Magnesium in Health and Disease

Pages with reference to book, From 246 To 250

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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 fonu. 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 ma 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 iomzed 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[1-5].

Table I. Biological functions of magnesium.

Relaxation of smooth muscle[1]
A bronchodilator and opens airways,
inhibits cholinergic
neuromuscular transmission[2]
Stabilises mast cells and T-lymphocytes[3]
Stimulates generation of nitric oxides[4]
Influences production of prostacycline[5]

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%[6]. 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 fonn. 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 Mgbasedon 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 bounded with albumin and 8%to globulin[7]. The association of Mg with globulin may be important because globulin value is affected in many disease states[8]. A study in vitro indicated that Mg binds selectively with alpha and beta globulins but not gamma globulin[8]. 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 perfonned 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 hypoalbumema7, 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[9].

Nutrition

Mg is obtained principally from the diet such as cereal, nuts, green vegetables, chocolate, legumes, nuts and dairy products[10]. A large percentage of Mg in our food is lost during cooking or refimng[11]. 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[12]. This probably exaplains 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[13]. They recommended 4.5 mg/kg/day as RDA of Mg on the basis of balanced studies and Mg intake[14]. Other studies recommended slightly higher RDA i.e., 6-10 mg/kg/day weight onthe basis of literature survey[15]. Itappears 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 overexcretionby the kidney. Studies have been performed all over the world to correlate Mg deficiency in different pathologiical 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[16]. 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 amountof Mg intake and the absorption[17].

The reabsorption and excretionofMg 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 proxmimal convuluted 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[18]. Expressing a Mg/Creatinine ratio will help to eliminate the variation of excretion between the sexes[13].

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 horneostasis. 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[19]. 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[20]. This may be a cause for the prevalence of low serum Mg among the stressed patients[21]. 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.

Table II. Tests to asses body's magnesium status.

1.	**Phyiologic assessment of magnesium**
	Renal excretion of magnesium
	Magnesium retention test
	Balance studies
	Isotopic studies
2.	**Free and ionized magnesium**
	Ion selective electrodes
	Nuclear magnetic resonance
	Fluorescent probes
3.	**Tissue magnesium**
	Muscle
	Mononuclear blood cells
	Red blood cells
	Serum

Ion selective electrode

Electrode (ionophore) has been developed for the detemiination of ionized Mg. This electrode can be placed in an appropriate membrane that has efficient selectivity for Mg[22]. 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 acetoxymethyl 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 Mgion. 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 tnphosphate (ATP). The ionized Mg concentration. is

inversely related to the distance between the alpha and beta phosphate peaks on the NMR spectrum[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.

Table III. Causes of magnesium deficiency.

Decreased absorption:	Intestinal resection, cardiac disease, chronic diarrhea
Non renal loss:	Chronic vomiting, Nasogastric aspiration, Excessive lactation, villous adenoma.
Renal loss:	Salt losing nephropathy, Barters syndrome, renal tubular acidosis, alcoholism, diuretic therapy, Glycosuria.
Endocrine:	Diabetes mellitus, Hyperparathyroidism, Post- parathyroidectomy.

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[26]. This is probably due to increased excretion of Mg[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[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 onMg deficient diet. This was directly related to the degree of Mg deficiency[28]. Mg depletion results in a leaky membrane of the vessel which cause alteration in electrolyte concentration[29]. Studies in humans and animals have indicated a marked correlation between the intracellular free Mg (for example in RBC) and blood pressure[30]. Therefore, it was thought thatMg supplementation may be helpful in the treatment of hypertension. However, a mixed type of result was obtained[31]. Dyckner and Wester found a significant decrease in systolic and diastolic pressure whentreated with Mg supplementationfor six months[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 whent treated with the same dose of Mg for one month[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[34]. The possible mechanism by which Mg may be a factor protecting from acute myocardial infarction has been explained[35]. It was pointed out that Mg supplementation results inthe reduction of arrhythmias[36] and helped by limiting ischeniic damage and reperfusion injuiy to the heart[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 atheroscloersis[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 humanendothelial cells[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[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[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, occuring 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 moities[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 deFrivation and deficiency, AT? dependent Na+,K, K4, 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[42]. The reason of this ischemia probably is due to the fact that AT? and the transport of cations (e.g., Na^4, K^4 and Ca2+ as well as anions (e.g. Cl, HCO3) 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 Ca2+ pump.

Conclusion

It is therefore concluded thatMg 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.

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