Special Article

Suboptimal magnesium status in the United States: are the health consequences underestimated?

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In comparison with calcium, magnesium is an "orphan nutrient" that has been studied considerably less heavily. Low magnesium intakes and blood levels have been associated with type 2 diabetes, metabolic syndrome, elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer. Almost half (48%) of the US population consumed less than the required amount of magnesium from food in 2005–2006, and the figure was down from 56% in 2001–2002. Surveys conducted over 30 years indicate rising calcium-to-magnesium food-intake ratios among adults and the elderly in the United States, excluding intake from supplements, which favor calcium over magnesium. The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0. Dietary Reference Intakes determined by balance studies may be misleading if subjects have chronic latent magnesium deficiency but are assumed to be healthy. Cellular magnesium deficit, perhaps involving TRPM6/7 channels, elicits calcium-activated inflammatory cascades independent of injury or pathogens. Refining the magnesium requirements and understanding how low magnesium status and rising calcium-to-magnesium ratios influence the incidence of type 2 diabetes, metabolic syndrome, osteoporosis, and other inflammation-related disorders are research priorities.

INTRODUCTION

Dietary magnesium received less attention than dietary calcium by the nutrition research community in the United States during the 20th century – a time of prolific and varied research in nutrition. The US Department of Agriculture (USDA) first published the values for the calcium, phosphorus, and iron content of foods in 1945, while the values for magnesium content were not reported until preliminary findings of the magnesium content of 444 food items first appeared in 1963.[1] Magnesium first became a standard nutrient in food composition tables in the revised USDA Agriculture Handbook published in November of 1976,[2] but as late as 1984, values for the magnesium content of foods were not as prevalent as those for many other nutrients and they were particularly limited for commercial food products.[3] The National Health and Nutrition Examination Survey (NHANES) has reported on intakes of magnesium, but beyond NHANES1 (personal communication, CDC-Info, 8-3-10) and its large study of the population's serum magnesium levels in 1971–1974,[4] funding has been insufficient for NHANES to include blood or urinary magnesium values among its vast array of measurements in representative samplings of the population.[5]

Almost half (48%) of the US population has been shown to consume less than the daily requirement of

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magnesium from foods.[6] Magnesium is widespread in foods and is regulated physiologically by both renal and gut conservation.[7] Overt signs of clinical magnesium deficiency have not been routinely recognized in the healthy population, but because magnesium deficiency has been associated with critical health issues, including cardiovascular disease (CVD),[8] type 2 diabetes mellitus (DM2),[9,10] and osteoporosis,[11] a review of current research and dietary trends is warranted.

DISEASE STATES ASSOCIATED WITH DIETARY MAGNESIUM

Although diets ordinarily consumed by healthy Americans often do not meet the Dietary Reference Intake (DRI) values for magnesium,[12] they are not generally recognized as leading to symptomatic magnesium depletion. However, a number of clinical disorders have been associated with a low-magnesium diet. It has been suggested that mild degrees of magnesium deficiency present over time may contribute to a number of disease states, including those outlined below.

Type 2 diabetes and metabolic syndrome

CVD risk factors are strongly associated with DM2,[13] and both CVD and DM2 are considered as components of metabolic syndrome, a magnesium wasting disease.[9,14,15]

Dietary magnesium intakes have been negatively associated with metabolic syndrome,[9,16–18] as have serum magnesium levels.[19] Both DM2 and metabolic syndrome have been associated with low serum magnesium,[10] but the lower levels of serum magnesium in individuals with DM2 may be a consequence of the disease and its hypermagnesuria rather than a cause.[20]

Risk of DM2 has been associated with low dietary magnesium intake,[21,22] which may be influenced by fiber and glycemic load[23,24] as well as other nutrients such as calcium[25,26] and chromium.[27]

Elevated C-reactive protein

In human studies, reports consistently link both magnesium intake and serum magnesium status with C-reactive protein (CRP), a measure of inflammation associated with CVD risk,[28–30] metabolic syndrome,[19] and DM2.[28,31] CRP was found to be inversely proportional to magnesium intake in epidemiological studies,[29] children,[32] the Women's Health Initiative study,[33] a cross-section of the Nurses Study,[34] patients with DM2 and metabolic syndrome (in whom the association was independent of fiber intake),[35] adults in NHANES,[36] and women over 45 years of age in the Women's Health Study.[37] In addition, serum magnesium has been consistently shown to be inversely proportional to serum or plasma CRP in overweight/obese patients,[19,38] in hemodialysis patients,[39] and in patients hospitalized for both heart failure and other causes.[30] In one study, CRP was significantly higher (and serum magnesium significantly lower) in patients admitted for heart failure versus those admitted for other causes[30]; this study also showed oral magnesium of 300 mg/day given to heart failure patients raised both intracellular and serum magnesium while lowering serum CRP compared with control heart failure patients who were not receiving oral magnesium and showed no change in CRP, no rise in cellular magnesium, and a lesser rise in serum magnesium.

Hypertension

A number of studies have demonstrated an inverse relationship between low dietary intake of magnesium and blood pressure.[37,40,41] Hypomagnesemia and/or reduction of intracellular magnesium ion (Mg^{2+}) also has been inversely correlated with blood pressure. Patients with essential hypertension were found to have reduced free magnesium concentrations in erythrocytes. The magnesium levels were inversely related to both systolic and diastolic blood pressure. Intervention studies with magnesium therapy in hypertension have led to conflicting results, but a recent review of 44 studies[42] concluded that 486 mg magnesium/day, which is 1.2 to 1.6 times the adult Recommended Dietary Allowance (RDA), is necessary to achieve significant lowering of high blood pressure, unless subjects have been taking antihypertensive medications; in such medicated subjects, the daily critical magnesium dose is lowered by half, to 243 mg magnesium/day. The review also showed that magnesium supplementation as high as 600 mg/day did not lower blood pressure in studies with a majority of subjects who were normotensive at baseline.[42] Other dietary factors may also play a role. A diet of fruits and vegetables that increased magnesium intake from 176 mg/day to 423 mg/day (along with an increase in potassium) significantly lowered blood pressure.[43] The addition of nonfat dairy products that increased calcium intake lowered blood pressure even further.

The mechanism by which magnesium deficiency may affect blood pressure is not clear, but it may involve aspects of inflammation such as decreased production of prostacyclins and increased production of thromboxane A2, as well as enhanced vasoconstrictive effect of angiotensin II and norepinephrine. Transient receptor potential melastatin 7 (TRPM7) is an ion channel and protein kinase that is highly permeable to both calcium and magnesium and has been suggested to be involved in magne-

sium homeostasis. Recently, it has been suggested that vascular TRPM7 channels, which transport magnesium, may be altered in hypertension.[40,44]

Atherosclerotic vascular disease

Another potential cardiovascular complication of magnesium deficiency is the development of atheromatous disease.[45] Lipid alterations, including low HDL cholesterol,[38,46] have been reported in hypomagnesemic human subjects.[47] Epidemiological studies have inversely related both serum magnesium levels[48] and magnesium levels in drinking water to cardiovascular death rates.[49–51]

Platelet hyperactivity is a recognized risk factor in the development of CVD. Magnesium has been shown to inhibit platelet aggregation against a number of aggregation agents.[52] Diabetic patients with magnesium depletion have been shown to have increased platelet aggregation. Magnesium therapy in these subjects returned the response toward normal.[53] The antiplatelet effect of magnesium may be related to the finding that magnesium inhibits the synthesis of thromboxane A_2 and 12-HETE, which are inflammatory eicosanoids that are thought to be involved in platelet aggregation.[52] Magnesium also inhibits the thrombin-induced calcium influx in platelets[52] and stimulates the synthesis of prostacyclin (PGI^2), the potent antiaggregatory eicosanoid.[54]

Sudden cardiac death

Occurrence of sudden cardiac death was reportedly reduced by almost 40% in subjects with serum magnesium levels of ≥1.75 mEq/L compared with subjects having serum magnesium levels of ≤1.5 mEq/L in 14,232 adults aged 45–64 years who were followed up for 12 years.[55] In addition, it was significantly reduced with either higher dietary or plasma magnesium levels in women who were followed up for 26 years in the Nurses Health Study.[56] Khan et al.[57] found apparently opposite results, reporting no significant differences in multivariable-adjusted hazards ratio for baseline serum magnesium and the development of hypertension, CVD, or all-cause mortality in 3,531 middle-aged subjects over an 8-year period. However, the hazard ratio was significant ($P = 0.04$) for the development of CVD and for death when adjusted for age and sex only, with magnesium as a categorical variable. Hypomagnesemia at the time of admission to an intensive care unit seems to be associated with high mortality in critically ill patients with DM2.[58]

Osteoporosis

Osteoporosis accounts for approximately 2 million bone fractures per year in the United States, at a cost of over $17 billion.[59] This condition has been associated with magnesium deficiency. Experimental dietary magnesium deficit in animals has been associated with a decrease in skeletal growth[11,60] and a reduction in osteoblastic bone formation. Markers of bone formation have also been reduced, suggesting a decrease in osteoblastic function in these magnesium-deficient animals. An increase in the number and activity of osteoclasts in the magnesium-deficient rat and mouse has been reported. Bone from magnesium-deficient rats has been described as brittle and fragile. Biomechanical testing has directly demonstrated skeletal fragility in the magnesium-deficient rat and pig. Such experimental studies have been mostly conducted using levels of severe magnesium deficiency not common in the human population; however, animals with magnesium levels at 10%, 25%, or 50% of the requirement (levels which are present in the US population) show bone loss, decreased osteoblasts, and increased osteoclasts by histomorphometry.[11] In humans, epidemiological studies have demonstrated a correlation between bone mass and dietary magnesium intake in the appendicular and axial skeleton.[11] Few studies have assessed magnesium status in patients with osteoporosis. Low concentrations of magnesium in serum and erythrocytes, as well as high retention of parenterally administered magnesium, have suggested a magnesium deficit; however, these results are not consistent from one study to another. Similarly, while low skeletal magnesium content has been observed in some studies, normal or even high magnesium content has been found in others. The effect of dietary magnesium supplementation on bone mass in patients with osteoporosis has not been studied extensively. The effect of magnesium supplements on bone mass has generally led to an increase in bone mineral density, but larger, long-term, placebo-controlled, double-blind investigations are required. There are several potential mechanisms that may account for a decrease in bone mass in magnesium deficiency; for example, magnesium is mitogenic for bone cell growth, which may directly result in a decrease in bone formation with magnesium deficit. A recent study suggested that the TRPM7 magnesium channel is critical for osteoblast function and that magnesium deficiency may thereby decrease bone formation.[61] Magnesium also affects crystal formation; a lack of magnesium results in a larger, more perfect crystal, which may affect bone strength. Magnesium deficiency results in a drop in both serum parathyroid hormone and 1,25(OH)$_2$D; because both hormones are trophic for bone, impaired secretion or skeletal resistance may result in osteoporosis. An increased release of inflammatory cytokines may result in activation of osteoclasts and increased bone resorption in rodents.[11,60]

Other disorders

Magnesium deficiency has been associated with migraine headache, and magnesium therapy has been reported to be effective in the treatment of migraine.[62,63] Because magnesium deficiency results in smooth muscle spasm, it has also been implicated in asthma, and magnesium therapy has been effective for treating asthma in some studies.[64–66] A decrease in intracellular magnesiumion shown during acute asthma attacks was followed by an increase as the attacks subsided.[67] However, neither diet nor serum magnesium values was associated with asthma prevalence in Taiwanese children[68]; no difference in plasma magnesium was found between asthmatic and nonasthmatic children in Iran, while erythrocytic magnesium was significantly lower in the asthmatic group.[69] Lastly, high dietary magnesium intake has been associated with a reduced risk of colon cancer.[70]

DIETARY MAGNESIUM STATUS IN THE GENERAL US POPULATION

Insufficient magnesium intake from food

The current RDA for magnesium, based on balance studies, is 400 mg/day for young adult males and 310 mg/day for young adult females and increases to 420 mg/day and 320 mg/day for men and women, respectively, over 30 years of age (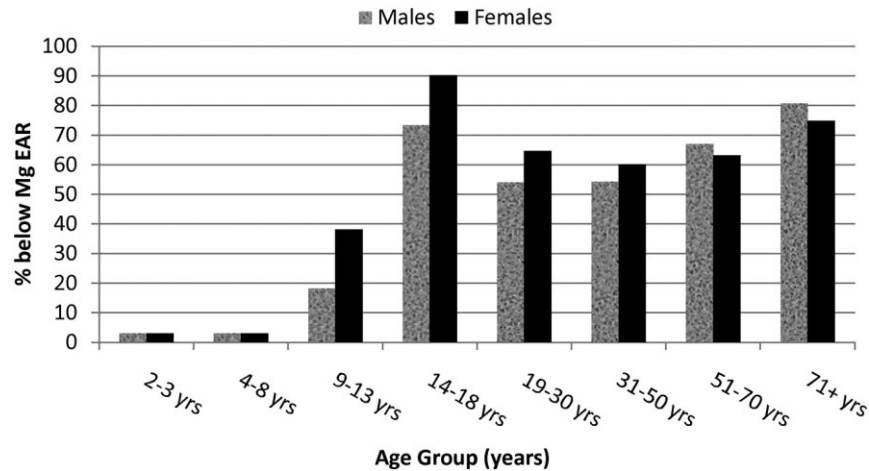Table 1).[12] The Estimated Average Requirement (EAR) for magnesium, i.e., the average daily amount deemed necessary for healthy individuals, is 330 mg/day for young adult males and 255 mg/day for young adult females, increasing to 350 mg/day and 265 mg/day, respectively, for men and women over 30 years of age.[12] Currently, almost half (48%) of the entire US population does not meet the EAR for magnesium from food consumed,[6] but this does not appear to be a static situation: This estimate is down from 56% for the same calculation using NHANES 2001–2002 food intake data.[71] Table 1 shows the percentage of various US age-gender groups ≥9 years of age who consumed less than the EAR for magnesium from food, using the same calculations of NHANES data from 2001–2002,[71] 2003–2004,[72] and 2005–2006.[6] This calculation for 2007–2008 intake data is not yet available. Only males aged 9–13 years show a possible increase in the percent inadequacy of magnesium intake from food, from 14% in 2001–2002 to 22% in 2005–2006; all other male age groups between 14 and 70 years show a possible decrease in the percent inadequacy, from 55–78% collectively in 2001–2002 down to 45–68% collectively in 2005–2006. Among elderly males ≥71 years, no change was observed from the high level of 80% who consumed less than the EAR for magnesium from food. These possible trends have not been tested statistically. For females, Table 1 shows a possible decrease in magnesium inadequacy for girls aged 9–13 years (from 44% in 2001–2002 to 30% in 2005–2006) and for all age groups ≥31 years, from 64–82% in 2001–2002 to 48–70% in 2005–2006. Females in the

Table 1 **Estimated average requirement (EAR) and recommended daily allowance (RDA) for US children, teens, and adults,[12] along with proportion of US children, teens, and adults consuming less than the EAR of magnesium (Mg) with their daily food diet according to NHANES 2001–2002,[71] 2003–2004,[72] and 2005–2006.[6]**

Age	RDA for Mg (mg/day)	EAR for Mg (mg/day)[12]	Percentage consuming <EAR 2001–2002	Percentage consuming <EAR 2003–2004	Percentage consuming <EAR 2005–2006
Males					
9–13 years[a]	240	200	14%	18.7%	22%
14–18 years[b]	410	340	78%	74.2%	68%
19–30 years[b]	400	330	55%	56.1%	51%
31–50 years[b]	420	350	61%	56.9%	45%
51–70 years[b]	420	350	70%	73.1%	58%
≥71 years	420	350	81%	81.0%	80%
All men ≥19 years[b]	–	–	64%	–	53%
Females					
9–13 years[b]	240	200	44%	40.4%	30%
14–18 years	360	300	91%	90.7%	89%
19–30 years	310	255	64%	64.8%	65%
31–50 years[b]	320	265	65%	67.0%	48%
51–70 years[b]	320	265	64%	70.4%	55%
≥71 years[b]	320	265	82%	72.5%	70%
All women ≥19 years[b]	–	–	67%	–	56%
All persons ≥1 year[b]	–	–	56%	56.6%	48%

[a] Age-gender group may be declining in Mg adequacy.
[b] Age-gender group may be gaining in Mg adequacy.

Figure 1 **Proportion of the US population below the Estimated Average Requirement (EAR) for magnesium (Mg). Average of three USDA surveys, 2001–2002,[71] 2003–2004,[72] and 2005–2006,[6] for each age-gender group.**

prime childbearing age group of 14–30 years, appear to show the same high level of inadequacy throughout the survey periods, about 90% for teens 14–18 years and 64% for women aged 19–30 years. Averaging the three surveys performed in 2001–2002, 2003–2004, and 2005–2006 (Figure 1) shows that over 50% of all adult groups of both sexes failed to meet the EAR, and for males and females aged 14–18 years, this figure rose to an average of >70% and 90%, respectively.

Accuracy of current EAR and RDA for magnesium

The estimates of magnesium deficits in the US population are based on the EAR and RDA of 1997.[12] The EAR for magnesium estimates the amount of daily magnesium that provides magnesium balance in 50% of the population. The RDA uses the EAR plus twice the standard deviation (based upon an assumption that the coefficient of variation is 10%) to estimate the amount of daily magnesium necessary to provide the EAR for 97.5% of the healthy population. The balance study most relied upon to set the EAR was a year-long study performed by Lakshmanan et al.[73] of 34 free-living subjects on self-selected diets; balance was measured during four 1-week-long periods. Duplicate plate composites of subjects' habitual diets were collected during balance periods for analysis of magnesium content. The level of magnesium found to supply balance in just above half of the men and just under half of the women was 4.3 mg/kg/day, an amount that was somewhat confirmed by Seelig's review[74] of 14 pre-1962 magnesium balance studies: in about half of the balance periods, males had a negative magnesium balance on intakes between 4.0 mg/kg/day and 5.9 mg/kg/day (depending upon whether a +15 mg correction for sweat losses was made), and in roughly half of the balance

periods, women had a negative magnesium balance on intakes between 4.0 mg/kg/day and 4.9 mg/kg/day.[74] The studies examined in the Seelig review were not included in the DRI assessment, as they were all performed before atomic absorption spectrophotometry was available for magnesium determinations.[12] A more recent magnesium balance study performed by Hunt and Johnson[75] used data from several metabolic unit studies at the Grand Forks Human Nutrition Research Center in a model that predicted neutral magnesium balance at 2.36 mg magnesium/kg/day for healthy persons, regardless of age or sex; this is just over half (55%) the magnesium level used by the DRI Committee to achieve balance in half the population. Conducted in 2006, the study was not available to the DRI Committee, which released its report in 1997. Serum magnesium values were not reported in the Hunt and Johnson study.[75] Lakshmanan et al.[3] reported serum magnesium values a bit below 0.80 mmol/L, which is considered within the normal range[4] but is also associated with impaired glucose tolerance and high fasting glucose[10] as well as chronic latent magnesium deficiency (CLMD),[76] a subtle chronic negative magnesium balance in a large number of people who appear healthy. Although in magnesium deficit, persons with CLMD show serum magnesium levels within the "normal" reference interval primarily due to magnesium contributions from bone maintaining the serum magnesium concentration. Such individuals might require a higher magnesium intake to achieve magnesium balance than do individuals who are fully magnesium replete, but this has not been measured directly. The inclusion of assumed healthy subjects with CLMD in magnesium balance studies may result in higher measures of magnesium balance and high variability.

The Hunt and Johnson[75] study predicted a magnesium EAR of 165 mg/day for healthy adults, which, using

magnesium intakes from the 2005–2006 NHANES study,[6] would result in 0% of all adult males and 7–19% of all healthy adult women having inadequate magnesium intake from food; this is remarkably less than the 53% of adult males and 56% of adult females who consume less than the current EAR for magnesium (Table 1). To evaluate how these two divergent estimates of US magnesium adequacy are to be viewed, the details below are provided.

The RDA is defined as the EAR plus two standard deviations of the EAR. Hunt and Johnson[75] reported two standard deviations or 95% of the prediction interval for a recommended magnesium RDA at 237 mg/day. Supporting this lower-than-current magnesium RDA for healthy adults is an NHANES study[36] that showed adults receiving less than 50% of the RDA of magnesium (i.e., <210 mg for males and <160 mg for females) were likely to have normal-range-but-elevated CRP levels (1.48- to 1.75-fold). Moreover, women over the age of 43 years showed elevated CRP levels (as well as other inflammation biomarkers) within the normal range at dietary intakes of magnesium below 230 mg/day.[34] The Shanghai Women's Study showed a significant negative association between dietary magnesium and diabetes at magnesium intakes below 213.8 mg/day (lowest quintile median); however, these subjects were also low in calcium.[26] There are also studies suggesting an adult magnesium RDA of 237 mg/day could be too low. Women above the age of 45 years showed raised levels of CRP as well as significantly more components of metabolic syndrome at total magnesium intakes of ≤250 mg/day.[37] Postmenopausal women in the lowest quintile of magnesium intake (low quintile median = 269.5 mg/day) showed CRP levels approaching and/or surpassing the high normal limit of 3.0 mg/L.[33] A study of middle-aged and older Chinese people reported magnesium intakes of 372 mg/day in the "normal" group and 315–332 mg/day in the "non-normal" groups associated with hypertension, impaired fasting glucose, or diabetes as well as lower erythrocytic magnesium, but no significant differences in the erythrocytic levels and dietary intakes of other minerals.[77] The Women's Health Study showed a significant negative trend for hypertension and magnesium intake when the lowest quintile median of magnesium intake was 250 mg/day,[37] and it has been reported that genetic variants of the magnesium channels, TRPM6 and TRPM7, increase the risk of DM2 in women whose intake of dietary magnesium is less than 250 mg/day.[78] Such studies suggest that part of the healthy adult population may have CLMD. Studies to determine the proportion of the "healthy" adult population with CLMD are needed to further the existing knowledge of magnesium requirements and enable a true evaluation of magnesium status in the US population.

The increasing ratio of calcium-to-magnesium intake from foods

Calcium intake from food in the United States has increased over time relative to magnesium intake, according to an analysis[79] of USDA surveys since 1977.[80–86] Between the USDA's 1977 and 2007–2008 surveys, the mean magnesium intake in young adults aged 19–34 years rose by 11–16%, while mean calcium intake in the same group rose by 32–43% (Figure 2). Similarly, the mean magnesium intake for adults aged 35–50 years rose by 12–18%, while the mean calcium intake for this group rose by 48–64% (Figure 3). Adults aged ≥50 years showed 11–40% increases in calcium intake from food, with increases in magnesium intake from food at ⁻2% to ⁺16% over the 13 years between 1994–1995 and 2007–2008 (data not shown). For all age-gender groups in this analysis, the percent increase in mean magnesium intakes compared closely with the percent increase in mean energy intakes, while the percent increase in mean calcium intakes was substantially higher (Figures 2 and 3); this suggests the increasing calcium-to-magnesium ratio comes from higher calcium intake via food selections, the rising calcium content of food, or both.

Contribution of supplement usage to magnesium and calcium-to-magnesium intake

Both food and supplement intakes of calcium and magnesium have increased in the US population over the past 15–30 years, with calcium intake increasing at a greater rate than that of magnesium. As a result, the ratio of calcium-to-magnesium intake from food appears to be increasing, a trend enhanced with mineral supplement usage. Less than 20% of the US population take magnesium supplements, mostly as MgO,[87] and in 2008, calcium sales accounted for 54% of all nutritional mineral sales, while magnesium represented only 15% of these sales.[88] While sales of magnesium supplements grew at twice the rate as sales of calcium supplements in 2008,[88] one study showed that US adults using calcium and magnesium supplements all raised their magnesium intake from below their EAR to above, yet all, and especially adult women, substantially increased their ratio of calcium-to-magnesium intake via supplement usage.[89]

The increasing calcium-to-magnesium ratio and potential concerns

Recent studies have linked calcium supplementation in older women with increased risk of heart attack. In a 5-year study of 1,471 postmenopausal women (mean age 74 years), subjects randomized to calcium supplementa-

Women < 35 yrs

■ Ca ▨ Mg

Men < 35 yrs

■ Ca ▨ Mg

% rise in mean intake, 1977 - 2007/8		
	Women	Men
Ca, mg/day:	+43%	+32%
Mg, mg/day:	+16%	+11%
Energy, kcal/day:	+13%	+14%

Figure 2 **Mean calcium (Ca) and magnesium (Mg) intakes from food, with percent increases in mean Ca, Mg, and energy intakes, 1977 through 2007–2008, US young adults aged <35 years.[79]**

tion experienced myocardial infarction (heart attack) significantly more frequently ($P = 0.01$) than subjects receiving placebo.[90] Additional evidence comes from a meta-analysis of 11 trials representing 11,921 women aged ≥40 years, which showed a 27% increase ($P = 0.038$) in heart attacks in the calcium-supplemented groups

(without vitamin D) compared to placebo.[91] When expanded to data from 28,072 participants in the Women's Health Initiative Calcium-Vitamin D Supplementation Study, the 25% increase in heart attacks with calcium supplementation (now with or without vitamin D) was confirmed ($P = 0.004$), and the 15% higher risk of

Women, 35 - 50 yrs

■ Ca ▨ Mg

Men, 35 – 50 yrs

■ Ca ▨ Mg

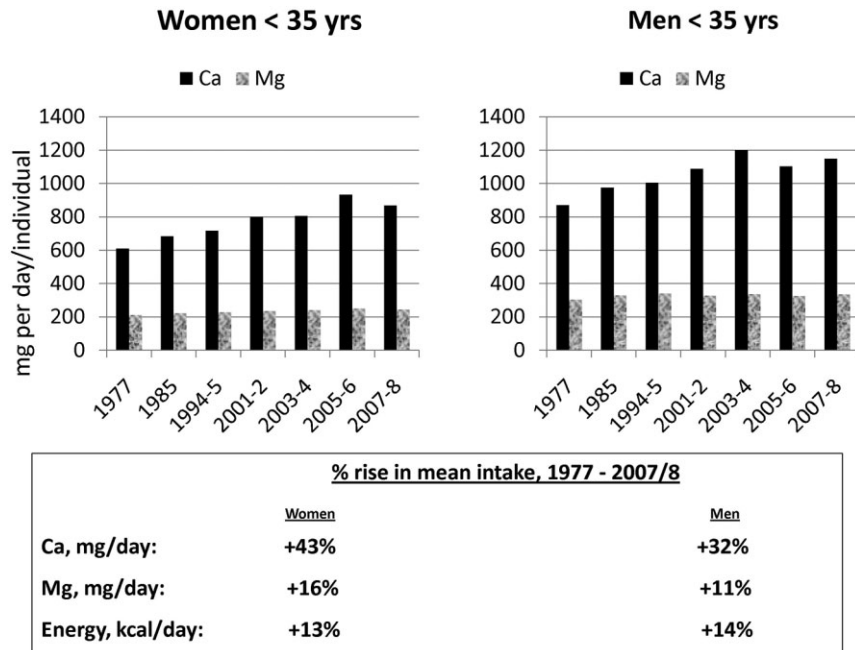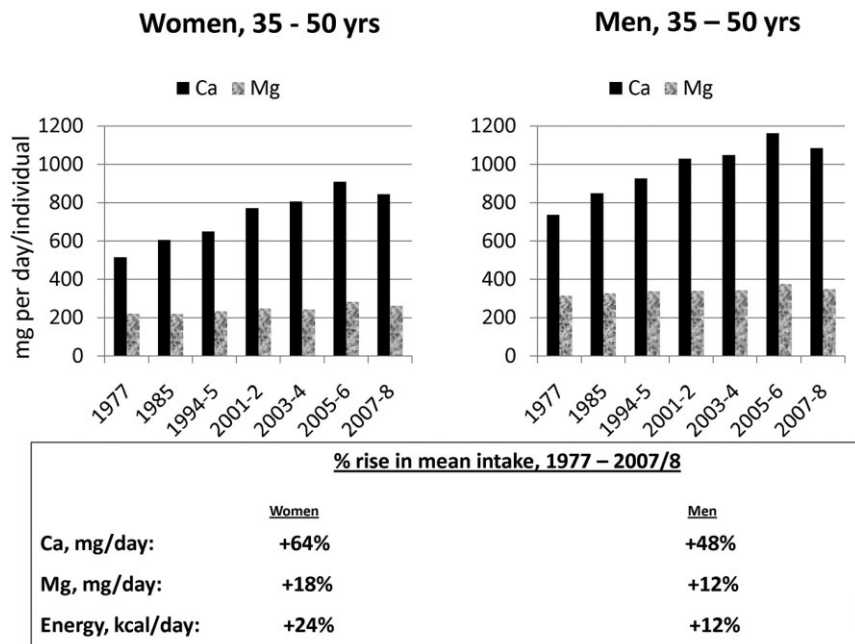| % rise in mean intake, 1977 – 2007/8		
	Women	Men
Ca, mg/day:	+64%	+48%
Mg, mg/day:	+18%	+12%
Energy, kcal/day:	+24%	+12%

Figure 3 **Mean calcium (Ca) and magnesium (Mg) intakes from food, with percent increases in mean Ca, Mg, and energy intakes, 1977 through 2007–2008, US adults aged 35–50 years.[79]**

stroke/heart attack ($P = 0.009$) with calcium supplementation in the larger sample reached significance.[92]

Dietary magnesium was not considered in the studies performed by Bolland et al.,[90–92] so it is not known if low magnesium status with concomitant high ratios of calcium-to-magnesium intake upon calcium supplementation may have contributed to the results. Evidence supporting the hypothesis that adequate magnesium intake may attenuate the risks associated with high calcium intakes by providing a lower calcium-to-magnesium ratio is seen in another study focusing on mortality. Kaluza et al.[93] found that dietary calcium intakes of 1,230 mg/day to over 1,600 mg/day were associated with a significantly lower rate of all-cause mortality than calcium intakes of less than 1,230 mg/day in a large study of men aged 45–79 years.[93] Calcium interaction with magnesium (and moderate ratios of calcium-to-magnesium intake, neither measured nor reported) may have been important in this recent Swedish study in which magnesium intake was not associated with all-cause, CVD, or cancer mortality.[93] Magnesium intakes were adequate in even the lowest tertile of magnesium intake, with subjects in the 5th-percentile of magnesium intake (355 mg/day) exceeding the EAR (350 mg/day) for adult men; this led the authors to conclude that all subjects had adequate magnesium status. However, calcium intakes were slightly less than adequate (<1,230 mg calcium/day) in the 7,786 men in the lowest tertile, with the 5th-percentile of calcium intake (798 mg/day) being approximately equal to the newly established calcium EAR (800 mg/day)[94] for men under the age of 70 years and 20% below the new calcium EAR (1,000 mg/day)[94] for men ≥70 years. Thus, this study found that men, all with adequate magnesium status and some with inadequate calcium intake, showed lower all-cause mortality as their calcium intake rose to adequate levels and beyond. This result is not surprising, as calcium is an essential nutrient necessary in adequate amounts for optimal health, nor does it suggest calcium intake is more or less important than magnesium intake in all-cause mortality. This study does show that above-adequate intake of magnesium does not lower mortality for CVD, cancer, or all cause, but it does not show whether the higher-than-adequate intakes of magnesium impacted the lower, less-than-adequate intakes of calcium or whether the ratio of calcium-to-magnesium intake was associated with mortality; this is where the calculation of individual calcium-to-magnesium ratios with statistical analysis could provide further knowledge.

Kaluza et al.[93] also confirm the Seelig[74] finding that above-optimal intakes of calcium (in this case >1,599 mg/day) in the face of fully adequate magnesium intakes will not cause a negative magnesium balance. This is probably not true in studies with less-than-adequate magnesium intakes: Seelig[74] showed that at magnesium intake levels between 4 mg/kg/day and 10 mg/kg/day, calcium intake levels close to 800 mg/day decreased magnesium retention in men. Men with magnesium intake levels at or above 6 mg/kg/day remained in positive magnesium balance, while those with magnesium intake levels at or below 5 mg/kg/day usually moved into negative magnesium balance on calcium intakes close to current EAR levels of calcium. Thus, for studies employing close-to-adequate magnesium intakes, one might expect positive magnesium balance (and thus no negative health impacts caused by magnesium deficit) with low calcium intakes but not with calcium intakes at or higher than EAR levels.[74] However, both men and women with magnesium intakes below 4 mg/kg/day showed less negative magnesium balance with EAR levels of calcium than with lower calcium intakes.[74] These complex interactions between calcium and magnesium mean that nutrition studies measuring either magnesium or calcium without the other can produce inconsistent results due to unintended or unknown rising or falling magnesium and/or calcium balance with concomitant health outcomes. Studies can be further complicated by the fact that diets which are low in magnesium are often low in calcium as well.[95] To fully understand the relationships between magnesium and/or calcium intakes and health, study of the ratio of calcium-to-magnesium intake as well as the degrees of both magnesium and calcium adequacy are necessary.

CALCIUM-TO-MAGNESIUM RATIO IN CALCIUM ACTIVATION, INFLAMMATION, AND METABOLIC SYNDROME

The importance of the cellular calcium-to-magnesium ratio for the physiological function of several tissues has been largely elucidated by Resnick,[96–98] who showed a strong physiological/cellular link between a rising intracellular ratio of calcium to magnesium and aspects of metabolic syndrome, including hypertension, hyperinsulinemia, insulin resistance, and left ventricular cardiac hypertrophy. Inflammatory syndrome can also be added to the effects of possible cytosolic calcium activation as a result of magnesium deficit[99] and its concomitant high calcium-to-magnesium ratio within cells.

Activation of calcium ion (Ca^{2+})-dependent signaling events occurs when intracellular levels of calcium are increased. This induces a range of downstream cascades, including the uncoupling mitochondrial electron transfer from ATP synthesis and the activation and overstimulation of enzymes such as proteases, protein kinases, and nitric oxide synthase.[100] In rodent studies, neuronal sources of a neuropeptide, substance P, contributed to very early pro-oxidant/proinflammatory changes during magnesium deficiency.[101] Such neurogenic inflammation

was systemic, affecting blood cells and cardiovascular, intestinal, and other tissues in this rat model, leading to impaired cardiac contractility similar to that seen in patients with heart failure.[101]

Mechanisms for such calcium activation occurring with magnesium depletion may be elucidated by active research of the TRPM channels. Patients with genetic primary hypomagnesemia and secondary hypocalcemia showed TRPM6 and its homologue TRPM7 to be key components of epithelial magnesium reabsorption, and TRPM7 has been characterized functionally as a constitutively active ion channel permeable for a variety of cations, including Ca^{2+} and Mg^{2+}, and regulated by intracellular concentrations of magnesium and/or magnesium-nucleotide complexes.[102,103] While TRPM6 appears to be involved mainly in regulating total body magnesium levels through the kidneys and gastrointestinal tract, TRPM7 may be more important in regulating intracellular Mg^{2+} homeostasis.[44] At physiological pH, both Ca^{2+} and Mg^{2+} bind to TRPM7, while currents for monovalent ions are inhibited.[104] Dysregulation of TRPM7 is associated with molecular processes that promote vascular calcification, including vascular smooth muscle cell transformation to an osteogenic phenotype. Magnesium normalized TRPM7 dysregulation and prevented calcification of vascular smooth muscle cells. Magnesium appears to negatively regulate vascular calcification and osteogenic differentiation through increased/restored TRPM7 activity and increased expression of anticalcification proteins. These new molecular insights suggest a protective role for TRPM7/magnesium in processes associated with vascular calcification.[105] Additionally, it has been recently proposed via protein structural analysis that Mg^{2+} plays an active role in the Ca^{2+}-ion-dependent regulation of cellular processes by stabilizing the resting state of some calcium-binding proteins that contain the EF-hand motif, a common building block of a large family of proteins that function as intracellular Ca^{2+} receptors.[106]

Magnesium deficiency may be a common link between stress, inflammation, and metabolic syndrome because magnesium deficiency at the cellular level can elicit calcium activation in an inappropriate response, i.e., the calcium-activated cascade is not triggered by an environmental injury or pathogen but rather as a result of a magnesium deficit that manifests in various tissues as aspects of CVD, DM2, and other health conditions associated with low magnesium. Active research on the recently discovered TRPM channels, which regulate both calcium and magnesium ion transport and calcium-binding proteins such as those with the EF-hand motif that depend upon adequate Mg^{2+} to remain "at rest," may lead to an understanding of possible mechanisms to explain how rising calcium-to-magnesium ratios at the cellular level may be among the root causes of metabolic syndrome and its links to DM2, CVD, osteoporosis, and other diseases. Other proteins important in the cellular transport of magnesium may yet be found[107] in the complex dynamics of magnesium homeostasis.

It is possible that the cellular calcium activation phenomenon is part of the pathology of a dietary magnesium deficit caused by low dietary magnesium, which can be exacerbated by a high dietary calcium-to-magnesium ratio, and this inappropriate calcium activation at the cellular level can lead to DM2, CVD, or other manifestations of magnesium deficiency if the magnesium inadequacy is not corrected.
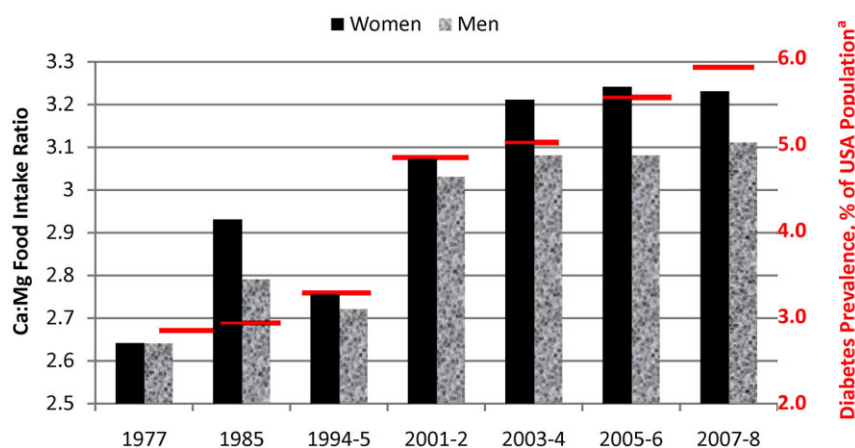
Figure 4 **Dietary calcium-to-magnesium (Ca:Mg) intake ratio from foods for US adults,[79] along with prevalence of diabetes.[109] The 1977 and 1985 intake surveys cover adults aged 19–50 years; all other surveys cover adults aged ≧20 years.**
[a]Diabetes prevalence: Age-adjusted percentage of civilian, noninstitutionalized population with diagnosed diabetes in the United States, 1980–2008, as reported by the CDC[109]

Considering this background, the following association is intriguing and warrants further research by means of measurement of the calcium-to-magnesium ratio in physiological studies as well as in nutrient intake studies.

RELATIONSHIP BETWEEN INCREASING CALCIUM-TO-MAGNESIUM INTAKE AND PREVALENCE OF DIABETES

Because symptoms of DM2 have been associated with intracellular calcium-to-magnesium ratios,[96–98] the relationship between the calcium-to-magnesium ratio from food intake and the incidence of DM2 is of interest. Between 1980 and 2008, the crude incidence of diagnosed DM2 in the US population increased 164%, and the age-adjusted incidence rose 143%.[108] The rate of change in the incidence of diagnosed DM2 has not been constant; rather, the incidence remained largely unchanged in the 1980s and increased sharply in the mid-1990s through 2008, the same timeframe in which the calcium-to-magnesium intake from foods for this population went from largely below 3.0 to largely above 3.0 (Figure 4). Proper statistical assessment of the increase in the calcium-to-magnesium ratio over the years is required to appropriately compare it with the incidence and prevalence of DM2 and to better assess the validity of this association. Informative results might also be gained by measuring and calculating the ratio of calcium-to-magnesium intake as part of individual medical and dietary exams as well as research studies.

CONCLUSION

It is clear that a substantial proportion of the US population does not meet the requirement for dietary magnesium as outlined by the RDA or EAR, and the ratio of calcium-to-magnesium intake for this population is rising. The possibility that some portion of the US population, who are assumed to be healthy and fully magnesium replete, in fact have a chronic latent magnesium deficit complicates the true assessment of this population with regard to magnesium status. Health consequences need to be considered for the 48% of persons in the United States who are not meeting the EAR for dietary magnesium, many of whom are also consuming lower than optimal levels of calcium. Moreover, the health consequences of the increasing ratio of calcium-to-magnesium from food should be addressed. The inclusion of serum and urinary magnesium reporting by NHANES would be beneficial. Longitudinal studies that include an assessment of initial magnesium status, prevalence of CLMD, and calcium-to-magnesium ratios in diet and/or tissues are necessary and clinical trials testing magnesium supplementation against placebo and phar-

maceuticals for cardiovascular risk factors/events, DM2, and osteoporosis should be research priorities.

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