Magnesium: The Fifth But Forgotten Electrolyte

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Magnesium (Mg) is the second most abundant intracellular cation and is a cofactor in more than 300 enzymatic reactions involving energy metabolism and protein and nucleic acid synthesis. Ionized Mg is the physiologically active form of the element. Protein-bound and chelated Mg buffer the ionized pool. Approximately half the total Mg in the body is present intracellularly in soft tissue, and the other half is present in bone. Less than 1% of the total body Mg is present in blood. However, the majority of our clinical laboratory information comes from the determination of total Mg in serum. Currently, the clinical laboratory evaluation of Mg status is limited primarily to the total serum Mg concentration and a 24-hour urinary excretion. Instrumentation to determine ionized Mg in serum (ion-selective electrode) and in soft tissue (nuclear magnetic resonance spectroscopy) should be available in the near future. Magnesium may be a factor in the treatment of acute myocardial infarction and the rate of atherosclerosis. Chronic changes of Mg status, that may be latent, are poorly understood and require a better knowledge of ionized Mg metabolism. (Key words: Magnesium; Metabolism; Laboratory tests; Hypomagnesemia) Am J Clin Pathol 1994;102:616–622.

Opinions vary concerning the importance of magnesium (Mg) in health and disease. The most frequent contact with this element is the total serum Mg concentration. Some clinicians view the total serum Mg concentration as “the fifth electrolyte,” needed in every patient, whereas others advocate it only in selected patients. Why this ambiguity about the importance of Mg in clinical medicine? In my opinion, the answer rests primarily in the location and equilibrium of this element in the body and in the absence of tests to assess ionized Mg and total body Mg status. There is less information about the factors that control Mg and its physiological role than there is about the other major cations. As a result, some overlook Mg, whereas others believe it has a major role in health and disease and should be added to the standard four electrolytes (sodium, potassium, chloride, and total carbon dioxide) determined on most patients (ie, the fifth electrolyte).

The future will bring a better understanding of Mg in health and disease. Ongoing clinical studies are answering important questions about Mg in certain diseases, particularly the diseases of the cardiovascular system. Breakthroughs in technology soon should provide new tests to determine ionized Mg. This paper will highlight some of these recent developments as the basics of Mg metabolism, the assessment of Mg status, and the role of Mg in certain diseases are reviewed.

BASICS OF MAGNESIUM METABOLISM

Magnesium is an element with an atomic number of 12 and a mass of 24.32 daltons. It is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. Magnesium serves as a cofactor for about 300 cellular enzymes, many of which involve energy metabolism. Magnesium also plays a role in protein and nucleic acid synthesis within the cell, which is its primary site of action. Information on state and equilibrium, distribution, nutrition, and absorption and excretion of Mg are reviewed.

State and Equilibrium

Magnesium is present in three different states in most biological systems: ionized (free), complexed to anions, and bound to protein. Because protein-bound and complexed Mg are unavailable for biochemical processes, only ionized Mg has biological activity. The ultrafiltration of serum is an example of the separation of Mg based on state; protein-bound Mg does not penetrate the filter, but free and complexed Mg do penetrate the filter.

Equilibrium among most tissue pools for Mg is reached slowly, if at all. Three studies using 28Mg found that the biological half-life for the majority of Mg in the body is between 41 and 181 days. This is particularly important to remember for the interpretation of laboratory data about Mg (ie, the total Mg concentration of a tissue, for example) may not provide information about the Mg status of other tissue pools, because equilibrium occurs slowly.

Distribution

The distribution of Mg among the body compartments of a 70-kg human is shown in Table 1. On the average, the human body contains approximately one mole of Mg. About half the Mg is present in bone, and the other half is intracellular in soft tissue and muscle (Table 1). Less than 1% of the total body Mg is present in blood. Thus, when Mg analyses are performed on serum or cellular elements of blood, the results relate to a small fraction of the total body Mg.

Nutrition

Although humans have an absolute requirement for Mg, there is controversy concerning the recommended dietary al-
lowance (RDA) of Mg for adults. In 1989, the Food and Nutrition Board, Commission on Life Sciences of the National Research Council, determined the RDA for Mg to be 4.5 mg/kg/day for adults. This value was based primarily on a review of balance studies and the intake of Mg by the U.S. population. In previous reports that were reviewed by the Research Council, Seelig recommended an optimal daily intake of Mg between 6 to 10 mg/kg/day based on her review of the literature. The key question is whether metabolic balance studies for Mg are a suitable estimate for the RDA. Based on our current knowledge of Mg metabolism, this question is difficult to answer. However, because the absorption of Mg by the gastrointestinal tract is inversely related to intake and total body Mg status, the information from balance studies may not be suitable to estimate the RDA. A large study conducted by the U.S. Department of Agriculture found that only 25% of the surveyed population (n = 37,785) had a Mg intake at or greater than the RDA, whereas 15 other studies found the average dietary intake of Mg at some fraction of the RDA.

The intake of Mg is related to the composition of food in the diet and the Mg concentration in the drinking water. The intake of Mg generally is directly related to caloric consumption, provided the majority of calories is not from refined sugars or alcohol. Cereal grains, nuts, legumes, and chocolate are relatively high in Mg; vegetables, fruits, meats and fish are intermediate; and dairy products and beverages are low in Mg. Refining or processing of food may greatly deplete Mg content. For example, the refining and processing of wheat to flour, rice to polished rice, and corn to starch depletes Mg by 82%, 83%, and 97%, respectively. The increase in the processing of food during this century has effected a decrease in the average daily intake of Mg from 410 mg/day in 1910 to less than 300 mg/day at present. Thus, modern food technology partially explains why a significant segment of the population has an intake of Mg below the RDA and may be predisposed to chronic, latent Mg deficiency.

Drinking water may be an important source of Mg. The majority of drinking water in the United States contains less than 10 mg/L of Mg. There are a few areas in the Midwest where the Mg concentration in water exceeds 10 mg/L. Studies in several countries have shown an inverse correlation between the Mg concentration of the drinking water and the prevalence of cardiovascular mortality. These population studies were the first to link Mg deficiency to cardiovascular disease. Later in the review, this relationship will be discussed further. Absorption and Excretion

Studies have focused on the gastrointestinal site for the absorption of Mg and the relationship between intake and fractional absorption. Early studies using a liquid cocktail containing Mg concluded that Mg was uniformly absorbed throughout the small intestine. More recent studies indicate that the majority of Mg is absorbed in the ileum and colon. Research shows an inverse curvilinear relationship between intake of Mg and fractional absorption, which ranges from 65% absorption at a low intake to 11% absorption at a high intake. Clinically, this suggests that treating Mg deficiency with oral supplementation may require an extended period.

The kidney is the major excretory organ for Mg and is primarily responsible for the control of the serum Mg concentration. Approximately 70% to 80% of plasma Mg is filtered through the glomerular membrane. The reabsorption of Mg along the nephron differs from that of the other major electrolytes. Only about 20% to 30% of the filtered Mg is absorbed along the proximal tubule, which is less than that for sodium, potassium, and calcium. Mg is unique because more than 50% of the filtered Mg is reabsorbed along the thick ascending limb of the Loop of Henle. Only about 6% of the filtered Mg (120-150 mg/24 hours) appears in the urine each day because of the effect of tubular reabsorption by the kidneys. There is a circadian rhythm to the excretion of Mg by the kidney, with the maximum excretion occurring at night.

ASSESSMENT OF MAGNESIUM STATUS

Assessing Mg status is problematic because there is no simple, rapid, and accurate laboratory test to indicate total body Mg status. For the past several decades, the clinical chemistry laboratory has offered two tests to assess Mg status: the total serum Mg concentration and Mg excretion in urine. These two tests address the “throughput” of Mg, but do not provide meaningful information about intracellular Mg. There are several other tests that may be of value to assess Mg status. These tests can be organized into three groups: tissue Mg, physiologic assessment of Mg, and ionized Mg (Table 2).

### Tissue Magnesium

Determinations of total Mg in tissue, primarily serum, have yielded most of the data on Mg. Red blood cells (RBCs), mononuclear blood cells (MBCs), and muscle have also been used to assess Mg status. These four tissues predominate the Mg data because of the ease of blood and muscle specimen collection. Assays for total tissue Mg have two difficulties: the physiologically active component of Mg (ionized Mg) cannot be specifically determined, and information about the total Mg concentration in one tissue may not provide information about other body pools of Mg.

**Serum.** The optimum specimen for determining Mg is

### Table 1. Distribution of Magnesium in the Adult Human

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Body Weight</th>
<th>Concentration</th>
<th>Content</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kg wet weight)</td>
<td>(mmol/kg wet weight)</td>
<td>(mmol)</td>
<td>Body Magnesium</td>
</tr>
<tr>
<td>Serum</td>
<td>3.0</td>
<td>0.85</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>2.0</td>
<td>2.5</td>
<td>5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>22.7</td>
<td>8.5</td>
<td>193.0</td>
<td>19.3</td>
</tr>
<tr>
<td>Muscle</td>
<td>30.0</td>
<td>9.0</td>
<td>270.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Bone</td>
<td>12.3</td>
<td>43.2</td>
<td>530.1</td>
<td>52.9</td>
</tr>
<tr>
<td>Total</td>
<td>70.0</td>
<td></td>
<td>1,000.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>
serum, rather than plasma, because an additive such as an anticoagulant could be contaminated with Mg or affect the assay procedure. Because the Mg concentration in RBCs is approximately three times greater than that in serum, it is important to prevent hemolysis and to harvest the serum promptly. The serum Mg concentration is increased by .05 mmol/L with the lysis of RBCs to effect a serum hemoglobin concentration of 1 g/L. 27

A reference system for Mg has been established by the National Reference System for Clinical Laboratory Standards of the National Committee for Clinical Laboratory Standards (NCCLS). The definitive method for Mg is isotope dilution/mass spectrometry, and the reference method is flame atomic absorption spectrometry (FAAS). Standard reference material (SRM) 929 is a preparation of Mg gluconate dihydrate available from the National Institute for Standards and Technology (Gaithersburg, MD). Furthermore, SRM 909 is a human serum with certified values for many analytes, including Mg. The determination of the total serum Mg includes three states: approximately 60% is ionized, nearly 33% is bound to protein, and the remaining 7% is complexed to phosphate, citrate, and other anions. 28-29 Approximately 75% of the protein-bound fraction is bound to albumin and the remaining 25% to globulins. 29 The total serum Mg concentrations (determined by FAAS) in a U.S. population were normally distributed, with the central 95 percentile for adults (aged 18-74) between .75-.96 mmol/L. 30 Even though the reference method for Mg is FAAS, only about 1.3% of clinical laboratories use this methodology. 31 Most clinical laboratories rely on a colorimetric method, using primarily calmagite or methylthymol blue as the chromophore. 32 The colorimetric procedures are more susceptible to interference by endogenous and exogenous compounds compared with FAAS. 33

The total serum Mg concentration, imperfect as it may be, is the entry level test to evaluate Mg status in humans. The serum Mg concentration is primarily controlled by the kidney and the dietary intake of Mg. With the exception of bone, the total serum Mg concentration has not been shown to correlate with other tissue pools of Mg. 34 In a study of 14 patients, Alfrey and colleagues found a correlation coefficient of .96 between bone and total serum Mg concentrations. 35 These results have not been confirmed by other investigators. However, a portion of the bone Mg pool is labile and available to partially support the serum Mg concentration in states of chronic Mg deficiency. 36 The serum Mg concentration may be of relatively acute changes in the intake or excretion of Mg. For example, in a patient treated with furosemide, a loop-blocking diuretic, the concentration may decrease suddenly. However, the relationship between the total serum Mg concentration and the total body Mg status of a patient is difficult to interpret for several reasons (eg, state, distribution, equilibrium, etc.). 37 For chronic changes in Mg status, the serum Mg concentration provides essentially no information. Thus, the primary value of the total serum Mg concentration is to determine acute changes in Mg status or establish a baseline value.

Red blood cells: The total RBC Mg concentration may be determined directly or indirectly using the total Mg concentration of whole blood and the hematocrit. Deuster and colleagues evaluated three methods (two direct and one indirect) for determining total Mg in RBCs and concluded that an indirect method using nitric acid to lyse the cells was reproducible, reliable, accurate, and easy to perform. 38 Nuclear magnetic resonance spectroscopy (NMRS) has been used to determine ionized Mg in RBCs. 39 The total RBC Mg concentration does not correlate with other tissue pools of Mg. Three studies found no correlation between total serum and total RBC Mg concentrations in normal individuals. 30 Six studies have documented no correlation between total RBC and total mononuclear blood cell (MBC) Mg concentrations in normal individuals. 34 One study found no correlation between total muscle and total RBC Mg. 35 However, the ionized RBC Mg was significantly greater in control subjects with a normal total serum Mg concentration than in hypomagnesemic patients. 40 Furthermore, when control individuals were given a low-Mg diet, there was a progressive fall in the total serum and ionized RBC Mg concentrations. 40 Thus, the ionized RBC Mg concentration deserves further study.

Changes in total RBC Mg have been linked to the following three diseases: hypertension, the premenstrual syndrome (PMS), and the chronic fatigue syndrome (CFS). There is conflicting information for total and ionized Mg in essential hypertension. An increase and no change have been reported for the total RBC Mg concentration in patients with essential hypertension compared to normotensive controls. 41,42 For ionized RBC Mg in essential hypertension, one study found a significant decrease, and another found no significant change compared to normotensive controls. 42,43 Three groups have found a decrease in total RBC Mg in women with PMS. 44-46 In a double-blind, randomized study, women with PMS who received an oral Mg preparation (1,080 mg of elemental Mg/day) showed improved symptoms over those who received placebo. 47 Lastly, patients with CFS had a significant decrease in total RBC Mg and benefited from intramuscular Mg. 48 Another study assessed Mg status in patients with CFS and in controls using the Mg retention test (see below) and found no difference between the two groups. 49 Thus, there may be a relationship between RBC Mg and the three diseases previously described, but more research is needed to understand this relationship.

Mononuclear blood cells: The use of the total MBC Mg test as a surrogate for the estimate of intracellular Mg was proposed by Ross and colleagues at the Second International Magnesium Symposium in 1976. 50 Several studies with normal individuals have not shown a correlation between total MBC Mg and that of serum or RBCs. 51 Two studies found a correlation between total MBC Mg and total muscle Mg in humans. Dyckner and Wester initially found a correlation (r = .74) between total MBC Mg and total muscle Mg concentrations with nine indi-
individuals (3 controls and 6 patients with hypertension), but the correlation became nonsignificant \((r = .22)\) when 16 patients with congestive heart failure were added to the study.\(^5\) Sjögren and colleagues found a significant correlation between total MBC Mg and total muscle Mg in patients with type I diabetes mellitus.\(^5\) Studies with rats depleted by administration of furosemide did not find a correlation between total MBC Mg and total cardiac or skeletal muscle Mg concentration.\(^5\) Additional studies are needed to determine the relationship between total MBC Mg and total muscle Mg. Thus, the value of the total MBC Mg test has yet to be determined.

**Muscle**: Muscle is an appropriate and important tissue for the assessment of Mg status because it contains approximately 27% of the total body Mg (Table 1). However, relatively few studies have determined total muscle Mg in humans because of the special skills and expense of the assay, which involves needle biopsy of the muscle, preparation of the tissue, and determination of Mg by FAAS.\(^5\) Several studies have documented a lack of correlation between muscle and serum or RBC total Mg concentrations.\(^5\) As indicated previously, the correlation between muscle and MBC total Mg for humans is equivocal. More promising is the use of NMRS to determine ionized Mg noninvasively in muscle in vivo. Thus, at present, total muscle Mg is a research test.

**Physiologic Assessment of Mg**

Tests in this category assess the physiologic balance of Mg in the individual. For accurate results, the individual should be free of medication that affects Mg metabolism. The following four tests can be included in this category: balance studies, isotope studies, renal excretion of Mg, and the Mg retention test. The first two techniques will not be discussed because they are limited to research and unavailable to the clinical laboratory.

**Renal excretion of magnesium**: A 24-hour urine specimen is required to accurately assess renal Mg excretion because it follows a circadian rhythm for excretion.\(^5\) Furthermore, it is important to add an acidifying agent to the specimen container before adding urine to prevent precipitation of Mg salts at alkaline pH. The results for this test depend on intake, absorption, and excretion of Mg. This test is of value for documenting Mg wasting by the kidney due to medication or aberrant kidney function. The daily normal renal excretion of Mg in humans is 3.6 ± 1.4 mmol for females and 4.8 ± 1.5 mmol for males.\(^5\) The difference between the sexes is essentially eliminated if the excretion results are expressed as the ratio of Mg to creatinine.\(^5\) Thus, this test can help document aberrant renal excretion of Mg.

**Magnesium retention test**: Measuring the percentage of Mg retained after parenteral administration of a Mg load is becoming a more popular method to diagnose total body Mg deficiency. Two studies have described the method and have established a reference interval for normal individuals.\(^5\) Three studies have reported an increase in the percentage of Mg retained, indicating a Mg deficit in patients, with a normal total serum Mg concentration.\(^5\) This test apparently assesses loss of Mg from the major exchangeable pool of Mg, bone. Cohen and Lao found a significant inverse correlation \((r = -0.992)\) between the results of the Mg retention test and the concentration of Mg in bone.\(^5\) Thus, this test appears to have clinical value for assessing Mg deficit primarily from bone. However, standardizing the dose of Mg, the length of time for infusion, and the length of time for collection of urine would improve the precision of the test and facilitate comparison of results among different studies.

**Ionized Magnesium**

The key to advancing our knowledge about magnesium metabolism is an assay that can determine ionized magnesium, the physiologically active fraction, in tissue and body fluids. To date, there is a limited amount of research data assessing ionized magnesium. The following three technologies appear promising for determining ionized magnesium: ion-selective electrodes, fluorescent probes, and NMRS.

**Ion-selective electrodes**: The art of developing an ion-selective electrode for magnesium is to synthesize an ionophore and place it in an appropriate membrane that has sufficient selectivity for magnesium. For the past 20 years, Dr. Wilhelm Simon and his staff at the Swiss Center for Chemical Sensors in Zurich, Switzerland, have evaluated approximately 200 different ionophores for magnesium.\(^5\) Some of the more recent ionophores seem suitable for an ion-selective electrode to determine magnesium in serum, plasma, or whole blood. At present, three companies (AVL in Schaffhausen, Switzerland, Kone in Espoo, Finland, and NOVA in Waltham, MA) are developing an ion-selective electrode for clinical use. In May 1993, the NOVA electrode was approved by the Food and Drug Administration for clinical use and is now on the market in this country. Early reports about these electrodes are favorable.\(^5\) However, each of these electrodes makes a correction to the ionized magnesium concentration based on the ionized calcium concentration. This indicates the difficulty in producing an ionophore and membrane for magnesium that are relatively free from interference by calcium. Thus, ion-selective electrodes for determining magnesium in serum, plasma, and blood are available. The future will determine the accuracy of these measurements and their relevance to patient care.

**Fluorescent probes**: Fluorescent probes are a relatively new research tool to determine intracellular ionized magnesium concentration. In the early 1980s, Tsien synthesized several compounds that would selectively bind calcium and undergo spectral changes.\(^5\) These compounds, fluorescent probes, have significantly advanced our understanding of the physiology of intracellular calcium. In 1989, Raju and colleagues modified one of the initial calcium probes, fura-2, to improve selectivity for magnesium.\(^5\) The compound furaptra (mag fura-2) exhibits a shift in the peak excitation wavelength for fluorescence when bound to magnesium or calcium. Thus, the change in fluorescence corresponds to the ionized magnesium and calcium concentrations weighted by their respective dissociation constants. These probes for Mg work within the cell, because the ionized calcium concentration is a small fraction of the ionized magnesium concentration. The acetoxymethyl ester form of furaptra crosses the cell membrane by passive diffusion. Once inside the cell, endogenous esterases deesterify the probe to the salt form, which binds magnesium. Determined with this probe, the cytosolic ionized magnesium concentration of isolated rat hepatocytes was 0.59 mmol/L.\(^5\) Other fluorescent probes for ionized magnesium have been described.\(^5\) London has reviewed the use of fluorescent probes, mainly mag fura-2, for the determination of intracellular ionized magnesium.\(^5\) At present, this technique is limited to the research laboratory, but may have a future place in the clinical laboratory.
Nuclear magnetic resonance spectroscopy. The technology of nuclear magnetic resonance spectroscopy permits an estimate of ionized magnesium noninvasively in vivo in humans or with tissue specimens in vitro. Although several isotopes (19F, 23Mg, and 31P) have been used to estimate ionized magnesium with this technology, the alpha and beta phosphate moieties of adenosine 5'-triphosphate (ATP) have been used most frequently. The ionized magnesium concentration is inversely related to the distance between the alpha and beta phosphate peaks on the NMRS spectrum. Two studies that used this technique to measure ionized magnesium in erythrocytes were cited previously. At present, we are using this technology to determine noninvasively ionized magnesium in the calf muscle of normal individuals and patients using a 4.0-Tesla NMRS system. Thus, this technology may be able to provide a good assessment of the intracellular ionized magnesium concentration without significant discomfort for the patient.

ROLE OF MAGNESIUM IN DISEASE ENTITIES

As more knowledge about magnesium metabolism has accumulated, the list of diseases possibly affected by altered Mg metabolism has increased. Some of the diseases that have been linked with a disorder of Mg metabolism are the following: cardiovascular disorders (acute myocardial infarction, atherosclerosis, hypertension, and arrhythmias), diabetes mellitus, alcoholism, aldosteronism, hyperthyroidism, renal tubular disorders, PMS, and CFS. Two diseases (acute myocardial infarction and atherosclerosis) for which there is recent information related to Mg deserve further comment.

Acute Myocardial Infarction

Intravenous magnesium therapy in patients with an acute myocardial infarction may reduce early mortality. Teo and colleagues did a meta-analysis of trials evaluating intravenous magnesium in suspected acute myocardial infarction from seven different groups of investigators. The collective results for the seven trials showed 25 (3.8%) deaths among 657 patients who received magnesium therapy, and 53 (8.2%) deaths among 644 patients who served as controls. This represents a 55% reduction in the odds of death (P < 0.001). The results of a recent trial by Woods and colleagues with 2,316 patients with suspected acute myocardial infarction who received either intravenous magnesium sulfate or physiologic saline showed a relative reduction of 24% of early mortality, which was independent of thrombolytic or antiplatelet therapy. The possible mechanisms by which magnesium may prevent early mortality in acute myocardial infarction have been explored. Thus, there is convincing evidence that the intravenous administration of magnesium at the time of an acute myocardial infarction will reduce early mortality.

Atherosclerosis

The rate of atherosclerosis may be related to Mg status. An inverse correlation between the hardness of drinking water and the incidence of cardiovascular disease was first reported by Kobayashi in 1957. Several additional studies have documented an inverse relationship between the Mg concentration of drinking water and cardiovascular mortality. In addition, a number of animal studies have documented an inverse relationship between the Mg content of the diet and the rate of atherosclerosis. Two recent studies have provided some insight into the relationship between Mg and the atherosclerotic process. Both of these studies found that Mg deficiency effects a proinflammatory condition with an excessive production of oxygen-derived free radicals. Further, there was greater susceptibility of lipoproteins to peroxidation with a state of magnesium deficiency. Thus, a state of chronic latent magnesium deficiency seems to favor free radical production and oxidation of lipid moieties. Previous studies have indicated that it is the oxidized form of cholesterol in low-density lipoprotein that is atherogenic. Thus, magnesium may be a factor in the atherosclerotic process.

In the past, Mg may have been forgotten, because the knowledge of other elements has been greater and more directly related to clinical medicine. As our knowledge about Mg increases and technology permits us to determine the ionized fraction, the importance of Mg for health and disease will be clearer.

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REFERENCES


