Relations of Magnesium Intake with Metabolic Risk Factors and Risks of Type 2 Diabetes, Hypertension, and Cardiovascular Disease: A Critical Appraisal

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Abstract: Magnesium is an essential mineral with several dietary sources including whole-grains, green leafy vegetables, legumes, and nuts. The western diets that are characterized by a high intake of processed foods contribute to a high prevalence of inadequate magnesium intake in industrialized countries. Accumulating data from animal models and small trials in humans support a pivotal role of magnesium in glucose homeostasis, insulin secretion and action. In observational studies, magnesium intake has been inversely associated with insulin resistance, type 2 diabetes mellitus (DM), hypertension, and cardiovascular diseases (CVD). Herein we systematically review the current literature from human population studies on dietary magnesium intake and a host of metabolic disorders, focusing primarily on type 2 DM, hypertension, and CVD. The available evidence indicates that dietary magnesium may favorably affect a cluster of metabolic abnormalities including insulin resistance, hypertension, and dyslipidemia, known as metabolic syndrome. The metabolic syndrome is prevalent worldwide and is associated with greater risks of major chronic diseases, particularly type 2 DM and CVD. Further, available epidemiologic data provide strong support for dietary recommendations to increase consumption of magnesium-rich foods for the primary prevention of the metabolic syndrome and associated chronic diseases. Future studies are warranted to assess the efficacy of magnesium supplementation in the prevention and/or treatment of metabolic syndrome and type 2 DM in human populations.

Keywords: Magnesium intake, metabolic risk factors, hypertension, insulin resistance, type 2 diabetes, cardiovascular disease.

INTRODUCTION

Magnesium is an essential mineral critical for many metabolic functions in the body. Magnesium is primarily found in many unprocessed foods, such as whole grains, green leafy vegetables, legumes, and nuts [1-3]. The Recommended Dietary Allowances (RDA) for magnesium is 420 mg per day for adult men and 320 mg per day for women. Magnesium requirement increases during pregnancy and lactation. Suboptimal intake of dietary magnesium has long been observed in the general population of industrialized countries [4]. Surveys indicate that the average magnesium intake in the US general population is far below the RDA, particularly among adolescent girls, adult women and the elderly [1, 3, 5, 6]. Because magnesium content is low in diets high in meats and dairy products and tends to be lost substantially during the refining and processing of foods, the adoption of a “Western diet” characterized by high intakes of red and processed meat as well as other components, including dairy products and other highly refined or prepared foods, is believed to contribute to the decline in magnesium intake during the 20th century [1-3].

Magnesium is a cofactor for hundreds of enzymes, particularly for those cellular reactions involved in the transfer, storage, and utilization of energy [3, 7, 8]. Magnesium balance is regulated by the interaction between dietary magnesium intake, intestinal absorption, renal magnesium excretion, and magnesium exchange from bone [9, 10]. Magnesium deficiency refers to depletion of total body stores and is associated with several acute and chronic illnesses [10, 11]. Although serum magnesium may not reflect total body magnesium stores, serum magnesium levels are commonly used as the standard for defining magnesium deficiency (also known as hypomagnesemia) [11, 12].

Abnormalities in intracellular magnesium homeostasis have been hypothesized to be a link between insulin resistance, type 2 DM, hypertension, and CVD [7]. The beneficial effects of magnesium intake may be explained by several mechanisms (see Fig. 1), including improvement of glucose and insulin homeostasis [13, 14], lipid metabolism [15-18], vascular or myocardial contractility [7, 8, 19], endothelium-dependent vasodilation [7, 8, 20, 21], anti-arrhythmic effects [10, 22], and anti-coagulant or anti-platelet effects [19, 20, 23, 24]. Although numerous epidemiologic studies have extensively examined the association between magnesium intake and chronic disorders, most of them are ecologic or cross-sectional by design and are potentially confounded by other aspects of diet, lifestyle or socioeconomic factors. Their results need to be interpreted cautiously, although these data help to postulate hypotheses, implicating a role of magnesium in the...
etiology of metabolic abnormalities. In observational studies, prospective cohort design is considered optimal for the study of long-term dietary intake in the primary prevention of chronic diseases. However, prospective data for magnesium intake are relatively limited. In human intervention trials, a randomized double-blinded and placebo-controlled trial is considered as the best approach to examine a cause-effect relation. However, short-term controlled trials are usually performed in the secondary prevention setting of chronic disease because of cost and logistical considerations.

This review focuses on epidemiologic evidence on magnesium intake and the risk of developing type 2 DM, hypertension, and CVD, including observational studies and intervention trials and highlights the potential role of magnesium intake in the development of these metabolic syndrome-related chronic diseases.

**METABOLIC RISK FACTORS**

In recent years, emerging evidence has linked abdominal obesity, abnormal glucose metabolism, hypertension, and dyslipidemia (low HDL cholesterol and elevated triglyceride) as a cluster of metabolic abnormalities defined as the metabolic syndrome [25, 26]. All components of the metabolic syndrome are risk factors for developing type 2 DM and CVD. Magnesium intake may protect against diabetes and CVD through improving these metabolic syndrome components.

**Abdominal obesity and Insulin Resistance**

Obesity, particularly abdominal or visceral adiposity, has consistently been demonstrated as a fundamental cause of insulin resistance and type 2 DM [25, 27]. Some epidemiologic studies have examined directly the effects of whole grains on body weight and weight changes [28-30]. The observed associations between improved insulin sensitivity and components in whole grains including magnesium have been attributed, at least in part, to the beneficial effects of whole grains on body weight or weight changes. However, few studies have specifically examined the direct effect of magnesium intake on body weight.

A large body of evidence from experimental data supports that magnesium may play a role in glucose and insulin homeostasis [7, 9, 31]. Although the underlying mechanisms are not well understood, several pathways, affecting insulin secretion and action, have been proposed to explain the influence of magnesium status on insulin resistance. First, intracellular magnesium balance is important in maintaining peripheral glucose utilization [32, 33] and tyrosine kinase activity critical for insulin receptor-mediated signaling [34]. Also, magnesium plays a role in glucose-stimulated insulin secretion in pancreatic β cells through its effects on cellular calcium homeostasis and/or oxidative stress [7, 35].

Epidemiologic evidence provides further support for an important role of magnesium in insulin sensitivity. Some cross-sectional studies have shown an inverse association between plasma or erythrocyte magnesium levels and fasting insulin levels in both diabetic patients and apparently healthy individuals [36, 37]. Several epidemiologic studies have also observed an association between dietary magnesium intake and insulin homeostasis. Humphries et al. used a 24-hour recalled interview to measure dietary intake of magnesium in 179 young nondiabetic black Americans [38]. They found that magnesium intake correlated positively with insulin sensitivity quantified by insulin clamp technique (r=0.25, P<0.02 for men) and inversely with the sum of insulin concentrations from 0, 30, 60, and 120 min during a 75-g oral glucose tolerance test (OGTT) among men (r=-0.22, P<0.05) [38]. Similarly, a significant inverse association between dietary magnesium intake and fasting insulin
concentrations was observed in several population-based cross-sectional studies [36, 39-41]. Such an inverse association was found in the Coronary Artery Risk Development in Young Adults (CARDIA) study of 2,643 black and 2,472 white men and women aged 18-30 years [40], among 15,248 middle-aged adults free of CVD in the Atherosclerosis Risk in Communities (ARIC) study (except among black men) [36], and 219 middle-aged women free of diabetes, CVD and cancer from the Nurses’ Health Study [39]. In a cross-sectional study of 349 nondiabetic women participating in the Women’s Health Study, this inverse association was evident only among overweight women, who were prone to insulin resistance [41]. However, as in any cross-sectional studies, the observed associations cannot be established as causal.

Few studies have examined the efficacy of magnesium supplementation in improving insulin sensitivity among nondiabetic individuals. Several short-term metabolic studies and small randomized trials have specifically addressed this issue but the results have varied. Rosolova et al. have reported a relationship between plasma magnesium concentration and insulin-mediated glucose disposal [37, 42]. In a study of 18 nondiabetic participants, those with low levels of fasting plasma magnesium (< 0.80 mmol/L) had significantly higher plasma glucose and insulin concentrations after a 75-g OGTT and were more resistant to insulin-mediated glucose disposal reflected by higher steady state plasma glucose concentrations after a modification of insulin suppression test than those with high levels of plasma magnesium (> 0.83 mmol/L) [42]. Both groups were comparable in terms of sex, family history of diabetes, history of hypertension, cigarette, alcohol consumption and steady state insulin concentrations. Similar associations between plasma magnesium concentrations and insulin-mediated glucose disposal were also observed when the same investigators enrolled 98 healthy nondiabetic individuals [37]. One nonrandomized trial examined the effect of magnesium supplementation on insulin sensitivity in 12 nondiabetic participants with normal body weight [13]. Magnesium-deficient diet (<0.5 mg/day) for 4 weeks led to approximately 25% reduction in an insulin sensitivity index determined by minimal model analysis using a modified intravenous glucose tolerance test [13]. Two randomized double-blind placebo-controlled trials have also assessed the effects of magnesium in both insulin secretion and action among nondiabetic patients [43, 44]. In one trial of 12 nonobese elderly participants, daily magnesium supplementation (4.5 g magnesium poidlate, equivalent to 15.8 mmol) for 4 weeks signification improved glucose-induced insulin response and insulin-mediated glucose disposal [44]. In another randomized double-blind placebo-controlled trial, 60 apparently healthy participants who had low serum magnesium concentrations and insulin resistance assessed using the homeostasis model analysis for insulin resistance (HOMA-IR) were randomly allocated to receive either magnesium supplement (2.5 g/day magnesium chloride [12.5 mmol elemental magnesium]) or placebo [43]. Magnesium treatment for 3 months significantly improved insulin resistance as reflected by fasting glucose (5.8±0.9 to 5.0±0.6 mmol/L), insulin (103.2±56.4 to 70.2±29.6 mmol/L), and HOMA-IR (4.6±2.8 to 2.6±1.1, P<0.0001) [43]. Due to limited evidence, the beneficial effect of magnesium supplementation in improving insulin sensitivity in nondiabetic people has yet to be conclusively demonstrated and future long-term and well-designed controlled trials are warranted.

**Dyslipidemia**

Dietary magnesium may be related to lipid metabolism independent of its effects on insulin sensitivity. Malkiel-Shapiro (1956) et al. first reported that intramuscular injection of magnesium sulfate lowered serum β-lipoprotein in patients with coronary heart disease [45]. Animal studies have also suggested favorable effects of magnesium intake on lipid metabolism [15, 46-48]. For example, Altura and colleagues noted that magnesium supplements lowered serum cholesterol by 24% and triglycerides by 33% and attenuated the development of atherosclerotic lesions in cholesterol-fed rabbits [15]. Several hypothesized mechanisms have been proposed to explain the impact of magnesium on lipid profiles. As a cofactor for many rate-limiting enzymes critical for lipid metabolism, magnesium may decrease the activity of lecithin:cholesterol acyl-transferase (LCAT) [17] and the HMG-CoA reductase, and increase lipoprotein lipase activity [49]. LCAT is an enzyme for the esterification of free cholesterol, which lowers LDL cholesterol (LDL-C) and triglyceride levels and raises HDL cholesterol (HDL-C) levels. HMG-CoA reductase is a rate-limiting enzyme in the cholesterol biosynthesis. Lipoprotein lipase is responsible for the conversion of triglycerides to HDL-C and thus leads to a decrease in hepatic VLDL-triglyceride synthesis and secretion.

Because of limited data in humans, epidemiologic evidence for the role of magnesium in improving blood lipid profiles remains controversial. In a cross-sectional study of 192 Mexicans with metabolic syndrome and 384 age and sex-matched disorder-free controls, low serum magnesium levels were independently related to dyslipidemia (defined as fasting triglycerides ≥1.7 mmol/L and/or HDL-C <1.0 mmol/L) [50]. In the ARIC cohort of women and men free of CVD, serum magnesium intake was inversely related to serum triglycerides and positively related to LDL-C among whites while dietary magnesium intake was positively associated with plasma HDL-C among whites, independent of age and BMI [36].

Several trials have evaluated the effect of magnesium supplements on blood lipids among normal or patients with hyperlipidemia. In the 1960s, a clinical trial reported that a combination of magnesium chloride and potassium chloride lowered α and β lipoproteins by 10% [51]. In a nonrandomized clinical trial, Davis et al. (1984) reported that oral magnesium chloride (18 mmol/day) for 118 days significantly decreased total cholesterol, LDL-C, and VLDL cholesterol (VLDL-C) concentrations and increased HDL-C in 16 patients with hyperlipidemia [16]. Four randomized, double-blind, placebo-controlled trials have been conducted to evaluate the effects of oral magnesium supplementation on blood lipids among nondiabetic participants. Among 33 apparently healthy Japanese, oral supplementation of magnesium hydroxide (548 mg [9.82 mmol] for men and 411 mg [7.36 mmol] for women daily) for 4 weeks significantly increased HDL-C and apolipoprotein (apo) A1.
and decreased serum LDL-C concentrations [17]. In the magnesium treatment group, HDL-C increased from 1.28±0.35 mmol/L to 1.37±0.34 mmol/L (7%); apoA1 from 1362±203 to 1386±195 mg/L (2%) while LDL-C decreased from 3.52±1.10 to 3.25±0.97 mmol/L (8%) after 4 weeks [17]. Magnesium supplementation also appeared to improve the lipid profile among hyperlipidemic patients with other overt chronic diseases. In a controlled trial by Rasmussen et al. 47 patients with ischemic heart disease and acute myocardial infarction (MI) were randomly allocated to either magnesium hydroxide (15mmol/day [360 mg]) or placebo for 3 month [18]. Magnesium supplementation led to a significant decrease in apo B (15%), minor increase of HDL-C (6%) and nonsignificant reduction in triglycerides and VLDL-C with no differences in apoA1 and LDL-C [18]. Magnesium supplementation was also observed to decrease total cholesterol and triglycerides in a trial of 30 patients with chronic renal insufficiency [52]. In contrast, one randomized, double-blind, placebo-controlled trial failed to demonstrate the efficacy of magnesium supplementation on improving lipid profile among healthy people [53]. In this trial of 50 normal volunteers, magnesium supplementation (magnesium oxide, 800 mg/day [20 mmol]) for 60 days did not result in any significant changes in lipid profile including total cholesterol, HDL-C, LDL-C, and VLDL-C concentrations and triglycerides [53]. Taken together, however, there is still insufficient evidence to draw definitive conclusions about the effect of magnesium supplement on lipid metabolism in non-diabetic patients.

The possible effect of magnesium on insulin homeostasis may partially explain its potential effect on lipid metabolism. One randomized double-blind placebo-controlled trial has examined the effect of magnesium supplementation on plasma lipid concentrations in people with insulin resistance [43]. Among 60 apparently healthy participants who had insulin resistance and low serum magnesium concentrations, magnesium supplementation (2.5 g/day magnesium chloride [12.5 mmol]) for 3 months significantly reduced total cholesterol (10.7%) and triglycerides (39.3%) and LDL-C (11.8%) and increased HDL-C (22.2%) [43]. Several studies (at least one nonrandomized trial and 6 randomized double-blind placebo-controlled trials) have focused on whether magnesium intake affects lipid profiles in diabetic patients [54-59]. A marked decrease in mean triglyceride levels after magnesium supplementation (300 mg/day elemental magnesium) was observed in one open trial of 9 patients with type 2 DM without insulin therapy [60]. In contrast, none of 6 randomized double-blind placebo-controlled trials found change in plasma lipids in type 2 DM patients after oral magnesium supplementation (15-30 mmol/day) from 6 weeks to 4 months [54-59]. Likewise, the effects of magnesium intake on plasma lipids in patients with type 1 DM were reported in a open study with 10 participants [61], but were not replicated in another double-blind, placebo-controlled study with 28 patients with type 1 DM [62]. Thus far, whether oral magnesium supplementation improves lipid profiles in diabetic participants remains unsettled.

Blood Pressure
A substantial body of research has accumulated for decades, implicating a pivotal role of magnesium intake in blood pressure (BP) regulation [8]. In vitro studies have shown that magnesium has multiple functions that may contribute to its antihypertensive effects [8]. Proposed underlying mechanisms include the inhibition of intracellular calcium mobilization as a calcium antagonist, attenuation of the adverse effect of sodium by stimulating activity of Na-K ATPase or increasing urinary excretion of Na, decreased release of catecholamine [8, 19], improvement of myocardial contractility [19], endothelium dependent vasodilation [8, 20, 63], and insulin secretion and action [7, 21].

However, epidemiologic evidence for the relationship between magnesium intake and hypertension has been inconclusive. Results from some, though not all, cross-sectional studies suggest that magnesium intake may reduce BP [63, 64]. However, prospective data regarding dietary magnesium intake and the development of hypertension are limited and have also yielded mixed results [65-68]. A significant inverse association between dietary magnesium intake and BP was reported in three large cohorts [65-67], but not in the ARIC study [68]. Several reviews have also examined the observational and trial data on magnesium intake and BP and have shown a small overall reduction in BP by magnesium supplementation [64, 69]. Overall, there is some evidence that magnesium intake may lead to a small-to-moderate reduction in both systolic and diastolic BP, which can have important beneficial public health consequences. Relevant epidemiologic evidence will be discussed in hypertension section below [68].

The Metabolic Syndrome
Metabolic syndrome comprises a constellation of metabolic abnormalities including visceral obesity, glucose intolerance, hypertension, and dyslipidemia [25, 26]. The evidence that magnesium favorably affects these metabolic abnormalities, though not entirely consistent, has led us to hypothesize that magnesium intake is related to a lower risk of metabolic syndrome. This notion has been supported by a small cross-sectional study [50]. In this population-based study of 192 Mexicans with metabolic syndrome and 384 age and sex-matched disorder-free controls, low serum magnesium levels was independently related to the metabolic syndrome defined by the presence of at least two of the features (hyperglycemia, high BP, elevated fasting triglycerides, low HDL-C, and obesity) [50]. However, there is as yet little evidence on whether dietary magnesium intake is related to the development of metabolic syndrome in a prospective or clinical trial setting.

Systemic Inflammation
Low-grade inflammation, as measured by C-reactive protein (CRP) with a high-sensitivity assay, has been associated with risk of CVD, insulin resistance, type 2 DM, hypertension, and features of the metabolic syndrome and the metabolic syndrome itself [70]. Accumulating evidence from animal and human studies suggests that magnesium may also play a role in immune function [71]. A cross-sectional study of 371 non-diabetic, non-hypertensive obese Mexicans reported an inverse association between serum magnesium concentrations and high-sensitivity CRP concentrations [72]. It thus seems plausible to speculate that the beneficial effects of magnesium on chronic diseases may
be partially mediated by its potential anti-inflammatory effect. Because of the limited data, however, uncertainties remain regarding whether and to what extent magnesium intake may improve low-grade systemic inflammation.

**TYPE 2 DM**

A large body of data from clinical case studies or cross-sectional studies provided further evidence for the correlation between blood glucose levels and type 2 DM [14, 36, 73-79]. Hypomagnesemia has been shown to occur frequently among patients with diabetes, especially those with poor metabolic control [75, 78, 80]. Polyruric diabetes due to hyperglycemia, coupled with hyperinsulinemia, tended to increase renal excretion of magnesium or decrease renal re-absorption of magnesium, thereby resulting in hypomagnesemia in type 2 DM [81, 82]. In addition, inadequate intake of dietary magnesium in diabetic patients may also be a possible cause for hypomagnesemia [83]. However, these results are inconclusive in testing the hypothesis regarding the role of magnesium due to confounding by other aspects of diet, physical activity, smoking, obesity, socioeconomic status, and drug therapies such as hypoglycemic medication, diuretics, and insulin. Thus, whether low plasma magnesium is a cause or consequence of suboptimal glycemic control remains inconclusive.

The prospective ARIC study showed an inverse association between serum concentrations of magnesium at baseline and subsequent risk of type 2 DM [84]. However, some studies have found that there is a lack of correlation between serum levels and dietary magnesium intake (r=0.06) [84-86]. Thus, such an association may not reflect the impact of long-term magnesium intake.

Results from prospective studies of magnesium intake and risk of type 2 DM have been generally consistent, however. Previous reports from the Nurses’ Health Study [87, 88], the Iowa Women’s Health Study [89], and the Health Professionals Follow-up Study [90] all indicated an inverse association between magnesium intake and risk of incident type 2 DM, although such an association was not found in the ARIC study [84]. In an earlier report from the Nurses’ Health Study, Colditz et al. documented 702 incident cases of type 2 DM among 84,360 US white women aged 34 to 59 years for a follow-up period of 6 years. Women in the highest quintile compared with the lowest quintile of magnesium intake had a relative risk (RR) of 0.68 (95% confidence interval [CI], 0.45-1.01; P for trend=0.02) for women with a BMI less than 29 and 0.73 (95% CI, 0.53-1.02; P for trend=0.008) for women with a BMI of 29 or higher [87]. In a cohort of 35,988 older US women in the Iowa Women’s Health Study with 1141 incident cases of type 2 DM, the multivariate-adjusted RR was 0.67 for women in the highest quintile versus the lowest quintile of intake (95% CI, 0.55-0.82; P for trend=0.0003) during 6 years of follow-up [89]. Consistent with these previous reports, two recent studies have independently showed a lower risk of type 2 DM related to higher intake of dietary magnesium [41, 91]. In an updated analysis of the Nurses’ Health Study followed for 18 years and the Health Professionals Follow-up Study followed for 12 years that documented 4,085 incident cases of type 2 DM among 85,060 women and 1,333 cases among 42,872 men, the multivariate-adjusted RRs for type 2 DM were 0.66 (95% CI: 0.60-0.73; P for trend<0.001) in women and 0.67 (95% CI: 0.56-0.80; P for trend<0.001) in men [91] comparing the highest with the lowest quintiles of magnesium intake. In another large cohort of 39,345 middle-aged and older US women participating in the Women’s Health Study with an average of 6 year follow-up, this inverse association remained significant albeit only among overweight women [41]. Among women with a BMI of 25 or more, those in the highest quintile of magnesium intake had a 22% lower risk of developing type 2 DM than did those in the lowest quintile (RR, 0.78; 95% CI, 0.62-0.99; P for trend=0.02) [41]. Because the extent to which magnesium intake influences insulin sensitivity may differ among women with different body weights, we speculated that the potential beneficial effects of high intake of magnesium may be greater among overweight persons who are prone to insulin resistance. This finding needs to be further evaluated in future studies.

In contrast, the ARIC study did not find a significant inverse association between magnesium intake and risk of incident type 2 DM in 12,128 participants during 6 years of follow-up [84]. Compared with individuals in the highest quartile of magnesium intake, the multivariate-adjusted RRs in the lowest quartile were 0.95 (95%CI, 0.52-1.74, P for trend=0.47) among black participants and 0.80 (95% CI, 0.56-1.14, P for trend=0.49) among white middle-aged US adults [84]. However, the relatively small number of incident cases in each ethnic group and less precise dietary assessment may have contributed to the absence of such an inverse association.

To reconcile the discrepancies of the results from these previous prospective cohort studies, the data regarding the association between dietary magnesium intake and incidence of type 2 DM were pooled using a classic random-effect meta-analysis [92]. A χ² statistic was used to test between-study heterogeneity [93]. As shown in Fig. (2), the summary estimate of RR was 0.78 comparing the highest category of dietary magnesium intake with the lowest category of intake (95% CI: 0.69-0.88; P= 0.11 for between-study heterogeneity). Thus, overall, the evidence from prospective cohort studies is strongly supportive of the role of magnesium intake in the development of type 2 DM.

There are as yet no clinical trials examining the efficacy of magnesium supplementation or consuming major magnesium-rich foods on the primary prevention of type 2 DM. In the 1980s, several nonrandomized and uncontrolled trials for secondary prevention in diabetic patients showed that oral magnesium supplementation may improve glucose tolerance and reduce insulin requirement among patients with type 2 diabetes [60, 94-96]. Nine randomized controlled trials of oral magnesium supplementation have been conducted to study diabetes-related phenotypes (e.g., glycemic control, or insulin sensitivity) among patients with type 2 diabetes [54, 55, 57-59, 94, 97-99]. A total of 370 patients with type 2 diabetes were enrolled in these 9 trials evaluating oral magnesium supplementation (median dose: 15 mmol/day [360 mg/day]) from 4 to 16 weeks (median:12 weeks) to improve diabetes control. Of them, four randomized double-blind trials showed beneficial effects by
oral magnesium supplementation on glycemic control among patients with type 2 diabetes [57, 97-99]. By contrast, five randomized double-blind placebo-controlled trials showed no beneficial effects of oral magnesium supplementation on glycemic control among patients with type 2 DM [54, 55, 58, 59, 94]. Because almost all trials included small numbers of participants and were of relatively short duration, these randomized controlled trials have been underpowered to reliably assess the efficacy of oral magnesium supplementation. In addition, differences in study population, duration of diabetes, glycemic treatment, and intervention periods, coupled with the fact that different magnesium doses and formulations used, have led to difficulties in interpreting the potential benefits of oral magnesium supplementation for patients with type 2 DM. Taken together, oral magnesium supplementation as adjunct therapy may be effective in improving glycemic control among type 2 DM patients. Side effects were relatively infrequent among diabetic patients in the magnesium treatment group. No severe adverse effects, including cardiovascular events or deaths, were reported. The most common side effects were gastrointestinal symptoms including diarrhea and abdominal pain [54, 55, 57-59, 94, 97-99]. However, the long-term benefits and safety of magnesium treatment on glycemic control remain to be determined in future large-scale, well-designed randomized controlled trials with long follow-up periods.

**HYPERTENSION**

The hypothetical relation between magnesium intake and BP was first suggested by the findings from ecologic studies...
that showed a negative correlation between water hardness and BP and/or hypertension [100, 101]. Interpretation of such comparisons at population levels is always problematic, because ecologic correlations based on grouped data at population level may not reflect the corresponding association at the individual level due to confounding (known as ecological fallacy) [102].

To date, the strongest epidemiological evidence relating dietary magnesium to hypertension comes from numerous cross-sectional studies. Results from most of these studies suggest that magnesium intake is inversely related to blood pressure in diverse populations [63, 64, 103]. In the Honolulu Heart Study, Joffres reported that dietary magnesium intake, of 61 dietary variables assessed using 24-hour dietary recall, had the strongest inverse correlation with both systolic and diastolic BP in 615 Japanese men aged 63-82 years [65]. Such a negative correlation between dietary magnesium intake and BP was also found in 419 Chinese men [104]. In a population-based cohort of 1,567 Spanish men and women aged 25-74, dietary magnesium intake assessed by a validated 72-hour recall was significantly correlated with only systolic BP among 1,357 normotensive and hypertensive participants without antihypertensive medication [105]. Nevertheless, gender and ethnic-differences for such a correlation was also observed. A Belgian study found a negative correlation between dietary magnesium using 24-hour food record and systolic BP in women only [106]. Simon et al. found a negative correlation between dietary magnesium intake assessed by 3-day food records and diastolic BP in white girls in 3 American cities, but not in African-American girls [107]. In a nationally representative sample of 6,046 white participants and 2,226 African-American participants in the National Health and Examination Survey III, Ford et al. reported that a negative correlation between dietary magnesium intake assessed using a single 24-hour dietary recall and hypertension prevalence was more evident in African Americans than whites [108].

Several large cohorts have cross-sectionally examined the association between magnesium intake assessed by a semiquantitative food frequency questionnaire (FFQ) and the prevalence of hypertension [36, 67, 109, 110]. The HPFS Study with 30,681 US male health professionals reported an inverse association between dietary magnesium and baseline systolic and diastolic BP independent of fiber intake after excluding those who reported hypertension at baseline and during 4 years of follow-up [67]. Similar associations were also found in 3,239 older female and male whites in the Rotterdam Study [109], in 20,921 younger and middle-aged Dutch men and women [111], 15,248 participants in the ARIC study, including US men and women, black and white [36], and 1,769 Indians (894 men and 875 women) [110]. Results from observational studies have been thoroughly reviewed elsewhere [64, 103]. A qualitative review of 29 observational studies concluded that there was an inverse association between dietary magnesium intake and BP, which was relatively consistent across studies using different study population and sample size, various methodologies of diet assessment, and statistical analyses [64]. However, the evidence from cross-sectional studies does not necessarily imply any causal relation due to the inherent limitation of this study design.

Prospective data regarding dietary magnesium intake and the development of hypertension are very limited [66-68]. In an earlier report in the Nurses’ Health Study, the association of various nutritional factors assessed using a 61-item FFQ in 1980 with subsequent risk of incident hypertension was prospectively examined in 58,218 US female registered nurses aged 34-59 years during the first 4 years of follow-up [66]. Witteman et al. reported a multivariate-adjusted RR of 0.78 (95% CI, 0.67-0.88; \( P \) for trend=0.03) for the highest versus lowest quintile of dietary magnesium intake in women [66]. In an updated analysis of the Nurses’ Health Study, Ascherio et al. analyzed the association between diet assessed using FFQ with 126 food items in 1984 and development of hypertension from 1984 to 1988 [112]. Among 41,541 US female nurses free of diagnosed hypertension, cancer, or cardiovascular disease, 2,526 women reported a diagnosis of hypertension during 4 years of follow-up [112]. They observed an inverse relation of dietary magnesium with reported BP but not with the incidence of hypertension. After adjusting for age, BMI, and alcohol intake, the RR of incident hypertension was 1.10 (95% CI: 0.92-1.32; \( P \) for trend=0.56) and the average BP was 1.3/1.0 mm Hg lower in women with high magnesium intake (≥350 mg/d) compared with those with low intake (<200 mg/d) [112]. A prospective study of 30,681 US male health professionals found a similar association during 4 years of follow-up [67]. After adjustment for age, BMI, and alcohol consumption, the RR for developing hypertension was 1.49 (95% CI, 1.15-1.92; \( P \) for trend=0.003) among men in the lowest quintile of dietary magnesium intake compared with those in the highest quintile of intake [67]. In contrast, the ARIC study failed to detect a significant association between dietary magnesium and hypertension [68]. The ARIC study followed 4,190 women and 3,541 men free of hypertension at baseline for six years to examine the relationship of serum and dietary magnesium with incident hypertension. After adjustment for age, race, BMI, waist-to-hip ratio, diabetes, education, family history of hypertension, physical activity and hormone replacement therapy in women, the multivariate-adjusted RRs were 0.77 (95% CI, 0.55-1.08; \( P \) for trend=0.22) for women and 0.85 (95% CI, 0.68-1.18; \( P \) for trend=0.21) for men comparing the highest quartile of magnesium intake (≥311 mg/day) to the lowest quartile (<189 mg/day) [68]. Although the ARIC study found a modest inverse association between serum magnesium levels and incident hypertension, the correlation between serum and dietary magnesium in this study was very low (correlation coefficient=0.053) [68]. Asides from differences in study characteristics, the use of 61-item FFQ in the ARIC study might have resulted in a nondifferential misclassification of dietary intake, which might have biased the associations towards the null.

There are several likely explanations for the remaining controversy regarding the relation between dietary magnesium intake and hypertension. First, it is difficult to separate completely the independent effect of magnesium from other dietary nutrients such as fiber, calcium, and potassium that also may have anti-hypertensive effects. Moreover, in these cohort studies, much controversy exists over whether baseline BP should be included in the multivariate models in the presence of a strong negative
correlation between dietary magnesium intake at baseline and baseline BP. On the one hand, baseline BP may be an intermediate variable between long-term dietary intake and the development of hypertension during follow-up. Further adjustment for baseline systolic blood pressure in the ARIC study was observed to substantially attenuate these associations [68]. On the other, the observed association might have been biased if baseline BP is a truly confounding factor. Further, without taking into account the presence of diagnosed or unidentified diabetic patients among participants may have led to residual confounding for the apparent association between magnesium intake and hypertension.

However, available evidence cannot rule out a small effect of high magnesium intake in lowering blood pressure. When the data from these prospective cohorts are pooled together [Fig. (2)], the summary estimate of RR is 0.87 comparing the highest category of dietary magnesium intake with the lowest category of intake (95% CI: 0.75-1.01; \( P=0.62 \) for between-study heterogeneity).

Numerous small clinical trials have assessed the therapeutic effect of magnesium supplements in hypertension but yielded inconsistent results [64, 69]. Many sources of heterogeneity may have contributed to the inconsistency in these trials including small sample size, incomplete randomization, the lack of blind in design, variable durations of follow-up, high rates of noncompliance, differences in magnesium treatment protocols, magnesium formulation and dose, and study populations. In a recent meta-analysis of clinical trials between 1983 and 2001, Jee et al. identified 20 randomized trials with a sample size from 13 to 461 participants (median: 31 per trial) and a follow-up period from 3 to 24 weeks (median: 8.5 weeks) [69]. Their results showed that magnesium supplementation led to a small overall reduction in BP in a dose-dependent manner. For each 10 mmol/day (240 mg/day) increase in magnesium dose, systolic BP decreased by 4.3 mmHg (95% CI: -6.3 to -2.2; \( P \) for trend <0.001) and diastolic BP by 2.3 mmHg (95% CI: -4.9 to 0; \( P \) for trend=0.09) [69]. Furthermore, the pooled results of 14 double-blind randomized trials among hypertensive patients showed that a 10 mmol/day (240 mg/day) increase in magnesium intake was associated with a decrease in both systolic BP (3.3 mmHg, 95% CI: -0.1 to 6.8) and a decrease in diastolic BP (2.3 mmHg, 95% CI: -1.0 to 5.6) [69]. Overall, the evidence from these trials suggests a modest antihypertensive effect by magnesium supplementation, although additional research is needed to assess whether magnesium therapy is beneficial for the general population.

**CARDIOVASCULAR DISEASES**

The relationship between magnesium and cardiovascular disease has been studied extensively for nearly seventy years. The first evidence in the English literature can be traced back to the 1935, when Zwilling reported that intravenous magnesium sulfate suppressed digitalis-induced cardiac arrhythmia in human [19]. Subsequently, many nonrandomized and uncontrolled clinical trials demonstrated that the use of different magnesium supplements, either oral or intravenous treatment, appeared to be protective against arrhythmias and death due to acute myocardial infarction (MI) or chronic heart failure [10, 19, 22]. Animal studies showed that magnesium deficiency accelerated atherosclerotic process and magnesium supplementation suppressed the development of atherosclerosis [15, 113]. Several lines of evidence from earlier autopsy studies showed lower magnesium content in the myocardium of patients with sudden coronary deaths than in those who died of other disease such as accidents [114-117]. Proposed mechanisms include inhibition of intracellular calcium overload due to ischemia [7, 8, 19], preservation of energy-dependent cellular activity by conserving cellular ATP [8, 9, 19, 21], anti-arrhythmic effect [10, 22], improvement of myocardial contractility [7, 8, 19], decreased release of catecholamine [8], delayed progression of myocardial ischemia [19, 20], reduced reperfusion injury [7, 19, 20], improved lipid metabolism [15-18], and anti-platelet effects [19, 20].

In the late 1950s, the hypothesis that magnesium lowers the risk of cardiovascular disease gained further support from ecologic studies. Since Kobayashi (1957) reported an inverse correlation between water hardness and the death rate from cerebrovascular disease in Japan [118], many ecological studies in different geographical area and diverse populations showed similar correlations relating the hardness of drinking water to reduced cardiovascular mortality [19, 101, 119-121]. As discussed above, the difficulties in the use of ecological data at population level for making causal inferences at the individual level is widely recognized because the potential confounding bias is due to inherent limitations of the study design [102]. It has been pointed out that magnesium intake from drinking water is in negligible amount compared with magnesium intake from diet [122], and thus might not be crucial in the prevention of magnesium deficiency.

Some large population-based cross-sectional studies have examined the correlation between magnesium status and CVD phenotypes. In the Framingham Offspring Study, an inverse association between serum magnesium levels and the prevalence rates of ventricular arrhythmias was observed among 3,327 participants free of clinically heart disease with a mean age of 44 years, after adjustment for age, sex, smoking, coffee, alcohol consumption, diuretic use, and systolic BP [123]. Similarly, a cross-sectional analysis of in the ARIC study showed a significant inverse association between serum magnesium and carotid intima-media thickness in women but found no association between dietary magnesium and carotid intima-media thickness in men or women [36]. Two large cohort studies have prospectively examined the relationship between serum magnesium levels and risk of developing CHD [124, 125]. Higher serum magnesium concentrations have been associated with a lower risk of coronary heart disease in both the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHEFS) [124] and the ARIC Study [125]. It is important to note that serum magnesium concentrations may not reliably reflect long-term magnesium intake or body magnesium status [125, 126]. Thus it is unclear whether such an association with serum magnesium reflects the impact of long-term dietary intake in the development of CVD.
Despite the data from ecologic and cross-sectional studies linking low magnesium intake and CVD, few epidemiologic studies have evaluated the role of magnesium intake in the primary prevention of CVD development. Of note, an inverse association between dietary magnesium and the risk of CHD, though generally weak, has been observed in two large cohorts [127, 128]. In the Honolulu Heart Study, 7,172 men aged 45 to 68 years of Japanese ancestry living in Hawaii were followed for 30 years and developed 1,431 incident cases of CHD [127]. The association between magnesium intake assessed by 24-hour dietary recall and CHD incidence was evident in the first 15 years of follow-up and tended to be weakened with time. The multivariate-adjusted RR of CHD in the first 15 years comparing the lowest (≤186 mg/day) to the highest quintile (≥340 mg/day) after adjustment for cardiovascular risk factors including dietary intake of cholesterol, potassium, fiber, saturated fat, calcium, protein, and sodium [127]. During the 12 years of follow-up of 39633 men in the HPFS, the aged-adjusted RR of CHD was 0.73 (95% CI: 0.62-0.87; P for trend<0.0001) in the highest quintile (median: 457 mg/day) compared with the lowest quintile (median: 269 mg/day) of dietary magnesium intake assessed by 131-item FFQ [128]. After adjustment for standard CHD risk factors and dietary factors (trans fatty acid, protein, cereal fiber, omega 3 fatty acid, and potassium), the linear trend was substantially attenuated towards the null (RR, 0.77; 95% CI, 0.56-1.06; P for trend =0.14) [128]. In the ARIC study with 13922 middle-aged US adults with 4 to 7 years of follow-up, dietary magnesium assessed by 61-term FFQ had a modest inverse association with risk of CHD in men but in women. After adjustment for age, race, ARIC center, education, smoking, alcohol, exercise, use of diuretics, waist-to-hip ratio, hormone therapy, systolic BP, diabetes status, and plasma levels of fibrinogen, total and HDL cholesterol, triglycerides, an inverse association between dietary magnesium and CHD risk remained for men (RR comparing the highest to the lowest quintile: 0.64; 95% CI, 0.42-0.98; P for trend =0.04) but not for women (P for trend=0.59) [125]. In contrast, in the Caerphilly cohort of 2172 men aged 45-59 with 10-year follow-up and 269 incident CHD events, dietary magnesium intake assessed by FFQ was not associated with CHD risk after controlling for traditional CHD risk factors [129]. The adjusted RR comparing the lowest quintile (<212 mg/day) to the highest quintile of intake (≥340 mg/day) was 1.52 (P>0.05) [129]. When the data from these prospective cohorts were pooled together [Fig. (2)], the random-effect pooled estimate of RR was 0.78 comparing the highest category of dietary magnesium intake with the lowest category of intake (95% CI: 0.60-1.02; P= 0.17 for between-study heterogeneity). Overall, the findings of cohort studies suggest that magnesium is unlikely to decrease substantially the risk of CHD, although a modest association cannot be ruled out.

The efficacy of magnesium treatment on the secondary prevention of CVD, especially arrhythmias and mortality after acute MI, has received much attention in many small clinical trials [22]. The apparently conflicting trial results have led to extensive discussions on this issue in many systematic reviews [19, 22, 130], meta-analytic analyses [131-134] and clinical commentaries [135-137]. In particular, three large secondary prevention trials in patients with MI have yielded inconsistent results. The first large randomized, double-blind, placebo-controlled study (The Second Leicester Intravenous Magnesium Intervention Trial, LIMIT2) showed that intravenous magnesium therapy before thrombolytic therapy caused a 24% relative reduction in mortality after 28 days following acute MI and a 25% lower incidence of left ventricular failure [138]. Subsequently, two large-scale randomized trials failed to support the efficacy of intravenous magnesium therapy for patients with acute MI [139, 140]. A critical examination of trial data with updated meta-analysis also raised serious doubts on the benefits of intravenous magnesium following MI [131]. Inconsistencies in the trial data may be due, in part, to differences in the time course of therapy and optimal dosage of magnesium for the prevention of CHD complications [135-137]. Thus, there is still considerable controversy about the true effect of magnesium therapy in the secondary prevention of CHD mortality or other complications.

Another area of controversy is the relationship between magnesium intake and the development and progression of stroke. Some animal studies [141-143], though not all [144], have suggested potential neuroprotective effects by magnesium supplementation in rodent stroke models. In addition to its cardiovascular effects, magnesium may also play a role in reducing cerebral ischemia, including inhibition of ischemia-induced glutamate release, N-methyl-D-aspartate receptor blockade, calcium entry via voltage gated channels antagonism, enhancement of mitochondrial calcium buffering, prevention of ATP depletion, and vasodilatation of cerebral blood vessels [145-147]. However, the relation between magnesium intake and stroke is less well studied in epidemiologic studies, especially large prospective studies. During 8 years of follow-up of the HPFS study with 328 strokes documented, dietary magnesium intake was inversely associated with risk of total stroke; the multivariate-adjusted RR was 0.70 (95% CI, 0.49-1.01) comparing the highest quintile of magnesium intake (median: 452 mg/day) to the lowest quintile (median: 243 mg/day). This inverse association was apparent among hypertensive men. Because the number of incident cases of hemorrhagic stroke was small, this study did not address differential effects of magnesium intake on stroke subtypes. Among 85,764 US women followed for 14 years, the Nurses’ Health Study showed no significant associations between magnesium intake and total stroke and stroke subtype, although a modest effect of magnesium on ischemic stroke could not be excluded [148].

The efficacy of magnesium treatment in the secondary prevention of stroke has been suggested in some small pilot trials [147, 149] but was not confirmed in the IMAGES study (Intravenous Magnesium Efficacy in Stroke), an international, multicenter, double-blind, placebo-controlled trial [150]. Magnesium treatment given within 12 hours of stroke onset in 2589 patients failed to reduce mortality or disability at 90 days, although subgroup analyses suggested possible benefit in ischemic lacunar strokes [150]. Taken together, the evidence is not convincing and this area requires further investigation.
CONCLUSION

The available evidence from human populations indicates that dietary magnesium intake may be associated with a host of metabolic disorders, including insulin resistance, dyslipidemia, type 2 diabetes, hypertension, and cardiovascular disease.

Errors in the dietary assessment, including potential dietary change over the course of follow-up and residual confounding by poorly measured or unmeasured variables and highly correlated nutrients, may have substantially limited the ability of large cohort studies to elucidate the causality of nutrient-disease relation.

While much uncertainty exists regarding the validity of epidemiological studies, obviously, the best approach to confirm a cause-effect relation is to perform a double-blinded and placebo-controlled randomized trial. Nevertheless, conducting such a trial would be difficult for primary prevention of chronic diseases such as type 2 DM and CVD because of cost, logistical, and compliance issues. The evidence for the benefits of magnesium supplementation in the secondary prevention of chronic disease remains a matter of debate. It is obvious that future large-well-controlled secondary prevention trials are warranted to unravel the efficacy and safety of magnesium supplements.

From a mechanistic perspective, there is compelling need for the development of a reliable method to measure total body magnesium store and levels of intracellular magnesium, or biologically active ionized or free magnesium. To date, serum magnesium concentrations are still the most commonly used method to define magnesium deficiency in humans but serum magnesium does not correlate well with total magnesium status or with intracellular magnesium pool [125, 126]. More accurate, reliable, and affordable means to assess individual magnesium status in large population studies would provide more informative answers regarding magnesium intake and the risk of metabolic-related disorders.

In addition, recent genetic studies about links between a mitochondrial mutation, TRPM6 (an ion channel kinase of the “transient receptor potential” gene family) mutations, and hypomagnesemia have shed light on the underlying molecular basis for magnesium metabolism [151-153]. However, there is little population data available investigating genetic susceptibility to magnesium deficiency. Future population-based genetic research will help identify genetic variants in modifying the metabolic effects of magnesium intake.

In summary, available evidence suggests that higher intake of magnesium may contribute to a reduction in the risk of type 2 DM, hypertension, and CVD. In particular, the evidence for the beneficial effect of magnesium intake on risk of type 2 DM is relatively consistent and parallels the findings from metabolic studies showing the role of adequate magnesium status in improving insulin sensitivity. Until more definitive data are available, the collective evidence regarding the potential benefits of magnesium intake is consistent with prevailing dietary recommendation for primary prevention of type 2 DM, hypertension, and CVD by consuming foods rich in vegetables, whole grains, legumes, and nuts.

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