

Advances in Biotechnology

Chapter 9

Magnesium as a Novel Regulator of Human Health and Diseases

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Abstract

Magnesium (Mg) plays an important role in various cellular processes such as DNA repair and replication, transporting potassium and calcium ions and signaling transduction. Dietary source which are rich in Mg includes seeds, cocoa, nuts, green leafy vegetables and almonds. The daily dietary intake of Mg is frequently found to be below than the recommended in western country. Certainly it is recognized that Mg deficiency may lead to many disorders of the human being for example diabetes, cardiovascular disease and TB. Moreover, Mg deficit also leads to inflammation and amplifies the level of free radicals where it causes oxidative DNA damage and tumor formation. The presented book chapter provides a summary of low Mg impact on human health and development of various diseases.

1. Introduction

Mg is the second most abundant divalent cation in living cell which is commonly found in the earth crust and other planets. Out of the eight main elements of earth crust, Mg is one of the four major elements to form the whole mass of earth. Mg is naturally obtained from the diet source such as cereal, wheat, nuts, green vegetables, soya, fish, chocolate, legumes, nuts and dairy products [1]. The maximum percentage of Mg in diet is lost during cooking or purification. It means that processed food contain less amount of Mg as a compared to raw food. For instance, Mg is exhausted by 82% in the conversion from wheat to flour [2]. This probably explains lower than recommended daily allotment (RDA) of Mg intake by the large population all over the world. In USA, Food and Nutrition Board Commission represents a data for RDA of Mg intake per day [3]. They recommended that Mg intake is 4.5 mg/kg/day as RDA of

Mg on the basis of balanced studies [4]. The average content of Mg for adult RDA in western societies is about 350 mg [5]. The actual amount of Mg requirement depends on the levels of metabolic activity and type of work, life style and disease [6]. It is intracellular element and more than half of its total body's content is incorporated in bone. Beside bones, the maximum concentration of Mg is available in muscles (27%) and soft tissue (19.3%), whereas serum has only 0.3% [7]. Some Mg is also bound in the form of ions with protein while only one third Mg is available in free form as protein bounded form is not accessible for biochemical process, only ionized Mg form is active for biological activity. The concentration found in the protein-bound Mg is 25% impelled with albumin and 8% to globulin [8]. The association of Mg with globulin may be important because globulin is key of minerals in metabolism and cofactor for hundreds of enzyme activity. Since Mg is a mineral which is not synthesized in our body it must be obtained through dietary foods or through supplements. Mg shortage can cause low serum potassium and calcium levels, retention of sodium, and low circulating levels of regulatory hormones. Mg metabolism is closely regulated by hormones but it appears that there is no particular hormone responsible to control Mg homeostasis [9]. These changes in Mg concentration cause neurological and muscular symptoms such as tremor and muscle spasms. Further Mg deficiency causes loss of appetite, nausea, vomiting, personality changes and death from heart failure. Some of the factors which can lead to Mg deficiency include the alcohol abuse, inadequately controlled diabetes, excessive or chronic vomiting or diarrhea. Thus the effect of inadequate and deficient intake levels of Mg is critical to human health [10].

2. Mg in cellular physiology

Mg play consequential role in many physiology activity including cell signaling, energy production, protein synthesis, oxidative phosphorylation, glycolysis and nucleic acid. Some cations may replace Mg for these function but other are strictly dependent upon the Mg, which indicates that cell must have minimum Mg to maintain their physiology conditions. Mg has an essential role in the active transport of calcium and potassium ions across cell membranes, this function is significant to nerve impulse conduction, muscle contraction, and normal heart rhythm [11]. High amounts of Mg are especially needed for cells to work in different organ actively from metabolically intensive such as heart, brain and muscle [6]. Slight changes in Mg concentration in body lead to major consequences. The deficiency of Mg is a manifestation of various pathologies. The deficiency of Mg play crucial roles in different types of disorder such as cardiovascular disease (cardiac death, atherosclerosis, heart failure), heart failure, thyroid and parathyroid, liver cirrhosis and gastrointestinal tract disease [12].

Mg ions play important role in cellular activity. By macromolecular surface binding they stabilize structures of proteins, nucleic acids, and cell membranes [13]. Mg activate many enzymes, which are important for those that perform hydrolysis and phosphate group transfer [12]. ATP hydrolysis to ADP is the most important stimulatory role of Mg in cell energy

metabolism [14]. Mg is combined with ATP, ADP and GTP, necessary for the many activities of enzymes that is involved in phosphate group transfer such as glucokinase, phosphofructokinase, phosphoglycerate kinase, pyruvate kinase [15]. In fact, all reactions involving ATP require the presence of Mg ions [16]. This ion also play important role in the nucleic acid and protein [14]. and maintaining genomic stability, through ensuring the fidelity of DNA replication and repair process. Almost more than half Mg is found in the nucleus is associated with nucleic acid and free nucleotides. In addition, Mg has a critical roles in modulating cell cycle progression, cell proliferation, differential and apoptosis [17].

The transporters which are involved in Mg homeostasis have been the main focus of research due to its importance in human health. Genetic screenings on human diseases and microarray-based expression studies have resulted in the identification of numerous Mg transporter proteins which can be ubiquitous or tissue specific. The ubiquitous transporter transient receptor potential melastatin type 7 (TRPM7), Mg transporter 1 (MagT1), and solute carrier family 41 member 1 (SLC41A1) [18,19]. The tissue specific Mg transporters such as transient receptor potential melastatin type 6 (TRPM6; kidney, colon), cyclin M2 (CNNM2; kidney) and cyclin M4 (CNNM4; colon) [20,21]. It has been reported that any conformational changes in these transporters can lead to deadly diseases like TB, cancer, diabetes etc.

3. Ubiquitous Nature of Mg

Mg is present in every organism like bacteria, fungi, virus and human being. Its importance and function is evolutionary conserved in all organisms as discussed in following sections.

3.1. Mg acquisition in bacteria

There are three classes of Mg transporters present in bacteria. CorA, MgtE and MgtA [22,23,24]. Most of bacteria contain multiple type of transporter either belonging to same or different classes. Whereas all these transporters can import Mg but they vary in the energy requirements for moving Mg, their ability to export Mg, the conditions under which the proteins are made, and their phylogenetic transportation within bacteria as well as in archaea and eukarya. Putative Mg binding sites present in the monomer merge in the extracellular cytoplasmic domain are thought to be control channel opening and closing in response to intracellular Mg level [25]. Mg Structurally MgtA is different from Cor A. As with Cor A, intracellular Mg is thought to be regulated by MgtA. P-type ATPases are Mg transporter family belong to MgtA class. These families of proteins need energy from the decomposition of adenosine triphosphate (ATP) to transport a variation of charged molecules. To relay of the phosphate group from ATP to the protein results in a symmetry change in the protein that stimulate Mg transport [26]. In addition to the regulation of transcription beginning by extra cytoplasmic Mg levels, transcription elongation into the protein-coding regions through Mg transporter

genes can respond to the concentration of Mg in the cytoplasm [27,28].

3.2. Mg acquisition in fungi

Mg is found abundantly in many fungi. However, their amount may vary between species. Mg is necessary for multiple fundamental biological activity, of yeast. For example in *Saccharomyces cerevisiae* importance of Mg for survival has been already proved. So far, there are three type of Mg transporters that has been identified in yeast. The Alr Mg transporter present in the cell membrane, the Mnr2 Mg transporter system present in the vacuolar membrane [29]. There are two Alr proteins (Alr1 and Alr2) which are orthologues of the bacterial CorA transporter, allocate with the latter a highly conserved GMN motif [6]. Both Alr1 and Alr2 located in the plasma membrane and perform the function of Mg importers [30]. The storage site of Mg in vacuole present within the yeast cell. The Mg^{2+}/H^{+} exchange mechanism was discovered to drive Mg entry into the organelles [31]. The vacuolar membrane protein that functions as putative Mg transporter exhibit similarities with Alr1 and Alr2 is responsible for Mg efflux from vacuoles. Genetic confirmation shows that this protein functions by releasing Mg into the cytosol under Mg-deficient conditions

3.3. Mg in virus

There is considerable amount of Mg present in DNA and RNA. Most of the virus that infect eukaryotes has Mg in their intracellular membrane that activate the specific transporter. For Example, XMEN diseases are very rare genetic disease mostly appearing in men that have mutation in the MAGT1 Mg transporter gene. MAG1 bring the Mg inside from the immune cells to support their function [32].

4. Mg and human health disorders

4.1. Mg in non infectious disease

Mg is an essential element that acts as an enzymatic catalyst and electrolyte. Because it is required for several biological processes, it has an extremely important role to play in health and disease (Fig. 1). The investigations has proved that the alteration in the physiology and metabolism of Mg induce the threat of developing metabolic diseases, viz. obesity, /type II diabetes obesity.

4.1.1. Mg and diabetes

Mg deficiency leads to diabetes mellitus, both type 1 and 2, with 25-39% of patients being affected [33]. There are several factors that affect Mg during diabetes as many of the enzymes involved in glycolysis are Mg dependent. Increased insulin resistance has been found in patients with reduced free Mg levels, and animal studies have shown proliferating glucagon

stimulation decreased insulin secretion and reduced insulin uptake with Mg deficiency. The past studies show that, hypomagnesemia is strongly associated with type 2 diabetes patient with hypomagnesemia show instantly decline in progression and have increased risk of diabetes complications. Experimental studies showed that patients along with hypomagnesemia have lower pancreatic beta-cell activity and are more insulin resistant [34]. Furthermore insulin receptor autophosphorylation is reliant on intracellular Mg concentrations, making Mg a straight role in the progress of insulin resistance. So Mg supplementation improved insulin sensitivity and metabolic control in a double-blind randomized trial, suggesting that Mg is an important factor in the etiology and management of diabetes mellitus [35,36].

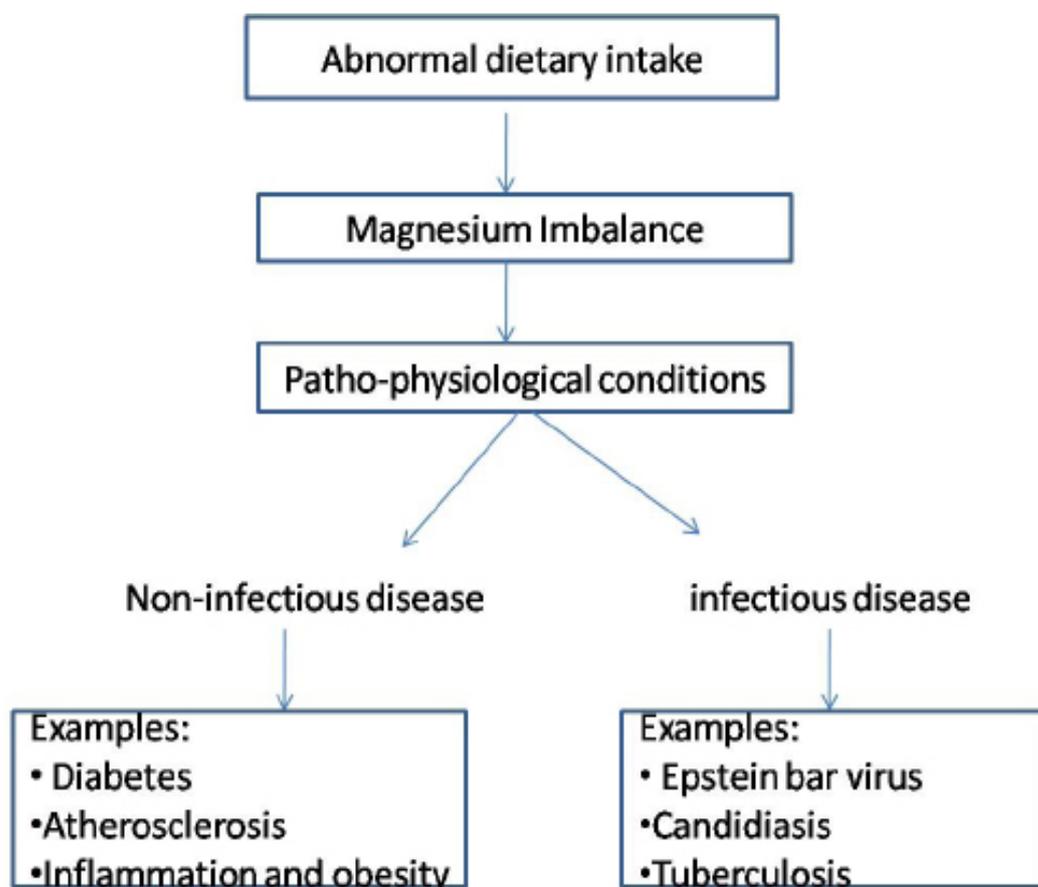


Figure 1: Mg imbalance leading to various health disorders

4.1.2. Mg and atherosclerosis

The epidemiological and experimental evidence links Mg deficiency and atherosclerotic cardiovascular disease. Mg deficiency contributes to atherosclerosis by effecting their lipid metabolism, blood pressure and platelet aggregation. Experimental evidence recommends that Mg deficiency characterized by increased VLDL, LDL, triglycerides, cholesterol and triglyceride-rich lipoproteins may play a role in the pathogenesis of atherosclerosis. In contrast to this, others recommend on experimental basis that a low concentration of high density lipoprotein (HDL) and apoprotein A1 may be important for Mg deficiency which causes atherosclerosis [37]. The biochemical mechanism of Mg deficiency is a factor for accelerating atherosclerosis

through HDL and/or LDL. The mechanism of atherosclerosis may be through the huge production of oxygen derived free radical caused by the chronic condition with in artery, occur due to Mg deficiency. It suggests that Mg deficiency favor the free radical production and oxidation of lipid moieties [38]. Further studies suggest the involvement of Mg with HDL and LDL that is responsible in the contribution for atherosclerosis.

4.1.3. Mg in inflammation and obesity

The low grade inflammation may lead to obesity. Because low Mg more often occur in obese than non-obese individuals [39,40,41], one of the stressor causing the activation of inflammatory pathways is Mg deficiency. The severe Mg deprivation, which instantly decrease extracellular Mg, results in inflammatory response in animals. Mostly inflammatory response is caused by an increase in intracellular calcium and the priming of phagocytic cells, which results in the release of inflammatory cytokines [42].

However, dietary Mg deficiency severe enough to cause a marked drop in extracellular Mg in some days is doubtful in humans. Through, animal deficiency findings support the suggestion that subclinical Mg deficiency can cause, or come up with, chronic inflammatory stress in humans through an effect on the cellular entry of calcium and its signaling that results in the release of inflammatory neuro-peptides, cytokines, prostaglandins, and leukotrienes [43,44].

4.1.4. Mg in cancer

Tumor cells restrain high concentrations of intracellular Mg. In tumor cell line, Mg can be transported into the cell even when extracellular Mg concentrations were low [45]. Mg uptake through divalent cation channel TRPM7 has been optional to stimulate tumor cell proliferation. TRPM7 expression is upregulated in hepatoma, pancreatic adenocarcinoma, gastric cancer, and breast cancer tissue [46,47]. Although TRPM7 has been primarily described as a Mg channel, it is also permeable for other divalent cations [48]. Given the involvement of Mg in cell proliferation, the influx of Mg through TRPM7 has been proposed as the main regulator of tumor growth. However, recent studies using prostate cancer cells suggest that TRPM7-mediated Ca uptake may also play an important role in tumor growth. The appearance of Mg transporter CNNM3 is increased in human breast cancer tissue [49]. CNNM3 binds oncogene PRL2 and facilitates the entry of Mg in the tumor cell to drive cell proliferation.

4.1.5. Mg in neurodegenerative diseases

Low serum Mg concentration is linked with a broad range of neurological diseases such as migraine and depression. Neuronal Mg concentrations are of main significance in the regulation of N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are vital for excitatory synaptic transmission and neuronal plasticity, therefore play an important role in developmen-

tal smoothness, learning, and memory [50]. Examples of neurodegenerative diseases comprise Parkinson's, Alzheimer's, and Huntington's disease. In case of Parkinson disease, there are low levels Mg concentrations in cortex, white matter, basal ganglia, and brain stem. In addition, Mg transporter SLC41A1 is located on the PARK16 locus that is linked with Parkinson's disease [51]. Recent characterization of the SLC41A1-pA350V single nucleotide polymorphism (SNP) linked to Parkinson's disease evidenced a gain-of-function effect.

4.2. Mg in infectious disease

Over past decades, emergence in the cases of infectious disease caused by fungi, bacteria and technology of Mg in ionized form used in the treatment in following sections. Virus have been on the climb worldwide. Due to their wide spread and continue use of antimicrobial drugs in treating infection has led to emergence of resistance among the various strains of microorganism that's lead to multiple drug resistance. The sufficient amount of Mg helps in the treatment of diseases such as hypertension, acute myocardial infarction and colorectal cancer [5]. So Mg has critical role in health and disease and ionized Mg may provide better insight about the Mg and its metabolism (Fig. 1). As our knowledge progress the advanced technology of Mg in ionized form used in the treatment in following sections.

4.2.1. Mg and epstein bar virus

It is most common virus in human and best known as the cause of infectious mononucleosis. It is particular associated with form of cancer, such as Hodgkin lymphoma, gastric cancer and condition which is linked to human immunodeficiency virus and CD8 T lymphocytes (CTLs). In recent year many primary immunodeficiency has been associated with abnormalities in ions channels and transporter, including those involved in permeability is calcium and Mg [54-57]. XMEN disease suggests that Mg is important for intracellular regulation of immune system.

4.2.2. Mg and candidiasis

The most common fungal pathogen of humans is *Candida albicans*. This is fourth most common cause of hospital acquired infectious disease and is the first cause of systemic candidiasis, with mortality rates approaching 50% [58]. *C. albicans* is a commensal fungus opportunistic human fungal pathogen that causes candidiasis in immuno-compromised condition such as in AIDS, organ transplant, diabetes, or in cancer patients, it results in mucosal, cutaneous or invasive mycoses [59]. Mg in fungi play diverse role as a counter ion for solutes, specially ATP and other nucleotides, DNA and RNA. By binding to RNAs and many proteins, Mg is also necessary to initiate and sustain physiological structures and acts as an important cofactor in catalytic processes. Mg also maintains membranes and dynamic conformations of macromolecules. In yeast, vacuolar Ca accumulation is blocked by increased Mg in the medium,

and *alr1_* mutants having lower Mg exhibit elevated Ca [60]. Gooday (1978) has previously suggested that Mg may play an important role in regulating this key enzyme in *C. albicans*. Moreover, *C. albicans* need Mg for germ-tube formation [61]. Mg-lacking media, metal ion chelators and the ionophore A23187 repressed germ-tube formation. Yeast-phase cells, which did not form germ-tubes, had a lower Mg content and failed to gather Mg when kept under conditions for germ-tube formation [62]. It suggests that Mg have a central role in regulating virulence of *C. albicans*.

4.2.3. Mg and tuberculosis

Mycobacterium tuberculosis, causing Tuberculosis (TB) remains a major health concern into the 21st century. It has been evaluate that up to one-third of the global population harbors the bacteria, with approximately 0.17 crores deaths due to TB yearly [63]. Further, the recent emergence of multi- and especially drug resistance strains highlights the continued relevance of this pernicious human pathogen [64]. The entire mechanism of pathogenesis is unknown, but likely involves a multi-factorial attack of the immune system [65]. The beginning biosynthetic enzyme (Rv3377c/MtHPS) involved in isoTb biosynthesis release noticeable inhibition by its Mg co-factor, key to the hypothesis that the depletion of Mg observed upon phagosomal absorb may act to trigger isoTb biosynthesis. While MTB is typically grown in relatively high levels of Mg (0.43 mM), transfer MTB to media with phagosomal levels (0.1 mM) led to a significant (~10-fold) increase in accumulation of the MtHPS outcome, halimadienyl diphosphate, as well as easily detectable amounts of the derived bioactive isoTb [66]. Moreover, the integral membrane protein PerM is important for MTB determination during chronic infection in mouse. Consequently PerM mutant need additional Mg as compared to wild type MTB for replication and survival in media with reduced Mg [67]. The survival defect of PerM mutant in low Mg and chronic infection are stable with Mg deprivation constitutes an IFN- γ dependent host defense strategy. It suggests that Mg is essential for bacterial growth and it serve as wide role like function as cofactor with ATP in several enzymatic processes.

5. Conclusion

Mg is crucial micronutrient whose bioavailability essentially impacts on several enzymatic processes in the cell hence further attention should be paid for having an enough content of this element in diet. Disorders of Mg metabolism are ordinary in hospital patients and are frequently unrecognized. Low Mg intake may be a contributor to many diseases including diabetes, cardiovascular disease and TB.

6. References

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