Magnesium in Health and Disease

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Abstract

This paper reviews the significance of magnesium (Mg) in health and disease. Mg is an intracellular element and after potassium, second most abundant cation found within the cell. Plasma contains less than 1% of body’s total Mg. Physiologically most active form of Mg is ionized fomu. Most of the plasma Mg is bound with albumin, globulin and proteins. This bound form of Mg is not available for biochemical actions. Binding of Mg with the specific globulin fractions may be indicative of certain disease patterns. Deficient serum Mg concentration may be a sign of various pathologies. Thus, the repletion of Mg may be helpful in the treatment of diseases such as hypertension, acute myocardial infarction and atherosclerosis. Role of Mg for the treatment of chronic disease, however, is poorly understood and requires a better knowledge of ionzed Mg metabolism.

Introduction

Magnesium (Mg) is the fifth major electrolyte (after sodium, potassium, chloride and bicarbonate), found in the plasma. It is involved as a co-factor in the catalysis of more than 300 metabolic reactions including synthesis of DNA,, RNA and proteins. After calcium, it is the second most abundant divalent cation present in serum. Some of its functions are described in Table 1.

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<th>Table I. Biological functions of magnesium.</th>
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<td>Relaxation of smooth muscle¹</td>
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<td>A bronchodilator and opens airways, inhibits cholinergic neuromuscular transmission²</td>
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<tr>
<td>Stabilises mast cells and T-lymphocytes³</td>
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<tr>
<td>Stimulates generation of nitric oxides⁴</td>
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<td>Influences production of prostacycline⁵</td>
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It is an extremely important element because of its association with a wide varieties of metabolic processes. Therefore, a slight variation in the body’s Mg concentration may result into a serious consequence. This paper highlights some of the important aspects of Mg in respect to its recent
development as the basics of Mg metabolism, laboratory assessment and the role of Mg in certain diseases.

**Physiology**

Like potassium, Mg is also an intracellular element. More than half of its total body’s content is incorporated in bone. After bone, the largest concentration of Mg is found in muscles (27%) and soft tissues (19.3%), whereas serum has only 0.3%. Out of the total serum Mg concentration, two-third is bounded with proteins and anions (citrate and phosphates). Therefore, only one-third is free and is in ionized form. Because protein-bound and complexed Mg are unavailable for biochemical processes, only ionized Mg is biologically active. The ultrafiltration of serum is an example of the separation of Mg based on binding states; protein-bound Mg does not penetrate the filter but free and complexed Mg does. Among the protein-bound Mg in serum, 25% is bound with albumin and 8% to globulin. The association of Mg with globulin may be important because globulin value is affected in many disease states. A study in vitro indicated that Mg binds selectively with alpha and beta globulins but not gamma globulin. The binding of Mg with the alpha and/or beta-fraction of globulin may be indicative of specific clinical conditions. Sufficient number of clinical trials have not been performed to establish a correlation between the Mg concentration and the globulin fractions. Therefore, further studies are needed. For the albumin bound Mg, a correction similar to calcium, may be required in the state of hypoproteinemia and hypoalbuminemia, by the formula “Mg2+ c = Mg2+ T + 0.005 (40-Albumin)”, where Mg2+ c is the corrected Mg concentration in mmol/L and Mg2+ T is total or experimentally determined Mg2+ concentration (mmol/L) and albumin in g/L. For the bone Mg, a portion of it is labile and available to partially support the serum Mg concentration in state of an acute Mg deficiency. This type of Mg may be of great importance at the time of acute changes due to increased excretion or decreased intake. Therefore, determination of serum Mg level is of great importance in assessing any acute changes in the body’s Mg content. For the chronic Mg deficiency however, the estimation of serum Mg essentially has no significance.

**Nutrition**

Mg is obtained principally from the diet such as cereal, nuts, green vegetables, chocolate, legumes, nuts and dairy products. A large percentage of Mg in our food is lost during cooking or refining. It is, therefore, expected that refined and processed food contain less amount of Mg than the coarse food. For example, it is known that Mg is depleted by 82% in the conversion from wheat to flour. This probably explains lower than recommended daily allowance (RDA) of Mg intake by the large population all over the world. Food and Nutrition Board Commission (USA) presented a data for RDA of Mg intake. They recommended 4.5 mg/kg/day as RDA of Mg on the basis of balanced studies and Mg intake. Other studies recommended slightly higher RDA i.e., 6-10 mg/kg/day weight on the basis of literature survey. It appears justifiable to have higher RDA since some Mg is lost during food processing. The food processing has been on rise all over the world. In spite of the higher RDA deficiency of Mg may occur due to various conditions such as inadequate intake through diet or over excretion by the kidney. Studies have been performed all over the world to correlate Mg deficiency in different pathological states. Some of the pathologies are discussed later in this review.

**Absorption and excretion**

Previous studies indicate that Mg is absorbed throughout the small intestine. Subsequently it was known that varying amount of Mg is absorbed throughout the ilium to colon. It was understood that a reverse relationship exists between the amount of Mg intake and the absorption. The reabsorption and excretion of Mg is regulated by the kidney. Unlike Na, K, Cl and HCO3, the predominant (>50%) site of Mg reabsorption is loop of Henle. About 20-30% Mg is reabsorbed by proximal convoluted tubules but are of less magnitude than Na+, K+ and Ca2+. Mg also undergoes circadian variation, therefore, a 24 hour urine specimen will be useful in assessing renal Mg wasting
due to medication or aberrant kidney function. In men daily normal excretion of Mg is 3.6±1.4 mmol/L and 4.8±1.5 mmol/L in females. Expressing a Mg/Creatinine ratio will help to eliminate the variation of excretion between the sexes.

**Hormonal control of Mg metabolism**

Mg metabolism is closely regulated by hormones but it appears that there is no particular hormone responsible to control the homoeostasis. There may be several hormones influencing the Mg balance. Parathyroid hormone (PTH) when administered, decreased renal excretion of Mg and calcium. It was later realised that patients with excess or deficient PTH had the same renal tubular reabsorption of Mg as that of untreated person. This probably indicates that PTH may not be a key regulatory of Mg metabolism. Other hormones that are known to influence renal function such as aldosterone, vitamin D, calcitonin, antidiuretic hormone and insulin may also be involved in the renal handling of Mg. An example is the intravenous administration of epinephrine which shows to decrease the serum Mg concentration. This may be a cause for the prevalence of low serum Mg among the stressed patients. In this regard, further studies are required to understand the complete mechanism of the hormonal regulation of Mg and its metabolism.

**Laboratory estimation**

Presently clinical laboratories determine total serum Mg concentration. Clinicians use this test as the basis for the diagnosis of patients. Physiologically most active form of Mg is ionized Mg. The estimation of ionized Mg on routine basis is uncommon. Upto now, the following three different methods have been developed for the determination of ionized Mg in the laboratory. The different tests to assess body’s Mg status are summarized in Table II.
Ion selective electrode
Electrode (ionophore) has been developed for the determination of ionized Mg. This electrode can be placed in an appropriate membrane that has efficient selectivity for Mg$^{2+}$. Any interference by the ionized calcium is corrected automatically by the electrode$^{23}$. The instrument at present is available in USA and used for determination of ionized Mg in serum, plasma and whole blood. It is hoped that very soon this instrument will find its way to other parts of the world as well.

Fluorescent probe
A fluorescent probe has been developed and later modified$^{24}$ for the measurement of intracellular Mg ions. The acetoxyethyl ester form of furapta-a fluorescent probe, crosses the cell membrane by passive diffusion. The intracellular esterase deesterifies the probe into the salt form. ‘The deestenfied probe thus binds Mg ion. This technique has revolutionized our understanding about the intracellular Mg ions. The use of this method at present is limited to the research laboratory but is expected to find a future role in clinical laboratories as well.

Nuclear Magnetic Resonance
This method utilises radio active adenosine triphosphate (ATP). The ionized Mg concentration. is
inversely related to the distance between the alpha and beta phosphate peaks on the NMR spectrum\textsuperscript{25}. This technique provides an estimation of intracellular Mg but its scope at present is limited to research laboratories. It is hoped that the technique will be useful in future to assess ionized Mg concentration on routine basis with least discomfort to the patient.

**Clinical status and role of Mg**

Causes leading to deficiency of Mg are listed in Table III.

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<td><strong>Decreased absorption:</strong> Intestinal resection, cardiac disease, chronic diarrhea</td>
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<td><strong>Non renal loss:</strong> Chronic vomiting, Nasogastric aspiration, Excessive lactation, villous adenoma.</td>
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<td><strong>Renal loss:</strong> Salt losing nephropathy, Barter's syndrome, renal tubular acidosis, alcoholism, diuretic therapy, Glycosuria.</td>
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<td><strong>Endocrine:</strong> Diabetes mellitus, Hyperparathyroidism, Post-parathyroidectomy.</td>
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Altered Mg metabolism is associated with varies clinical states of diabetes mellitus, alcoholism, aldosteronism, hyperthyrodism, hypertension, pregnancy and cardiovascular disorders.

**Pregnancy**

Low serum Mg concentration appears to have association with pregnancy. It now known that pregnancy induces a significant reduction of serum Mg concentration\textsuperscript{26}. This is probably due to increased excretion of Mg\textsuperscript{27}. Other clinical factors may also be involved. Therefore, Mg supplementation seems necessary during pregnancy to improve maternal health, fetal outcome, reduction in the incidence of preterm labour, vaginal haemorrhage and premature delivery\textsuperscript{27}.

**Hypertension**

There appears to be a correlation between the Mg metabolism and hypertension. Experiment on mesentric microcirculation showed a reduction in the microvascular lumen size when the rat was fed on Mg deficient diet. This was directly related to the degree of Mg deficiency\textsuperscript{28}. Mg depletion results in a leaky membrane of the vessel which cause alteration in electrolyte concentration\textsuperscript{29}. Studies in humans and animals have indicated a marked correlation between the intracellular free Mg (for example in RBC) and blood pressure\textsuperscript{30}. Therefore, it was thought that Mg supplementation may be helpful in the treatment of hypertension. However, a mixed type of result was obtained\textsuperscript{31}. Dyckner and Wester found a significant decrease in systolic and diastolic pressure when treated with Mg supplementation for six months\textsuperscript{32}. With this therapy, there was no significant change in the serum.
concentration and excretion of Mg. Another study did not show any change in blood pressure when treated with the same dose of Mg for one month\textsuperscript{33}. Thus, further studies are needed to determine the efficacy of Mg treatment for the clinical condition such as hypertension.

**Acute myocardial infarction**
Mg exerts a profound effect on the function of myocardium. A study performed on 30 patients with symptomatic heart failure indicated that the severity of the disease was lowered after administration of magnesium chloride\textsuperscript{34}. The possible mechanism by which Mg may be a factor protecting from acute myocardial infarction has been explained\textsuperscript{35}. It was pointed out that Mg supplementation results in the reduction of arrhythmias\textsuperscript{36} and helped by limiting ischemic damage and reperfusion injury to the heart\textsuperscript{35}.

**Atherosclerosis**
It has been suggested by the studies on animals that an inverse relation may exist between the Mg content of the diet and the rate of atherosclerosis\textsuperscript{37}. Yokoyama in 1994 showed a correlation between the low serum Mg concentration and the atherogenic level of low density lipoprotein (LDL) on uptake and metabolism of LDL by cultured human endothelial cells\textsuperscript{38}. The result indicated a substantial accumulation of LDL into the subendothelial space (electron microscopic examination). This may be a cause to initiate atherosclerotic process\textsuperscript{38}. In contrast to this, others suggested on experimental basis that a low concentration of high density lipoprotein (HDL) and apoprotein Al may be responsible for Mg deficiency which in turn results in atherosclerosis\textsuperscript{39}. The basis of the biochemical mechanism by which Mg deficiency is a factor accelerating atherosclerosis through HDL and/or LDL, is not fully understood. It appears that the mechanism of atherosclerosis may be through the excessive production of oxygen derived free radicals caused by the effect of proinflammatory condition within the artery, occurring due to Mg deficiency. At this point it is probably right to say that a clinical condition such as chronic latent Mg deficiency favours free radical production and oxidation of lipid moieties\textsuperscript{41}. Therefore, further studies are indicated to assess the involvement of Mg with HDL or LDL that is responsible in the contribution for atherosclerosis.

**Cardiac ischemia**
In case of Mg deprivation and deficiency, A T? dependent Na+, K+, and Ca++ pump across the cell membrane or within the cell may be jeopardised resulting in physiological and functional impairment to the cell. Such a condition is known as magnesium ischemia\textsuperscript{42}. The reason of this ischemia probably is due to the fact that AT? and the transport of cations (e.g., Na\textsuperscript{+}, K\textsuperscript{+} and Ca\textsuperscript{2+} as well as anions (e.g. Cl, HCO\textsubscript{3}⁻) are Mg dependent. Further report indicates that Zinc and iron deficiencies may be helping in the acceleration of Mg depletion as a secondary impairment to the Na+, K+ and Ca\textsuperscript{2+} pump.

**Conclusion**
It is therefore concluded that Mg is an important element as an electrolyte and enzymatic catalyst. Because of its involvement in numerous biological processes, it has an extremely critical role to play in health and disease. Laboratory estimation of ionized Mg may provide better insight about the Mg and its metabolism. As our knowledge progresses and advanced techniques become available, the information about the ionized Mg and its metabolism would be more clear.

**References**
1993;33:85-91.
29. Reinhart RA, Desbiens NA.Hypomagnesemia in patients entering the ICU. Crit. CareMed.,
31. Flink EB, Stutzman FL, Anderson AR et al. Magnesium deficiency after prolonged parenteral fluid
administration and after chronic alcoholism complicated by delirium tremens. 3. Lab. Clin.Med.,
33. Richard CW. Hall MS. Jaffe Jr.Hypomagnesemia: physical and psychiatric symptoms JAMA,
34. Sueta CA, Clark SW, Dunlap SN at al. Effects of acute magnesium administration on the frequency
35. Shechter M, Kaphnosky E, Rabinowitz B. The rationale of magnesium supplementation in acute
37. Ouchi Y, Tabata RE, Stergiopoulos K et al. Effects of dietary magnesium on development of
38. Yokoyama S, Nishida HI, Smith TL at al. Combined effects of magnesium deficiency and an
atherogenic level of low density lipoprotein on uptake and metabolism of LDL by cultured human
39. Nosue T, Kobayashi A, Uemasu F et al. Magnesium status, serum HDL cholesterol and
40. Rayssiguier Y, Gueux E, Bussiera L et al. Dietary magnesium affects susceptibility of lipoproteins
41. Steinberg D, Parthasarathy S, Carew TE et al. Beyond cholesterol: Modification of low density
42. Newman JC and Amarasingham JL. The pathogenesis of eclampsia: The magnesium isehemia
43. Fisch LS and Mimouni F. Hypomagncsernia following correction of metabolic acidosis: A case of