da Rocha Romero et al. Nutrire (2017) 42:6
DOI 10.1186/s41110-017-0031-4

Nutrire

REVIEW Open Access

Mg status in inflammation, insulin resistance, and associated conditions

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Abstract

Magnesium (Mg), an essential ion for the human body, is involved in various enzymatic reactions, particularly those related to energy transfer, storage, and transport. Longitudinal studies show that hypomagnesaemia (Mg serum concentration <0.75 mmol/L) and Mg dietary inadequacy (daily intake < EAR (Estimated Average Requirement) for age/gender) are conditions related to metabolic disorders of the immune and cardiovascular system and often occur in obese and diabetic individuals. Poor eating habits, reduced Mg content in food and water are the main causes of the decrease in Mg intake by the general population. In clinical practice, the serum concentration of this mineral is the most widely used marker for diagnosing deficiency. However, the serum concentration does not reflect the nutritional Mg status since it can be maintained by mobilization of body storage, mainly the bone. Thus, the use of serum concentration as the only routine biomarker of Mg status may hinder the diagnosis of Mg deficiency. In clinical and experimental research, different methods for Mg status assessment are proposed (plasma, erythrocyte, urine), but they are seldom used in clinical routine. In some countries (such as USA and Brazil) the average daily Mg dietary ingestion of more than 60% of the adult population is lower than the Estimated Average Requirement for age and gender, and these data are not too different for individuals with chronic non-communicable diseases. It is unclear whether it is an actual reduction of Mg consumption or if the recommendations are overestimated. If we assume that the recommendations are correct, the question is if this condition constitutes a risk factor for chronic diseases or the hypomagnesemia described in some diseases is a consequence of physiopathological changes. This review has the latest information of human and animal studies about Mg status evaluated from plasma, erythrocyte and urine, dietary inadequacy, and its relation to inflammation and to components of metabolic syndrome.

Keywords: Hypomagnesemia, Chronic diseases, Inflammation, Metabolism

Background

Magnesium (Mg) is the fourth most prevalent cation in the human body and the second in intracellular concentration. It is a cofactor of more than 300 enzymatic reactions, in particular those related to DNA, RNA, and protein synthesis, and it is also an important factor in the control of cell proliferation [1, 2]. Mg exerts structural and also dynamic functions, for example, in formation of enzyme-substrate complexes, in allosteric activation of various reactions, in modulation of ion channels, and in stabilization of cell membranes. The most recognized function of Mg, associated to ATP, is the activation or deactivation of cellular signal transduction pathways, an example of which is insulin signaling [3, 4].

Evidence suggests that a disruption in Mg availability and metabolism could be considered the cause and/or result in pathological conditions such as cardiovascular diseases, hypertension, diabetes, and metabolic syndrome [4] due to the Mg role in the modulation of inflammation processes, carbohydrate metabolism, regulation of vascular tone, and myocardial metabolism [5]. In this context, we have focused this review in Mg status, dietary recommendations and the influence of Mg deficiency in the risk of diseases associated with inflammation and components of metabolic syndrome.

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Mg compartmentalization and physiology

About 60% of body Mg is found in mineralized tissues (bones and teeth), and the remaining 40% is distributed in skeletal muscle and other tissues [6]. Serum Mg concentration is regulated by the balance between intestinal absorption (particularly in proximal jejunum and ileum), urinary excretion and reabsorption and retention and bone mobilization [7].

Mg intestinal absorption occurs by passive non-saturable transport when concentration in the intestinal lumen is above 20 mEq/L and by active saturable transport in intraluminal concentrations up to 20 mEq/L, the main mechanism of absorption in cases of dietary restriction. In this condition, TRPM6 channel (transient receptor potential, subfamily melastatin 6), an ion channel of approximately 230 kDa molecular weight fused with an α kinase is used. Abundant in the intestine (especially ileum, cecum and colon), it is also present in the apical membrane of the distal convoluted tubule of the kidney, and it is responsible for renal Mg reabsorption [8, 9]. Another channel, TRPM7, present in all cell types, may be an important sensor of Mg homeostasis. Both channels are downregulated by high intracellular levels of the mineral [10, 11].

Thus, the kidneys are essential for Mg homeostasis since they control Mg serum concentration mainly by modulating its excretion in urine. Under physiological conditions, approximately 2400 mg of plasma Mg are filtered by glomeruli, and of these, approximately 95% are readily absorbed, i.e., 3 to 5% are excreted in urine [12]. As mentioned before, the largest body Mg compartments are bone's surface and matrix. In the bone surface, Mg functions as a buffer to maintain extracellular concentration constant: whenever there is a reduction in plasma Mg there is a rapid release of surface Mg attached to the bone into the blood compartment [13].

Reduction of plasma Mg concentrations between 0.4 to 0.5 mmol/L (severe hypomagnesemia) is a relatively rare condition, and it is often associated with electrolyte imbalance such as hypokalemia and metabolic acidosis. Signs and symptoms of severe hypomagnesemia include weakness, apathy, tetany, paresthesia, and arrhythmia [14, 15].

Dietary Mg recommendations

The major dietary sources of Mg are whole grains, dark green leafy vegetables, nuts, and vegetables [16]. Such foods are often present in the mediterranean diet, which is inversely associated with chronic non-communicable diseases [17, 18]. The US Department of Agriculture (USDA), based on the Dietary Guidelines for Americans, released MyPlate (replaced by the MyPyramid in 2011) in order to encourage the American people to make healthier food choices. In Brazil, the National Program of Food and Nutrition emphasizes practices that promote better nutrition and population health to encourage the population to consume healthy foods and decrease macro and micronutrients (including Mg) deficiencies in adults and children [19].

Mg nutritional requirements for adults were determined in balance studies [20]. The design of these studies must comply basic requirements such as sufficient length for variations in the approximately 12 days of metabolic adaptation to mineral intake and also the evaluation of the association between the consumption of habitual diet and Mg intake levels that can cause adverse effects. However, as some studies that were used to define the Mg recommendations were not strictly controlled there were speculations about the derived recommendations [20, 21]. In this context, a detailed study by Hunt and Johnson [22] analyzed 27 balance studies conducted by the US Department of Agriculture in order to define Mg recommendations for men and women. The authors concluded that the zero balance (when output equals intake) is achieved at intakes of about 165 mg/d Mg for healthy adults, regardless of age or sex. This suggests that the Estimated Average Requirement (EAR) for Mg in adults aged 19–50 years might be lower than that defined by the US Institute of Medicine [20]. The EAR of 165 mg found by Hunt and Johnson converts to an RDA of 237 mg/d [23] (considering EAR plus two standard deviations, as proposed by IOM) which is lower than the current RDA ranging from 310 to 420 mg/d [20].

Moreover, recent findings show that Mg intake of less than 250 mg/day associated or not with serum Mg concentration of 0.75 mmol/L sets a subclinical Mg deficiency, which may be related to pathological conditions [24]. The reduction in the Mg intake by the population is due to process that affect Mg content in food such as water purification, food processing, and the impact of high yield cultivars in lowering Mg concentrations of wheat and vegetable crops over the past 50 years [25, 26] and to change in dietary habits, for example, increased intake of refined and processed grains [27].

The European Food Safety Authority (EFSA) [28] used data from 13 dietary surveys made in healthy subjects (adults and children) in 9 countries of the European Union (EU) and proposed 350 and 300 mg/d Mg, respectively, as adequate intakes for adult men and women and between 170–300 mg/day Mg for children according to the age.

Briefly, there are still important issues to be informed about Mg recommendations, requiring strictly delineated research to discuss new recommendations for the intake of this mineral.

The questions are (1) are the DRIs [21] for Mg overestimated or at least overestimated for some populations? (2) Are the methods the authors have been using to determine Mg inadequacy comparable?

Although there are differences among Mg recommendations in different countries, the values are similar. On the other hand, it is important to have a method to evaluate inadequacy that takes into account within and between personal variations in dietary intake mesurements. The European recommendation uses half the consumption range of the reference population and not exactly the median as proposed by the DRI [20].

Biomarkers for assessment of Mg status

Currently, serum Mg is the most widely used parameter to evaluate Mg status in humans. However, serum compartment is less than 1% of the total content of body Mg, thus, the incorporation of other markers that reflect Mg body stock should be encouraged [29].

The determination of Mg levels in muscles and bones, the primary Mg stock compartments, allows reliable evaluation of Mg status and are widely used in experimental studies. However, this method is invasive and impractical for routine clinical use. Other methods that could easily be adapted to laboratory routine include determination of intracellular (leukocyte and erythrocyte), urinary, and fecal Mg concentrations [30]. The tolerance test can also be used to investigate Mg deficiency [31]. Once the patient is carefully monitored on an outpatient basis during the analysis, the test is safe, reproducible, and reliable.

Mg serum concentration used as the single biomarker to diagnose Mg deficiency should be considered with caution also because Mg depletion in cells and bones can coexist with normal serum levels [7, 32]. For example, Sales et al., in an animal study, observed that 70% dietary Mg restriction in association with increased fat intake resulted in reduced urinary Mg excretion and decreased bone Mg concentration without changes in plasma levels [33]. Likewise, obese women with low dietary Mg intake had low urinary excretion and plasma concentration but had normal erythrocyte Mg [34]. Therefore, defining and diagnosing Mg deficiency in the population is still a challenge, and the impact of Mg low consumption may be underestimated [1, 2].

Some interesting data show that the consumption of Mg by the population is not appropriate. For example, data from the National Health and Nutrition Examination Survey (NHANES, 2005–2006) indicated that approximately 60% of all American adults did not meet the recommended average intake (EAR) for Mg [35]. In Brazil, the Family Budget Survey (2008–2009) held in all regions of the country evaluated the dietary intake of 34,000 individuals through food records. A 70% probability of inadequate Mg intake mainly in urban areas was reported. Mg is one of the nutrients with the highest percentage of inadequacy in the age group of 19–59 years for both sexes, estimated by the proportion of individuals with consumption below the EAR of 255–265 mg/d for women and 330–350 mg/d for men) [36].

Another Brazilian study conducted with students from a public university found high frequency of what they called Mg subclinical deficiency. The average of plasma Mg in the studied population was close to the lower limit of the reference range (0.76 ± 0.06 mmol/L) and 17% of individuals had low Mg erythrocyte (<1.65 mmol/L). Additionally, a high probability of inadequate Mg intake around 70% for women and 94% for men was observed [37].

The Brazilian Osteoporosis Study (BRAZOS) that evaluated the intake of nutrients related to bone health found that only 20% of the participants reached the Mg daily recommendation (350 mg for men and 265 mg for women). The authors concluded that great part of the studied population had dietary Mg inadequacy but as biomarkers of Mg assessment were not evaluated the diagnose of Mg deficiency was jeopardized [38]. Urinary Mg is an indicator most useful for population studies to be a sensitive biomarker to changes in Mg status resulting from variations in Mg intake [39].

Rocha et al. [40], in the cross-sectional study with 50 pregnant women at a public university hospital in Brazil, evaluated the dietary intake and status of Mg and calcium (Ca). The results showed that despite the high probability of dietary inadequacy of Ca and Mg (58 and 98%, respectively), erythrocyte, and plasma levels of two minerals were adequate due to a strong reduction in their urinary excretion.

Literature is controversial as to the relation of dietary Mg inadequacy with some chronic diseases. On one hand, experimental studies with rats clearly demonstrated the impact of the Mg restriction on its status [41, 42], and on the other hand, human studies do not provide evidence that the moderately low Mg consumption necessarily leads to Mg deficiency [37, 43]. This fact is due possibly to differences in the level of restriction between human and animal studies. For instance, in experimental studies it is possible to impose moderate to severe restriction; in population studies, on the other hand, Mg inadequacy assessed through dietary evaluation is not too expressive. For example, the BRAZOS study in which 2344 people were evaluated, the lowest level of Mg individual intake was 138 mg/day, that is 52 and 40% of the EAR for women and men, respectively [38]. Gobbo et al. performed a systematic review and meta-analysis to investigate associations of circulating and dietary Mg with risk of cardiovascular disease and showed that Mg average intake in studies included was 289 mg/d (82% of the EAR) [44].

Mg and inflammation

Mg deficiency is a condition that causes changes in cell proliferation of the immune system, increases the production of proinflammatory molecules, and influences

the onset or worsening of many diseases [24]. In recent decades, studies on Mg deficiency in rats have demonstrated changes in immune system cells evidenced by mast cells degranulation, increase in polymorphonuclear leukocytes and phagocytosis [45–47]. Changes in the thymus can also be observed in deficient animals. Rats fed diets with only 7% of the recommendation for rodents (35 mg/kg/diet) for a short period showed thymocytes with alterations in the expression of genes involved in the protection and repair of cells against oxidative stress [48]. Malpuech-Bregère et al. suggest that the activation of imune cells is the first consequence of severe acute (8 days) Mg restriction (32 mgMg/Kg) in weanling rats [46].

In humans, clinical and epidemiological studies suggest that Mg is associated with inflammatory process and oxidative stress. Data from a study conducted with individuals older than 51 years showed that 58% of them were consuming less than the EAR for Mg, and this fact was associated with increased plasma C-reactive protein [49]. A case-control study evaluated the Mg status and oxidative stress and inflammation in preeclampsia compared to a control group. They found that although Mg intake was below the EAR in both groups (did not achieve 85% probability of adequacy) only in pre-eclampsia the concentration of inflammatory cytokines and plasma and erythrocyte Mg were high. The authors suggest that the increased circulating levels of Mg may be a secondary effect of typical features of preeclampsia (vasoconstriction and peripheral vascular resistance) [50].

Sugimoto et al. [1] evaluated in vitro the immunomodulatory role of Mg in mononuclear cells from the maternal peripheral blood of women treated with MgSO 4 (6 mg/dL) and mononuclear cells from umbilical cord blood. The authors observed the reduction in TNF-α and IL-6 reduced expression of IkBα and NFkB activation. They also found in vitro that mononuclear cells exposed to 2.5 mM $MgSO_4$ decreased the production of inflammatory cytokines after stimulation with different TLR ligands, suggesting that Mg possibly has a broad spectrum anti-inflammatory activity.

In USA, the Women's Health Initiative Observational Study evaluated women of different ethnicities, aged 50–79 years, the association between dietary Mg intake and concentration of systemic inflammation biomarkers (CRP, IL-6, TNF-R2) and endothelial dysfunction (sICAM-1 and sVCAM-1) and E-selectin. The authors observed that an increase of 100 mg/d Mg intake was associated with a decrease in concentration of these inflammatory and endothelial biomarkers [51].

Given the above information, dietary Mg inadequacy seems to be associated to the emergence and evolution of diseases of inflammatory etiology such as obesity, insulin resistance, metabolic syndrome, and cardiovascular disease [34, 52, 53].

Mg and obesity, diabetes, and metabolic syndrome

Konishi et al. [54] showed that women in the highest quartile of Mg intake had significantly lower risk of diabetes when compared to women in the lowest quartile. They found no association between Mg intake and risk of diabetes in men. The differences between men and women are due to the fact that women have lower Mg body stores and consequently increased risk of Mg depletion. In China, Xu et al. [55] evaluated serum and urinary concentrations of Mg in groups with different morbidities. Subjects with type 1 diabetes (DM1, $n = 25$), type 2 diabetes with and without complications (DM2, $n = 137$), with change in fasting glucose (IFG, $n = 12$) or decreased glucose tolerance (IGT $n = 15$) were evaluated. The authors found that all groups had lower serum Mg concentrations compared to the matched control group and Mg urinary concentration was significantly higher in DM2 and DM1 groups compared to the control. In these cases, hyperinsulinemia and hyperglycemia may affect renal Mg transporters and, consequently, urinary Mg excretion increases [56].

Wang et al. [57] described an inverse association between dietary Mg intake and glucose, insulin and HOMA-IR in 234 non-diabetic subjects of both genders and also the benefit of higher level of Mg intake from foods for glycemic control. In experimental conditions, rats under hyperlipidemic and moderately Mg-restricted (70% of recommendation) diet exhibited lower hepatic insulin sensitivity, as evidenced by reduced phosphorylation of IR β, Akt, and IRS-1, without any change in the circulating blood glucose or insulin levels [33]. This study draws attention to the molecular changes caused by the reduction of Mg intake prior to installation of insulin resistance.

Guerrero-Romero and Rodriguez-Moran [58] studied obese and non-obese individuals of both genders, aged 20–65 years, with and without metabolic alterations (hyperglycemia, insulin resistance, hypertension, and increased triglycerides). The authors found that hypomagnesemia was positively associated with these alterations in both groups. They also observed that in obese patients, hypomagnesemia was strongly related to high levels of triglycerides and insulin resistance. On the other hand, normomagnesemia was more frequent in healthy subjects. In obese children and adolescents, serum Mg levels were inversely correlated with the degree of obesity and positively with an unfavorable lipid profile, as well as high blood pressure [59].

Study with diabetic patients has demonstrated an inverse correlation between serum Mg and fasting insulin level. They also described a highly significant correlation between Mg and insulin sensitivity indices: homeostasis model assessment of insulin resistance

(HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) [60].

In spite of the number of studies that have established the relationship between minerals and components of MS, more research is required to evaluate the effects of increased Mg intake and the reduction of the risk for type 2 diabetes and cardiovascular disease. It is well established that Mg modulates vascular tonus, coronary blood flow, contractility, and excitability of heart muscle and that dietary Mg restriction may be related to increased risk factors for cardiovascular disease and atherosclerosis [61]. It is worth mentioning that there is no consensus on what level of intake is required to effectively reduce the risk of disease and also what level of restriction is related to adverse health outcomes.

Ferrè et al. [62] in experimental testing in vitro with human umbilical vein endothelial cells (HUVEC) evaluated the effects of 24 h Mg restriction on the path of NFkB by electrophoretic mobility shift assay (EMSA) and used proteomic analysis to investigate proteins involved in inflammation and atherogenesis. Their results showed major proteins in atherogenesis as RANTES, IL-8, PDGF-BB, TIMP-2, and GM-CSF, as well as activation of the NFkB in the culture medium with low concentration of Mg (0.1 mM).

In humans, authors have demonstrated the relationship between low Mg intake and increased cardiovascular risk factors. Among them, Bain et al. [63] investigated the association between dietary Mg and blood pressure, total cholesterol and risk of cardiovascular event in a random population of adult men and women ($n = 4443$) from the EPIC-Norfolk cohort ($n \sim 25.639$). They showed that low Mg consumption was associated with increase of blood pressure, total cholesterol, and risk of cardiovascular event. The results of this study suggest that increasing dietary Mg could positively impact hypertension and risk of cardiovascular accident in men and total cholesterol levels in both sexes.

A cross-sectional study of high relevance by Guerrero-Romero et al. [64] evaluated the association between of pre-hypertension and hypertension with serum Mg in healthy Mexican children. The study population was divided into two groups ($n = 3954$) aged 6 to 10 years and 11 to 15 years. The results showed that serum Mg levels < 0.74 mmol/L were associated with pre-hypertension and hypertension in the two groups. The cross-sectional study of Rodriguez-Moran and Guerrero-Romero [65] demonstrated, in adults the relationship between serum Mg concentration and pre-hypertension. This study included apparently healthy adult volunteers ($n = 514$), in Mexico. Of these, only 175 met all inclusion criteria and were divided into two groups: control ($n = 107$) and pre-hypertensive patients ($n = 68$). The pre-hypertensive individuals had lower serum Mg (0.73 mmol/L) and high triglyceride levels when compared to the control group. However, due to limitations of the studies (for example, lack of evaluation of other risk factors for hypertension and of habitual dietary Mg intake), more research is needed to clarify the relationship between Mg intake and hypertension in adults and children remained undefined.

In summary, low Mg consumption and decreased plasma Mg levels apparently are risk factors for cardiovascular disease associated with dyslipidemia, inflammation, and endothelial dysfunction. Thus, increasing Mg intake may be a useful approach to prevent these conditions. Nevertheless, it is noteworthy that Mg upper limit of ingestion is 350 mg/d through supplements, and population intervention possibilities should be evaluated with caution.

Conclusions

There is a growing number of studies conducted to elucidate the mechanisms by which reduced Mg consumption contributes to the etiology of chronic diseases. Nevertheless, it is not clear whether dietary Mg inadequacy predisposes to or increases the progression of metabolic diseases or both, or if these patological conditions lead to impairment of Mg homeostasis. Although there are many evidences that the reduction of Mg intake contributes to the development of chronic disease, it is not yet clear on what level of daily dietary intake it is processed in humans. In this scenario, biomarkers as Mg in plasm, urine, erytrocyte are important for Mg status assessment. Mg decompartmentalisation in cases of some morbidities and the effect of Mg supplementation before or after the onset of the disease deserve to be investigated.

Abbreviations

CRP: C-reactive protein; EAR: Estimated Average Intake; GM-CSF: Granulocyte macrophage-colony stimulating fator; IKBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL: Interleukin; IL-6: Interleukin 6; MAGT1: Mg^{2+} transporter 1; Mg: Mg; $MgSO_4$: Mg sulfate; NFkB: Nuclear transcription factor kappa B; NK: Natural killer; NKG2D: Natural killer group 2 member D; PDGF: Platelet-derived growth factor; RDA: Recommended Dietary Allowance; sICAM-1: Soluble intercellular adhesion molecule-1; sVCAM-1: Soluble vascular cell adhesion molecule-1; TIMP: Inhibitor of metalloprotease; TLR: Toll-like receptor; TNFα: Tumor necrosis factor alpha; TNF-R2: Tumor necrosis factor receptor 2; TRPM6: Transient potential melastatin type 6; TRPM7: Transient potential melastatin type 7

Authors' contributions

AR and FL performed the bibliographic research and writing. CC made the general supervision and textual revision. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 13 September 2016 Accepted: 5 November 2016
Published online: 16 March 2017

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