunction**
	Hypercalcemia
	Volume expansion
	Genetic disorders
	Bartter/Gitelman syndrome
	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
	Autosomal dominant/ recessive isolated hypomagnesemia
Hypermagnesemia	
Kidney disease	
Magnesium infusion	
Massive oral ingestion	
Magnesium enemas	
Miscellaneous	
Usually mild	
Some cases of primary hyperparathyroidism	
Familial hypocalciuric hypercalcemia	
Hypercatabolic states, such as the tumor lysis syndrome	
Lithium ingestion	
Milk-alkali syndrome	
Adrenal insufficiency, perhaps due to volume depletion and hemoconcentration	

CONCLUSION

Magnesium homeostasis depends on its uptake in the intestine, storage in bone tissue, and excretion by the kidneys. Despite recent advances in understanding magnesium physiology, magnesium levels are still not routinely evaluated in daily clinical practice. We contend that sMg should be determined as part of standard practice, alongside routine sodium, potassium, and calcium measurements. This strategy facilitates the detection of magnesium disturbances and application of effective treatment strategies. Measurement of sMg should be routine for critically ill patients, where hypomagnesemia is common and associated with poor outcomes. Magnesium has been considered as a treatment for several major diseases including preeclampsia, stroke, myocardial infarction, and asthma in several large-scale clinical trials over the last few decades. These observations have triggered interest in magnesium among several research fields, including the heart, brain, and lungs. Magnesium will never again be "a forgotten cation."

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