Magnesium Balance and Measurement

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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