Dietary Magnesium and Chronic Disease

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Although official magnesium (Mg) dietary reference intakes are open to question, a significant number of adults likely have intakes that are in the range of 50%-99% of the requirement. This moderate or marginal (subclinical) deficient Mg intake generally is asymptomatic. Animal studies, however, indicate that moderate or subclinical Mg deficiency primes phagocytic cells for the release of proinflammatory cytokines leading to chronic inflammatory and oxidative stress. Human studies have found that dietary Mg is inversely related to serum or plasma C-reactive protein (CRP). Individuals with apparently deficient Mg intakes have an increased likelihood of serum or plasma CRP ≥3.0 mg/L, considered an indicator of chronic inflammatory stress that increases the risk for chronic disease. In addition, elevated serum or plasma CRP in individuals with chronic disease is decreased by Mg supplementation, which suggests that Mg decreases the risk for chronic disease. The importance of dietary Mg intake on the risk for chronic disease through affecting inflammatory and oxidative stress is supported by numerous meta-analyses and systematic reviews that have found dietary Mg is inversely associated with chronic diseases such hypertension, ischemic heart disease, stroke, metabolic syndrome, diabetes, and colorectal cancer.

Key Words: Dietary magnesium deficiency, Inflammatory stress, Oxidative stress, C-reactive protein, Chronic disease risk

INTRODUCTION

Magnesium (Mg) is an element of critical nutritional importance for humans. Mg is a cofactor in over 600 enzymatic reactions vital for metabolic pathways that include DNA, RNA, protein, and ATP synthesis; cellular energy production and storage; glycolysis; and cellular second messenger systems.[1,2] Mg stabilizes ribonucleotides and dexoyribonucleotides for DNA duplication, transcription, and maintenance, and transfer RNA function. Mg regulates cellular ion channels, transporters, and signaling, which govern calcium, potassium, and sodium movement in and out of the cell. These cellular functions result in Mg being a controlling factor in nerve transmission, skeletal and smooth muscle contraction, cardiac excitability, vasomotor tone, blood pressure, and bone turnover.

Because Mg has so many critical functions, the body has mechanisms to maintain circulating and tissue levels. The kidney is critical to this maintenance. Nutritional experiments have shown that during low intakes of Mg, its amount excreted in the urine is decreased, percent absorbed from the diet is increased, and if necessary, body reserves (mostly in bone) are used.[1,2] When dietary intakes are adequate, the opposite occurs with Mg increasing in the urine and body reserves while the percent absorbed from the diet is decreased. The response of the body to maintain Mg homeostasis has made it difficult to establish status indicators of the presence of a Mg-deficient state.[3,4] This difficulty is compounded by mild or moderate Mg deficiencies (subclinical Mg deficiency) being mostly asymptomatic.[4] Thus, without a reliable biochemical or physiological indicator, a low dietary intake of Mg has been used to show an association between Mg and several chronic diseases. These conditions include hypertension, cardiovascular disease, metabolic syndrome, type 2 diabetes, CKD, osteoporosis, and neurological disorders as described in other articles in this publication.

MAGNESIUM REQUIREMENTS

The association between dietary Mg and chronic disease sometimes does not correlate well with deficient Mg intakes indicated by current dietary reference intakes (DRIs) or dietary reference values (DRVs) set by official committees. The inconsistent finding of correlations may be caused by DRIs suggesting a deficient intake not being correct. In the United States and Canada, DRIs set in 1997[5] for adults aged between 19 and 30 years, and 31 and 70 years, respectively, were recommended dietary allowances (RDAs) of 310 and 320 mg/d for women and 410-420 mg/d for men, and estimated average requirements (EARs) of 255 and 265 mg/d for women and 330 and 350 mg/d for men. The RDA is daily intake determined to meet the requirement of 98% of the healthy population, and the EAR is a daily intake determined to meet the requirement of 50% of the healthy population. These DRIs have been questioned because they were determined in the absence of a sensitive and reliable indicator of Mg status and the lack of balance data from well-controlled studies.[6,7] Since 1997, improved balance data have been reported for the determination of Mg DRIs,[7] which indicate that these DRIs are too high for many nonobese, healthy individuals.[7] In spite of this, the European Food Safety Authority released an opinion in 2015 that the adequate intake (AI) for adult females and males are 300 and 350 mg (12.34 and 14.40 mmol), respectively.[8]

The compelling data for resetting of Mg DRIs or DRVs to better assess the occurrence of deficient intakes include those from 27 tightly controlled metabolic ward studies.[6] Analysis of the cross-sectional data resulted in the finding of neutral balance and prediction interval values and considering surface, phlebotomy, menstrual, and seminal losses, that suggested the Mg EAR and RDA for a healthy 70-kg male or female would be 175 mg (7.20 mmol)/d and 250 mg (10.28 mmol)/d, respectively.[7] The balance data

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also found a neutral Mg balance per kg body weight that indicated individuals weighing more or less than 70 kg should have EARs and RDAs higher or lower than 175 (7.20 mmol) and 250 mg (10.28 mmol)/d, respectively.[7] For example, the suggested RDA for individuals weighing 100 kg would be 355 mg (14.60 mmol)/d and for individuals weighing only 50 kg would be 175 mg (7.20 mmol)/d. Body weight may be the reason that DRIs often are set higher for men than women; men are likely to weigh more. A higher requirement for Mg because of body weight also may be the reason for reports that a low Mg status occurs more often in obese than nonobese individuals.[9-11] It should be recognized that the metabolic unit balance data came from healthy individuals under optimal dietary and environmental conditions. The Mg requirement is likely increased by factors such as increased oxidative and inflammatory stress,[11] certain foods (eg, high in fiber/phytate), and medications (eg, proton pump inhibitors) that inhibit absorption and excessive alcohol intake or medications (eg, diuretics) that increase excretion.[2,12]

CLINICAL SUMMARY

- Moderate or subclinical Mg deficiency commonly occurs in industrialized countries such as the United States and Canada.
- Subclinical Mg deficiency primes cells to produce cytokines that lead to chronic inflammatory and oxidative stress.
- Dietary Mg deficiency is a significant factor in the occurrence of diseases that are associated with chronic inflammatory and oxidative stress.

Numerous associative studies also indicate that the preceding RDAs and AIs set for Mg are too high for most individuals. These studies show an association between dietary Mg and chronic inflammatory stress evidenced by elevated C-reactive protein (CRP),[13] cardiovascular disease risk,[14] cardiovascular events,[15] cardiovascular mortality,[16,17] hypertension,[18] and the metabolic syndrome.[19,20] In these associative studies, the most significant differences occurred when the mean lowest intake was <250 mg (10.28 mmol)/d, which support the suggested Mg RDA or AI of 250 mg (10.28 mmol)/d for a healthy 70-kg individual regardless of gender.

Regardless of the DRIs or DRVs used, surveys indicate that a large number of individuals routinely have intakes of Mg in deficient amounts in countries where unrefined foods of plant origin are not major components of the diet. A 2005-2006 survey conducted in the United States found that close to half of the population consumed less than the Mg EAR daily.[21] Mg intakes less than the EAR for females were 48% in ages 31-50 years, 55% in ages 51-70 years, and 70% in ages 71 and over; for males, it was 45% in ages 31-50, 58% in ages 51-70, and 80% in ages 71 and over. Even if the EAR and RDA are revised to 175 mg (7.20 mmol)/d and 250 (10.28 mmol)/d, respectively, for a healthy 70 kg person, the survey suggests that almost 50% of adult females and 25% of adult males would have intakes less than the revised RDA. Many individuals weigh more than 70 kg, and thus, it is likely that more than 25% of adults have usual intakes less than the EARs suggested by improved balance data. Most of the deficient Mg intakes would be in the range of 50%-99% of the requirement. Mg deficiency in this range is considered moderate to marginal, or subclinical, has also called chronic latent Mg deficiency,[22] and generally does not cause overt pathological signs. However, as indicated in the following, subclinical Mg deficiency can have significant pathological consequences.

MAGNESIUM DEFICIENCY ASSOCIATION WITH CHRONIC INFLAMMATORY AND OXIDATIVE STRESS

Animal Findings

Most chronic diseases associated with a deficient Mg intake have been characterized as having a chronic inflammatory and/or oxidative stress component. Animal experiments have shown that severely limiting Mg intake to less than 10% of the requirement results in an inflammatory response characterized by leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins, and excessive production of free radicals or oxidative stress.[23] Relatively short-term moderate to marginal or subclinical Mg deficiency alone has not been found to markedly affect variables associated with chronic inflammatory stress in animals.[24,25] Animal experiments indicate that an extended period of moderate Mg deficiency is needed to see an effect on inflammatory or oxidative stress. Long-term feeding (22 months) of a diet containing 150 mg (6.2 mmol)/kg increased plasma interleukin-6 and erythrocyte thiobarbituric acid reacting substances and oxysterols in rats.[26] Long-term feeding of such a diet during aging also increased the risks of increased blood pressure and aorta media thickness and large artery rigidity.[27] Reduction of dietary Mg to 50% of the requirement for 3 months increased the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-1β in osteoclasts and megakaryocytes in rats.[28]

Animal studies, however, have shown that an extended period of a moderate Mg deficiency is not needed to increase inflammatory or oxidative stress when other factors that can cause such stress are present. After 8-10 weeks, a moderate Mg deficiency increased serum thiobarbituric acid concentration, an indicator of increased reactive oxygen species formation (oxidative stress), in rats fed an atherogenic diet.[29] A moderate Mg deficiency has been found to increase oxidative or inflammatory stress in response to chemical oncogens[30] and low dietary vitamin E.[31] The indication that Mg deficiency can become evident with a short-term deficiency in the presence of inflammatory and oxidative stress conditions is supported by findings showing that a severe Mg deficiency exacerbates such stress caused by other factors, including selenium