Magnesium, inflammation, and obesity in chronic disease

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About 60% of adults in the United States do not consume the estimated average requirement for magnesium, but widespread pathological conditions attributed to magnesium deficiency have not been reported. Nevertheless, low magnesium status has been associated with numerous pathological conditions characterized as having a chronic inflammatory stress component. In humans, deficient magnesium intakes are mostly marginal to moderate (approximately 50% to <100% of the recommended dietary allowance). Animal experiments indicate that signs of marginal-to-moderate magnesium deficiency can be compensated or exacerbated by other factors influencing inflammatory and oxidative stress; recent studies suggest a similar happening in humans. This suggestion may have significance in obesity, which is characterized as having a chronic low-grade inflammation component and an increased incidence of a low magnesium status. Marginal-to-moderate magnesium deficiency through exacerbating chronic inflammatory stress may be contributing significantly to the occurrence of chronic diseases such as atherosclerosis, hypertension, osteoporosis, diabetes mellitus, and cancer.

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INTRODUCTION

Based on dietary intake recommendations, subclinical or marginal magnesium deficiency commonly occurs throughout the world. In the United States, the Food and Nutrition Board set the estimated average requirement (EAR) for magnesium at 255–265 mg/day for females and 330–350 mg/day for males. Also in the United States, data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) indicated that in about 60% of all adults the usual magnesium intakes from food do not meet the EAR. In addition, it is estimated that about 10% of adults older than 19 years have magnesium intakes from food and water that are about 50% of the US recommended dietary allowance (RDA) of 310–320 mg/day for females and 400–420 mg/day for males. Yet, widespread pathological conditions attributed to dietary magnesium deficiency have not been reported. As a result, an expert consultation for the Food and Agriculture Organization/World Health Organization concluded that evidence was lacking for nutritional magnesium deficiency occurring with consumption of diets supplying a range of magnesium intakes, some of which contain considerably less than the RDA for the United States and Canada as well as the recommended nutrient intake for the United Kingdom. However, epidemiological and correlation studies indicate that a low magnesium status is associated with numerous pathological conditions, including atherosclerosis, hypertension, osteoporosis, diabetes mellitus, and some cancers (colon, breast), which has resulted in some individuals concluding that magnesium deficiency is a greater nutritional problem than currently recognized. Recent findings provide some possible reasons for these divergent conclusions about the nutritional importance of magnesium.
INFLAMMATORY RESPONSE TO MAGNESIUM DEFICIENCY IN ANIMALS

Most pathological conditions associated with a low magnesium status have been characterized as having a chronic inflammatory stress component. Over 75 years ago, evidence was presented that suggested magnesium deficiency results in an inflammatory response. Evidence obtained in the past 25 years, mostly from animal experiments, has confirmed that severely limiting magnesium 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. Severe human magnesium deficiency caused by low dietary intake, based on dietary surveys, is unlikely; most people will have intakes that meet at least 50% of the RDA. Moderate-to-marginal or subclinical (approximately 50% to <100% of requirement) magnesium deficiency alone apparently does not markedly affect variables associated with chronic inflammatory stress in animal models. This suggests that dietary magnesium deficiency is not the primary cause of chronic diseases for which chronic low-grade inflammation is thought to be a major factor. However, some animal findings indicate moderate magnesium deficiency can enhance the inflammatory or oxidative stress induced by other factors. Such findings suggest that subclinical magnesium deficiency may play a contributory role in many pathological conditions by affecting the severity or presence of chronic inflammatory stress, which also results in oxidative stress.

Limited animal experiments have shown that a period of prolonged subclinical magnesium deprivation that results in no or minor abnormalities can have marked pathological consequences when some type of stress is applied. Over 50 years ago, Hegsted et al. found that growth of rats fed 250 mg (10.3 mmol) magnesium/kg diet (50% of their requirement) was not depressed. However, when the rats were maintained in a cold environment (13°C), growth was depressed in comparison with rats fed adequate amounts of magnesium. In one experiment, all six rats that were stressed further by feeding a diet high in calcium died within 24 days; all six rats in each of two groups fed adequate or higher amounts of magnesium survived. Recently, Chaudhary et al. found that 90 mg (3.70 mmol) magnesium/kg diet fed to rats, which metabolize fructose differently than humans, increased lipid peroxidation and decreased antioxidant enzymes (superoxide dismutase, glutathione-S-transferase, and catalase) more when the rats were fed high amounts of dietary sucrose instead of starch (increased oxidativestress). High dietary sucrose and fructose have also been found to increase indicators of chronic inflammation and oxidative stress in severely magnesium-deprived rats. Adrian et al. found that a long-term moderate magnesium deficiency (150 mg [6.2 mmol] magnesium/kg diet) during aging (which results in increased cardiovascular risks) increased the risks of increased blood pressure and aorta media thickness with increased collagen content and elastin/collagen ratio, which leads to large artery rigidity.

In addition to inflammatory and/or oxidative stress enhancing or inducing obvious abnormalities in subclinical or moderate magnesium deficiency, animal experiments have shown that preventing oxidative or inflammatory stress can prevent or alleviate signs of magnesium deficiency. Treatment with a specific substance P receptor blocker (L-703606) substantially attenuated the inflammatory and oxidative stress responses to almost normal in rats that were fed 90 mg (3.70 mmol) magnesium/kg diet for 3 weeks. In addition, treatment with antioxidant drugs and nutrients (vitamin E, propranolol, and probucol) was found to diminish the development of focal myocardial inflammatory lesions in rats under similar magnesium-deficient conditions. Estrogen, which is anti-inflammatory, was found to protect male rats from the adverse effects of magnesium deficiency. This effect is consistent with the finding that female rats are less susceptible to inflammation induced by magnesium deficiency than males. Recently, Rude et al. found that knockout of the inflammatory cytokine tumor necrosis factor-α (TNFα) receptor in mice reduced the adverse effects of magnesium deficiency on bone.

MAGNESIUM DEFICIENCY AND CHRONIC INFLAMMATION IN HUMANS

Human studies also indicate that a low magnesium status is associated with increased inflammatory and oxidative stress. C-reactive protein (CRP) is a well-documented indicator of low-grade or chronic inflammation. Several studies have found that magnesium intake was inversely related to elevated serum or plasma CRP. An analysis of 5,007 child participants (age range: 6–17 years) in the 1999–2002 NHANES found that children consuming less than 75% the RDA were 1.94 times more likely to have elevated serum CRP than children consuming more than the RDA for magnesium. A similar analysis of 1999–2002 NHANES data for 5,773 adults aged >17 years found a 1.48–1.75 times increased likelihood of elevated serum CRP for those consuming less than the RDA for magnesium. The odds ratio for an intake level less than 50% the RDA was 1.75 with a 95% confidence interval of 1.08–
The analysis also found that adults over the age of 40 years with a body mass index (BMI) >25 who consumed less than 50% of the RDA for magnesium were 2.24 times more likely to have elevated serum CRP. Among the adults with dietary magnesium intakes less than 50% of the RDA, individuals taking magnesium supplements of at least 50 mg/day were 22% less likely to have elevated serum CRP. A validated semiquantitative food questionnaire was used in a cross-sectional study of 1,653 Italian adults between the ages of 45 and 64 years. An elevated serum CRP (≥3 mg/L) was found in 42.5% of adults in the lowest magnesium intake tertile (median: 241.2 mg/day); elevated serum CRP was found only in 18.3% and 14.4% of subjects in the upper two tertiles (median intakes of 308.2 and 397.9 mg/day, respectively). In a cross-sectional study of 657 women aged 43–69 years in the Nurses’ Health Study, an age-adjusted linear regression analysis found that magnesium intake was inversely associated with plasma CRP concentration. Recently, a linear regression analysis of 3,173 postmenopausal women aged 50–79 years in the Women’s Health Initiative Observational Study found that magnesium intake, as assessed with a semiquantitative food questionnaire, was inversely associated with three plasma inflammatory biomarkers – CRP, TNF-α-R2, and interlukin-6 (IL-6). Low serum magnesium concentrations have also been shown to be associated with elevated CRP. In a cross-sectional study of 488 apparently healthy Mexican children, 109 (22.3%) and 101 (20.7%) had elevated serum CRP and low serum magnesium, respectively; 87.1% exhibited both. Adjusted multivariate logistic regression analysis found an odds ratio of 4.1 (95% confidence interval of 1.3–10.8) for an association between low serum magnesium and elevated serum CRP. An inverse relationship between serum magnesium and CRP concentrations was found in 68 patients with heart failure; a 300 mg (12.3 mmol)/day magnesium supplement attenuated the elevated serum CRP. Low magnesium status is also often found in people with the metabolic syndrome and type 2 diabetes, which are associated with higher plasma CRP concentrations.

**CHRONIC LOW-GRADe INFLAMMATION IN OBESITY**

Recently, some studies associating a low magnesium status with chronic inflammatory stress have involved obese subjects. Obesity, affecting over 35% of the US adult population, is a major risk factor for chronic diseases that have been associated with a low magnesium status, such as type 2 diabetes, atherosclerosis, and cancer. The seminal finding that TNF-α was overexpressed in adipose tissue of obese mice provided the first evidence of a link between obesity and chronic inflammation. Since then, numerous experimental, epidemiological, and clinical studies have confirmed that obesity is associated with chronic low-grade inflammation and abnormal cytokine production, increased acute-phase reactants, and activation of inflammatory signaling pathways involved in obesity-related disease development. Obese adipose tissue is infiltrated with macrophages, which are an important source of inflammatory cytokines. In humans, TNF-α expression is higher in adipose tissue from obese than from lean individuals. Adipose tissue also produces other proinflammatory factors such as interleukin-6 (IL-6) and various adipokines that mediate chronic inflammation, including leptin (pro-inflammatory) and adiponectin (anti-inflammatory). CRP production by the liver is regulated by TNF-α and IL-6.

Abnormal amounts of circulating TNF-α, IL-6, CRP, adiponectin, and leptin have been used to confirm the association between obesity and chronic inflammation in humans. For example, in a cross-sectional study of 16,573 individuals in the third NHANES study (1988–1994), logistic regression analysis showed that odds ratios for an elevated serum CRP concentration among individuals with a body mass index (BMI) of 25–<30, 30–<35, 35–<40 and ≥40 were 1.51, 3.9, 6.11, and 9.30, respectively. In a cross-sectional study, CRP, IL-6, and leptin increased significantly with increasing adiposity. Circulating adiponectin was found to be decreased by obesity.

**MAGNESIUM DEFICIENCY IN OBESITY**

Several studies have indicated that a low magnesium status in obesity is associated with chronic inflammation indicators, or with diseases with a chronic inflammation component. In a cross-sectional population-based study of 192 subjects, 91 had elevated serum concentrations of TNF-α; 7 (10.9%) with lean BMIs <25, 31 (48.4%) with overweight BMIs ≥25–<30, and 43 (67.2%) with obese BMIs ≥30. The multivariate odds ratios between low serum magnesium and elevated TNF-α concentrations in obese subjects was 1.8 (P = 0.001), whereas in lean and overweight individuals, the ratios were 1.1 (P = 0.12) and 1.3 (P = 0.09), respectively. Corica et al. found that 12 hypertensive obese subjects had significantly lower plasma magnesium concentrations than 25 non-obese healthy volunteers, while 26 normotensive obese subjects did not. This finding is consistent with magnesium supplementation lowering blood pressure in hypertensive, but not in normotensive, overweight Korean adults. Corica et al. also found a significant negative correlation between waist-to-hip ratio and plasma magnesium in obese subjects. Huerta et al. found that serum magnesium was significantly lower in 24 obese children than in 24 sex and puberty-matched lean controls. The obese children also exhibited increased fasting insulin and glucose.
MECHANISM OF ACTION OF MAGNESIUM DEFICIENCY IN INFLAMMATION AND OBESITY

Why chronic low-grade inflammation develops in obesity is not well understood. Not all obese people have increased indicators of inflammatory stress; thus, other factors including nutritional factors may be involved in its development. Because a low magnesium status apparently occurs more often in obese than non-obese individuals, one of the stressors causing the activation of inflammatory pathways may be magnesium deficiency. There is no question that severe magnesium deprivation, which rapidly decreases extracellular magnesium, results in an inflammatory response in animals. The inflammatory response most likely is caused by an increase in intracellular calcium and the priming of phagocytic cells, which results in the release of inflammatory cytokines.

However, dietary magnesium deficiency severe enough to cause a marked drop in extracellular magnesium in a few days is unlikely in humans. Nonetheless, animal deficiency findings support the suggestion that subclinical magnesium deficiency can cause, or contribute to, chronic inflammatory stress in humans through an effect on the cellular entry of calcium and its signaling that results in the release of inflammatory neuropeptides, cytokines, prostaglandins, and leukotrienes. Even a minor reduction in extracellular magnesium may be enough to increase intracellular calcium, especially if another factor is present that affects the mechanism through which magnesium regulates calcium entry. One of these mechanisms is the N-methyl-D-aspartate (NMDA) receptor. A reduction in extracellular magnesium lowers the threshold levels of excitatory amino acids (e.g., glutamate) needed to activate this receptor. Activation of this receptor allows the influx of calcium into the cell. The importance of the NMDA receptor in the inflammatory response to magnesium deficiency is indicated by the finding that NMDA receptor blockade decreased pro-inflammatory prostaglandin E2 in plasma and inhibited cardiac inflammation indicators in the heart, which were induced by magnesium deficiency in the rat. An NMDA antagonist also prevented hyperalgesia in rats. Obesity may accentuate the low extracellular magnesium effect through adipose tissue increasing circulating leptin. Leptin enhances NMDA receptor activation.

Decreased intracellular magnesium affecting cellular calcium handling may be another mechanism through which a subclinical magnesium deficiency can influence inflammatory stress. Intracellular magnesium can decrease without a marked change in plasma magnesium in humans fed a moderately magnesium-deficient diet. This is evidenced by decreased erythrocyte magnesium without much change in serum magnesium in women fed a moderately magnesium-deficient diet in carefully controlled metabolic unit studies. The moderate magnesium deprivation (approximately 107 mg/day for 72 days) decreased urinary calcium excretion and increased calcium balance without affecting plasma calcium concentration in postmenopausal women, which suggests intracellular calcium retention. This is consistent with an animal study showing that a moderate magnesium deficiency (220 mg/kg diet for 10 weeks) increased calcium absorption and balance in rats.

It has been postulated that calcium channels are controlled by regulatory gates that have binding sites for magnesium. Magnesium binding to the gate of the calcium channel blocks calcium influx into the cell. Low intracellular magnesium results in decreased blocking of the gate and increases in calcium influx.

Aberrations in calcium channels affecting the amount of ionized calcium in the cell have been reported to occur in obesity. Increased intracellular calcium has been found in animal models of obesity and in adipocytes of obese humans. Thus, changes in calcium handling may be responsible for some of the chronic inflammatory stress in obesity. Because magnesium has a regulatory role in calcium channel gates, changes in intracellular calcium handling in obesity may be exaggerated by low intracellular magnesium or small declines in extracellular magnesium induced by a subclinical magnesium deficiency. The relationship between magnesium and cellular calcium handling suggests further study is needed to determine whether subclinical magnesium deficiency can have pathological implications in conditions in which intracellular calcium or calcium signaling is abnormal; one of these conditions is obesity.

MODIFICATION OF THE INFLAMMATORY RESPONSE TO SUBCLINICAL MAGNESIUM DEFICIENCY

It should be emphasized that the study of the contribution of subclinical magnesium deficiency to chronic inflammation and resultant oxidant stress causing chronic disease will be challenging because these effects can be ameliorated by numerous other nutritional factors. As indicated above, animal experiments have shown that signs of magnesium deficiency can be ameliorated or prevented by antioxidant and/or anti-inflammatory factors. This suggests that the anti-inflammatory or antioxidant effects of numerous dietary factors could act by preventing inflammatory stress.
induced by a marginal-to-moderate magnesium deficiency. Among these dietary factors that ameliorate inflammatory and/or oxidative stress in obesity are omega-3 long-chain polyunsaturated fatty acids, coenzyme Q10, and phytochemicals in foods such as blueberries, cherries, grape seed, and green tea. Also, as indicated above, animal experiments indicate that inflammatory and oxidative stress induced by magnesium deprivation may be exaggerated by dietary conditions that would have an effect similar to that of high intakes of sucrose and fructose in rats; other dietary conditions with roles in obesity may include low intakes of vitamin A, vitamin C, and zinc. Both low and high dietary intakes of calcium may exaggerate the response to subclinical magnesium deficiency. Low calcium intake can lead to a 1,25-dihydroxyvitamin D-mediated increase in intracellular ionized calcium concentrations, which, as indicated above, can lead to inflammatory stress. High dietary calcium apparently interferes with the transport of magnesium across the cell membrane of non-excitable cells, such as those involved in intestinal transport. This interference is supported by findings such as the following: children who consumed the RDA for magnesium were in negative magnesium balance if their calcium intake was high. Calcium apparently competes with magnesium in a ubiquitously expressed constitutive ion channel, transient receptor potential melastatin 7 (TRPM7), which plays a central role in magnesium homeostasis. Exacerbation of a low magnesium status may have contributed to the finding that calcium supplementation increased vascular events in postmenopausal women.
CONCLUSION

The above review does not give a clear indication of the extent to which dietary magnesium deficiency-induced pathobiological conditions may occur in the 60% of the adult US population consuming less than the RDA for magnesium in the United States. It also does not refute the conclusion that there is little evidence of specific pathobiological conditions being caused only by dietary magnesium intakes that are below the RDA. However, the findings above reveal there is a basis for marginal-to-moderate dietary magnesium deficiency contributing significantly to the occurrence of diseases with a chronic inflammatory stress component, such as atherosclerosis, hypertension, osteoporosis, diabetes mellitus, and cancer; the findings may also explain why epidemiological and correlation studies have shown a low magnesium status is associated with these diseases. The suggestion that a subclinical magnesium deficiency can exaggerate inflammatory stress may be especially significant in obesity, which clinical magnesium deficiency can exaggerate inflammatory stress component, such as atherosclerosis, hypertension, osteoporosis, diabetes mellitus, and cancer; the findings may also explain why epidemiological and correlation studies have shown a low magnesium status is associated with these diseases. The suggestion that a subclinical magnesium deficiency can exaggerate inflammatory stress may be especially significant in obesity, which is characterized as having a chronic low-grade inflammation component and increased incidence of a low magnesium status. The possible relationships among magnesium, inflammation, obesity, and chronic disease are summarized in Figure 1.

Studies to further clarify the role of magnesium in obesity and comorbid conditions, and factors that affect that role, are needed to establish whether or not dietary magnesium deficiency is a significant nutritional concern. Meanwhile, it seems prudent to encourage intakes of magnesium near the RDA, particularly for individuals with physiological or nutritional characteristics that make them prone to increased inflammatory and/or oxidative stress.

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