

Review Article

Magnesium Plays a Salient Role in the Cells

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Abstract

Magnesium is an important macromineral. Major amount of magnesium is present in the bones. Magnesium absorption takes place at the small intestine and magnesium levels are maintained by the kidneys. Magnesium is a fundamental mineral in the mammalian cells. Magnesium acts as a co-factor for many enzymes, especially enzymes involved in carbohydrate and lipid metabolism. Magnesium is necessary for muscle contraction by acting as a calcium antagonist, cellular proliferation, apoptosis, immune response, etc. Now a days hypomagnesemia is very commonly seen condition associated with predominant diseases like diabetes, hypertension, cardiovascular diseases, obesity, etc. Several authors have reported that low serum magnesium levels, insulin resistance and hyperlipidemia are interrelated. Hypomagnesemia may play a causative role in the development of diabetes, oxidative stress, thrombosis, atherosclerosis, etc. Hence magnesium importances should be highlighted in the research field.

Keywords: hypomagnesemia, hyperlipidemia and atherosclerosis.

Introduction

Magnesium is the fourth most abundant cation and the second most abundant intracellular cation next to potassium in the human body.^(1,2)

Body distribution

Approximately 22 – 26 g of magnesium is present in the normal adult body. Bones contains 67% of magnesium in which 30% serves as a reservoir to normalize the serum concentration. 31% of magnesium is present intracellularly. About 2% of magnesium is present extracellularly. (Figure 1) Within the normal range, intracellular magnesium is maintained except in conditions like hypoxia, prolonged magnesium depletion.^(3,4)

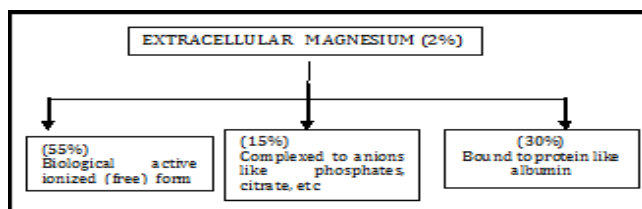


Figure 1 Distribution of extracellular magnesium

Magnesium Homeostasis

Recommended daily allowance (RDA) for magnesium is 400 mg for men and 300 mg for female. Major sources for magnesium are cereals, beans, leafy vegetables and fish.

Gastrointestinal metabolism

Magnesium absorption occurs predominantly in the small intestine by paracellular simple diffusion at high concentration and specific transports at low concentrations. Active intestinal magnesium absorption done by transient receptor potential channel melastatin 6 (TRPM6), which is present at the brush border membrane of the small intestine. Many factors like high intake of calcium, fat, phosphoric acid, etc will affect magnesium absorption in the small intestine.

Renal metabolism

The main way through which the body maintains its magnesium balance is kidney. Kidney reabsorbs 95% of magnesium.

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Glomerular filtration

Approximately 70 to 80% of plasma magnesium is ultra filterable in the ionic form and complexed with anions. The % of ultra filterable magnesium depends on glomerular filtration, volume status, various metabolic states like acidemia, reduced negatively charged species in serum.

Proximal tubules

15 to 25% of magnesium is reabsorbed in the proximal tubules by passive transport.

Loop of Henley

Approximately 65 to 75% of magnesium reabsorption take place by the paracellular pathway in the thick descending limb of nephron. Paracellular magnesium reabsorption is facilitated by claudin 6 which is a tight junction protein.

Distal convoluted tubules (DCT)

DCT reabsorbs 5 to 10% of magnesium. Even though DCT reabsorbs very small amount, it is important because it determines the final urinary magnesium concentration. Magnesium reabsorption at the DCT occurs through the TRPM6. It has been postulated that magnesium binds to divalent binding protein such as parvalbumin or calbindin- D28k, which transports across the cell to the basolateral membrane. Magnesium is taken into the interstitium by a basolateral Na/Mg²⁺ exchanger or ATP dependent magnesium pump. Parathyroid hormone, calcitonin, glycagon and vasopressin play an important role in magnesium homeostasis.^(1,5)

Communication between intracellular space and extracellular space

i, Movement of magnesium from intracellular space to extracellular space

Transport of magnesium from intracellular space to extracellular space occurs in a cascade manner (Figure 2).

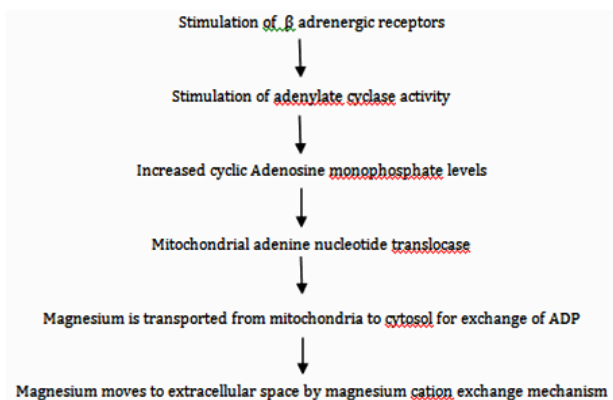


Figure 2: Movement of magnesium from intracellular space to extracellular space

ii, Movement of magnesium from extracellular space to intracellular space

This movement depends on the concentration gradient (Figure 3).

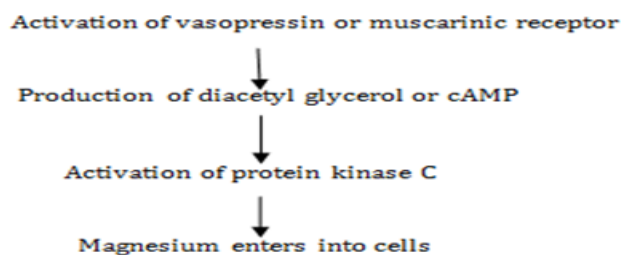


Figure 3: Movement of magnesium from extracellular space to intracellular space

iii, Storage of magnesium within the cell

Calcium plays an important role in magnesium storage inside the cell. Magnesium present in the cytosol enters the mitochondria with exchange of PI by the calcium mediated exchange magnesium. Mitochondria stores the magnesium. Ca²⁺-Mg²⁺ exchanger or transport protein located in the endoplasmic reticulum allows the entry of magnesium and stored in the endoplasmic reticulum or nucleus⁽⁶⁾

Magnesium And Health

Metabolic functions of magnesium: Magnesium is an important mineral in the mammalian cells. Magnesium is necessary for more than 300 biochemical reactions in the body.⁽⁷⁾ Enzymes need magnesium as a cofactors are carboxylase, transketolase, glucose 6 phosphatase, peptidase, adenylyl cyclase, ribonuclease, kinase, DNA polymerase, hexokinase, arginase, enolase, galactokinase, LCAT, lipoprotein lipase, HMG CoA reductase, etc. Magnesium act as a allosteric activator for enzymes like ATPase, alkaline phosphatase, calcium ATPase, phosphofructokinase, etc. Especially it is a critical cofactor for many enzymes in carbohydrate and lipid metabolism.⁽¹⁾ Magnesium is essential for enzyme activator which play an important role in neuromuscular excitability and cell permeability. This leads to muscle contraction. It is a regulates ion channels especially calcium channel. Magnesium competes with calcium for binding sites of voltage operated calcium channels (VOCC). This results in decreased calcium channel activity which lowers intracellular calcium levels and finally leads to vasodilation.⁽⁸⁾

It also play an important role in mitochondrial functions. It is a salient element in cellular proliferation and apoptosis. Magnesium is involved in both cellular and humoral immune response. It is involved in DNA synthesis and repair.⁽¹⁾ Magnesium is also required for hormone secretion. It plays an important role in insulin hormone – insulin receptor interaction and favours the glucose entry into the cell.⁽⁹⁾ Magnesium increases the body's ability to utilize calcium, phosphorus, sodium, vitamin C, E and B complex.⁽²⁾ In the brain, magnesium is predominantly complexed with ATP. This complex is required for cellular biological processes.⁽¹⁰⁾

Clinical Significance of Magnesium

Normal serum magnesium level is 1.8 to 2.4 mg/dl.

Hypomagnesemia

Serum magnesium level below 1.8 mg/dl is defined as hypomagnesemia. Causes for this condition are reduced intake, reduced intestinal absorption, renal disease, a variety of drugs eg. antibiotics, loop diuretics, chemotherapeutic agents, etc.

Hypermagnesemia

Serum magnesium level above 2.4 mg/dl is defined as hypermagnesemia. Causes for this condition are increased intake, renal failure, familial hypocalciuric, hypercalcaemia, hypothyroidism, addison's disease, etc.

Assessment of Serum Magnesium Levels

Serum magnesium is most commonly measured by photometric methods. Some laboratories use atomic absorption spectrometry to measure magnesium.

Photometric Methods

Several metallochromic indicators eg. Calmagite, xylyl blue, magon, methyl thymol blue, chlorophosphan-aza III, arsenzol, etc. bind selectively to magnesium and give colour at alkaline P^H . Formazan dye forms a complex with magnesium at alkaline P^H which is measured in film reflectance photometry.

Free Ionic Magnesium

Serum contains more free magnesium form than the other forms and free ionized magnesium is biologically active. This free ionic magnesium is measured by ion selective electrode (ISE) instruments.^(11,12)

Enzymatic Methods

Recently these enzymatic methods have been developed with hexokinase and isocitrate dehydrogenase that use $Mg - ATP$ as cofactors. The rate of the enzyme catalyzed reaction is dependent on the concentration of magnesium.

Magnesium and Diseases

Magnesium and Diabetes Mellitus

Diabetes mellitus is a disorder of heterogeneous etiologies may be with absolute or relative deficiency of insulin and the common denominator is hyperglycemia.⁽¹³⁾ Many studies show a close relationship between diabetes mellitus and magnesium deficiency. Study conducted in several European countries shows a low serum magnesium level in diabetics. Low serum magnesium is a strong independent predictor of type II diabetes.^(14,15) In low magnesium level conditions, defective tyrosine kinase activity at the insulin receptor level, impaired hormone and receptor interaction. This leads to worsening of insulin resistance. Diabetes mellitus can lead to osmotic diuresis or use of diuretics and hypolipidemic agents also increases urinary magnesium loss. So magnesium deficiency

in diabetes can be both as a cause and consequence.^(16,17) Insulin regulates the intracellular magnesium concentration by stimulating $ATP-Mg$ dependent Ca^{+} pump.⁽¹⁸⁾ There is evidence of associations between hypomagnesemia and various complications of type II diabetes like neuropathy, retinopathy, foot ulcers, etc.⁽⁷⁾ Serum magnesium levels are inversely related to the severity of diabetes.⁽¹⁹⁾ Hypomagnesemia was also observed in people with impaired fasting glycemia.⁽²⁰⁾

Magnesium And Dyslipidemia

Magnesium deficiency has been shown to cause heart disease in persons according to review of literature. A link between magnesium deficiency and insulin resistance, diabetes, hyperlipidemia was observed by many studies.⁽²¹⁾ Magnesium plays an important role in lipoprotein lipase activity and this enzyme clears triglycerides from blood. Lecithin cholesterol acyl transferase (LCAT) is present in HDL and magnesium is required for its activity. LCAT converts free cholesterol to cholesterol esters. Then HDL transports cholesterol to liver from blood. $Mg-ATP$ complex is the controlling factor for the rate limiting enzyme HMG CoA reductase in the cholesterol synthesis.⁽¹⁸⁾ Pyrophosphatase catalyzes the hydrolysis reaction in the first step of lipid degradation. The energy released in this step is used for the fatty acid activation and these fatty acids undergo oxidation. Pyrophosphatase also requires magnesium for its activity.⁽²²⁾ In magnesium deficiency, enzymes are not effective and leads to dyslipidemia (Figure 3).

Magnesium And Obesity

Magnesium balance may help in maintaining the normal body weight. Magnesium may form insoluble complexes with fatty acids in the intestine and prevents the dietary fat absorption. In adipose tissues, magnesium stimulates the adenyl cyclase activity and increased production of cAMP. These changes play an important role in glucose homeostasis. Magnesium plays a salient role in the maintenance of normal body weight.⁽⁴⁾

Magnesium and oxidative stress

Magnesium deficiency leads to increased production of pro inflammatory molecules. Magnesium has an inhibitory effect on nitric oxide synthase activity in endothelial cells. During magnesium deficiency, increased nitric oxide generation. Magnesium deficiency leads to increased oxygen derived free radicals production. Decreased antioxidant enzymes activities like glutathione peroxidase, superoxide, dismutase, catalase, etc. are observed in magnesium deficiency. Magnesium maintains the glutathione concentration. Glutathione helps in regeneration of other antioxidants like ascorbate and tocopherol. In magnesium deficiency, decreased levels of these antioxidants are observed. Thus all these events lead to lipid peroxidation and oxidative stress.^(40,41)

Magnesium and thrombosis

Magnesium may induce prostacyclin synthesis and release from endothelial cells or magnesium can interfere with platelets stimulating factors. These events can lead to decrease in platelet aggregation. Reduced magnesium in

platelets leads to decreased guanylyl cyclase activity, decreased cGMP levels in platelets and thus results in increased platelets aggregation.⁽⁴⁾ Magnesium deficiency leads to reduced fibrinolytic capacity. Magnesium inhibits the coagulation process is a salient function.⁽¹⁸⁾

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