

Review Article

Magnesium and metabolic syndrome: A systematic review of epidemiologic evidence

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ABSTRACT

Background: Epidemiologic evidence regarding the relation of magnesium intake or status and metabolic syndrome (MetS) has been inconsistent and inconclusive. **Objective:** A comprehensive quantitative and qualitative assessment of current epidemiological evidence on magnesium and MetS were performed. **Design:** We systematically reviewed observational studies and randomized trials of dietary magnesium intake, blood status, or supplements and the MetS. We also performed a dose-response meta-analysis of observational studies to assess the strength and shape of the association between dietary magnesium intake and the MetS. **Data Source:** The search covers all the publications in PubMed and Cochrane Library up to August 2014. **Study Selection:** In total, 66 epidemiological articles reported the associations of dietary magnesium intake, blood levels, or magnesium supplements with the MetS and its components were included. **Results:** In observational studies, magnesium intake or blood magnesium status has been inversely associated with the metabolic components and prevalence of MetS. The meta-analysis results showed that magnesium intake was inversely associated with the risk of MetS; each 100 mg increment in magnesium intake was significantly associated with a reduction of 7% in the prevalence of MetS (odds ratio: 0.93; 95% confidence interval: 0.90-0.96; *P* for trend < 0.0001). Some small randomized trials with short duration support the potential prevented and therapeutic efficacy of magnesium in individual metabolic components. **Conclusions:** Available observational evidence suggests a possible protective effect of magnesium on MetS. However, prospective data has been limited. Future large-scale, well-designed longitudinal studies and randomized controlled trials are needed to clarify a cause-and-effect relation between magnesium and the MetS.

Key words: Magnesium, meta-analysis, metabolic syndrome, systematic review

HIGHLIGHTS

1. This meta-analysis comprehensively summarized the current epidemiologic evidence of the associations between magnesium intake or serum magnesium levels and metabolic syndrome.
2. Accumulated epidemiologic data indicated a possible protective effect of magnesium in preventing the risk of metabolic syndrome and its five individual components.

3. On average, each 100 mg/day increase of dietary magnesium intake significantly leads to a 7% reduction in the prevalence of metabolic syndrome.

INTRODUCTION

Magnesium is an essential mineral critical for many metabolic functions of the human body rich in many unprocessed foods, such as whole grains, green leafy vegetables, legumes, and nuts.^[1-3] The dietary reference intake (DRI) for magnesium is 420 mg/day for adult men (over age 30), and 320 mg/day for women (over age 30).^[1-3] Several national surveys show that the average magnesium intake in the US general population is far below the DRI, particularly among adolescent girls, women, and the elderly^[1,3-5] because magnesium content in food tends to be lost substantially during the processing of “Western diet.”^[1-3]

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Magnesium is a cofactor for hundreds of enzymes, particularly for those cellular reactions involved in the transfer, storage, and utilization of energy.^[3,6,7] Magnesium deficiency commonly indexed by blood magnesium levels has been hypothesized to be a link among insulin resistance (IR), type 2 diabetes mellitus (DM), hypertension, and cardiovascular disease (CVD).^[6] Normal levels of serum magnesium are within a narrow range and do not correlate well with dietary intake of magnesium. The beneficial effects of magnesium intake or status on a host of metabolic disorders may be explained by several mechanisms, including improvement of glucose and insulin homeostasis,^[8,9] oxidative stress,^[6,10,11] lipid metabolism,^[12-15] vascular or myocardial contractility,^[6,7,16] endothelium-dependent vasodilation,^[6,7,10,17] anti-arrhythmic effects,^[18,19] anti-coagulant or anti-platelet effects,^[16,17,20,21] and anti-inflammatory effects.^[22,23]

The metabolic syndrome (MetS) is a constellation of conditions that individually and more specifically in combination, elevate the risk of cardiometabolic disease. This constellation generally includes five conditions: Overweight or abdominal obesity; high triglycerides; low high-density lipoprotein cholesterol (HDL-C); high blood pressure (BP); and impaired fasting glucose or IR. Although numerous epidemiologic studies have extensively examined the association between magnesium intake and cardiometabolic disease, 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. In observational studies, prospective data for magnesium intake are relatively limited. In human, intervention trials and short-term trials are usually performed and suggest that oral magnesium supplementation with relatively infrequent side effects and no severe adverse effects may be effective in improving metabolic profiles in apparently healthy individuals without chronic diseases.

This review focuses on a systematic assessment of available epidemiologic evidence of magnesium intake and the MetS and its five individual components, which may serve as empirical data for future prospective study or clinical trial design.

MATERIALS AND METHODS

Search strategy and selection criteria

We searched in PubMed and the Cochrane Library for relevant articles published up to August 2014. The search term included “magnesium,” “Mg,” “micronutrients,” “MetS,” “IR syndrome,” “glucose intolerance,” “obesity,”

“central obesity,” “hyperlipidemia,” “hypertension” and “metabolic disease.” Searches were limited to publications in English language. We also checked the relevant meta-analysis, reviews and relevant articles to identify other possible studies not indexed in those two databases above.

Selection of articles

We also performed a meta-analysis to address the possibility of the linear or nonlinear relationship between dietary magnesium intake and MetS. The studies included in this meta-analysis were concerned on the relationship between MetS and magnesium intake in adults:

1. Prospective studies or cross-sectional studies;
2. Prevalence of MetS was the primary outcome or secondary outcome;
3. Dietary magnesium intake was the exposure of interest; and
4. The studies that reported the odds ratios (ORs) or risk ratios (RRs) and 95% confidence intervals (CIs) for the prevalence of MetS.

Data extraction

Two researchers (XZ and YS) independently reviewed and extracted the useful data from the identified articles for meta-analysis. Any discrepancies were consistent by discussion. The following information of the original data were extracted carefully, including general information, study characteristics, participant characteristics, and outcome measures (ORs/RRs, quartile range of the magnesium dietary intake and the median of the range, sample size of each quartile group, and the variables adjusted in statistical model).

Statistical analysis

We applied the meta-regression model to test the linear dose-response relationship between magnesium intake and the risk of MetS and calculate the pooled ORs and 95% CIs across categories of magnesium intake. The median or mean level of magnesium intake in each quantile category was assigned to the corresponding OR. If not reported, we calculated the means or the midpoint of the lower and upper bound in each category instead. For extreme open-ended categories, half the width of the adjacent category was used to obtain the midpoint values. The cases numbers of each category were also collected for meta-regression analysis. We also explored the possible linear and nonlinear relationship between magnesium intake and MetS by drawing quadratic polynomial spline regression curve. All analyses were conducted by using STATA statistical software (Version 13, STATA Corp., College Station, TX, USA). Two-tailed $\alpha < 0.05$ was defined as statistical significance.

RESULTS AND DISCUSSIONS

Magnesium and metabolic syndrome components

In recent years, emerging evidence has linked abdominal obesity, abnormal glucose metabolism, hypertension, and dyslipidemia (low HDL-C and elevated triglyceride) as a cluster of metabolic abnormalities defined as the MetS.^[24,25] All components of the MetS are risk factors for developing type 2 DM and CVD.

Visceral obesity

Obesity, particularly abdominal or visceral adiposity, has consistently been demonstrated as a fundamental cause of IR and MetS.^[24,26] Some epidemiologic studies have examined directly the effects of whole grains on body weight and weight changes.^[27-29] The observed associations between improved insulin sensitivity and magnesium components in whole grains have been attributed, at least in part, to the beneficial effects of whole grains on body weight or weight changes. However, only few studies have specifically examined the direct effect of magnesium intake on body weight and indicated that the serum magnesium levels were slightly lower in the obese population.^[30,31] A case-control study showed that both serum and intracellular magnesium were inversely related with body mass index (BMI) in patients with MetS.^[32] While another case-control study in Turkey indicated a positive relationship between BMI and the serum magnesium levels among obese children without IR.^[33] Some studies indicated a possible modifier effect of body weight on the relationship between dietary or serum magnesium and IR or type 2 diabetes.^[33-36] Therefore, the relation between obesity and magnesium is still controversial and confounded by the effect of insulin. More well-designed prospective studies need to be performed for comprehensively clarifying the relationship between obesity and magnesium.

Glucose intolerance and insulin resistance

Experimental data support a role of magnesium in glucose and insulin homeostasis.^[6,37,38] 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 IR. Intracellular magnesium balance is critical for peripheral glucose utilization^[39,40] and insulin receptor-mediated signaling.^[41] Magnesium also plays a role in glucose-stimulated insulin secretion in pancreatic β cells through its effects on cellular calcium homeostasis and/or oxidative stress.^[6,42]

Epidemiologic evidence suggests 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.^[43,44] Several epidemiologic studies have also found an association between dietary magnesium intake and insulin homeostasis.^[45] Similarly, a significant inverse association between dietary magnesium intake and fasting insulin concentrations was also observed in several population-based cross-sectional studies.^[36,43,46-48] However, the observed associations cannot be established as causal.

Several short-term metabolic studies and small randomized trials have specifically examined the efficacy of magnesium supplementation in improving insulin sensitivity among nondiabetic individuals, but the results have varied. Four randomized, double-blind placebo-controlled trials have assessed the effects of magnesium in both insulin secretion and action among nondiabetic participants.^[49,50] In one trial of 12 nonobese elderly participants, daily magnesium supplementation (4.5 g magnesium pidolate, equivalent to 15.8 mmol) for 4 weeks significantly improved glucose-induced insulin response and insulin-mediated glucose disposal.^[50] In another randomized double-blind placebo-controlled trial, 60 apparently healthy participants who had low serum magnesium concentrations and IR assessed were randomly allocated to receive either magnesium supplement (2.5 g/day magnesium chloride [12.5 mmol elemental magnesium]) or placebo.^[49] Magnesium treatment for 3 months significantly improved IR 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 homeostatic model assessment IR (HOMA-IR) (4.6 ± 2.8 to 2.6 ± 1.1).^[49] A randomized controlled trial (RCT) in 52 normomagnesemic, overweight, insulin resistant, nondiabetic subjects indicated that the 6 months supplementation of Mg-aspartate-hydrochloride dosed 365 mg/day significantly improved the HOMA-IR and glucose disposal.^[51] While, a recent cross-over RCT in health young males with family history of MetS or type 2 DM found a null effect of oral supplements of magnesium-pidolate on the IR.^[52] Due to limited and controversial evidences, the beneficial effect of magnesium supplementation in improving insulin sensitivity in nondiabetic and normal weight people has yet to be conclusively demonstrated, and future long-term and well-designed controlled trials are warranted.

Dyslipidemia (high triglycerides and low high-density lipoprotein)

Dietary magnesium may be related to lipid metabolism independent of its effects on insulin sensitivity. Malkiel-Shapiro *et al.* first reported that intramuscular injection of magnesium sulfate lowered serum β -lipoprotein in

patients with coronary heart disease.^[53] Animal studies have also suggested favorable effects of magnesium intake on lipid metabolism.^[12,54-56] As a cofactor for many rate-limiting enzymes critical for lipid metabolism, magnesium may decrease the activity of lecithin: Cholesterol acyl-transferase^[14] and 3-hydroxy-3-methylglutaryl coenzyme A reductase, and increase lipoprotein lipase activity^[57] which will indirectly decrease the lipid levels.

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 Mexicans, low serum magnesium levels were independently related to dyslipidemia.^[58] In the Atherosclerosis Risk in Communities cohort study, serum magnesium was inversely related to serum triglycerides and positively related to low-density lipoprotein cholesterol (LDL-C) while dietary magnesium intake was positively associated with plasma HDL-C.^[43] Several trials have evaluated the effect of magnesium supplements on blood lipids among normal lipid or hyperlipidemic patients. In the 1960s, a clinical trial reported that a combination of magnesium chloride and potassium chloride lowered α and β lipoproteins by 10%.^[59] A non-RCT in 1984 reported the significantly decreased total cholesterol, LDL-C, and very LDL cholesterol (VLDL-C) concentrations and increased HDL-C in 16 patients with hyperlipidemia after an oral magnesium chloride (18 mmol/day) for 118 days.^[13] 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.^[14] 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.^[14] One randomized, double-blind, placebo-controlled trial failed to demonstrate the efficacy of magnesium supplementation in improving lipid profile among healthy people.^[60] In a trial of 50 healthy 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.^[60] There is still insufficient evidence to draw definitive conclusions about the effect of magnesium supplementation on lipid metabolism in nondiabetic patients.

Indeed it is difficult to tease out the causal effect of magnesium on lipid metabolism independent of glucose and/or insulin homeostasis. Among healthy participants with IR and low serum magnesium concentrations, magnesium supplementation for 3 months significantly increased the lipid profile in a randomized, double-blind placebo-controlled trial.^[49] While among normomagnesemic, insulin resistant, overweight, nondiabetic subjects, a null effect of magnesium supplementation (Mg-aspartate-hydrochlorid, 365 mg/day [15 mmol]) on lipid profile was reported in another trial.^[51] Several studies (one nonrandomized trial and 6 randomized, double-blind placebo-controlled trials) have focused on whether magnesium intake affects lipid profiles in diabetic patients.^[61-66] However, none of six 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.^[61-66] Thus far, whether oral magnesium supplementation improves lipid profiles in nondiabetic or diabetic participants remains unsettled.

Blood pressure and hypertension

A substantial body of research has accumulated for decades, implicating a pivotal role of magnesium intake in BP regulation.^[7] Proposed underlying mechanisms of antihypertensive effects include the inhibition of intracellular calcium mobilization, attenuation of the adverse effect of sodium, decreased release of catecholamine,^[7,16] improvement of myocardial contractility and vascular smooth muscle tone,^[16] endothelium-dependent vasodilation,^[7,17,67] systemic inflammation,^[22,23] and insulin secretion and action.^[6,10]

The hypothetical relation between magnesium intake and BP was suggested by the results from ecologic studies that showed a negative correlation between water hardness and BP and hypertension.^[68,69] However, due to the problematic ecologic correlation^[70] and the confounding from dietary,^[71] such comparison may be a lack of evidence effectiveness in the prevention of MetS.

The majority of epidemiologic data relating dietary magnesium to lower prevalence of hypertension is provided by numerous cross-sectional studies. Results from most, but not all cross-sectional studies suggest that magnesium intake reduces BP in diverse populations.^[67,72] Results from observational studies have been thoroughly reviewed elsewhere.^[72,73] 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

populations and sample sizes, various methodologies of diet assessment, and different statistical analyzes.^[72] 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 on the relation of magnesium intake with the development of hypertension, though limited, are available.^[74-76] A previous meta-analysis was conducted to reconcile the results discrepancies from previous prospective cohort studies and yielded a summary RR of 0.88 comparing the highest category of dietary magnesium intake with the lowest category of intake (95% CI: 0.80-0.97; $P = 0.87$ for between-study heterogeneity).^[23] Considering the partial influence shared by other highly correlated variables such as fiber, calcium, and potassium, dietary magnesium may have only a modest effect on the risk of hypertension.

Numerous small clinical trials have assessed the therapeutic effect of magnesium supplements in hypertension but yielded inconsistent results.^[72,77] Many sources of heterogeneity may have contributed to the inconsistency in these trials including small sample size, incomplete randomization, the lack of blinding in design, variable duration of follow-up, high rates of noncompliance, and differences in magnesium treatment protocols, magnesium formulation and dose, and study populations. In a 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).^[77] 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).^[77] 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 diastolic BP (2.3 mmHg, 95% CI: -1.0 to 5.6).^[77] 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.

Magnesium and metabolic syndrome

Metabolic syndrome comprises a series of metabolic abnormalities including visceral obesity, glucose

intolerance, hypertension, and dyslipidemia.^[24,25] 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 MetS. Regardless of diverse definitions used for the MetS as an entity in different studies, this notion has been supported by epidemiologic evidence summarized in Table 1.

Two cross-sectional studies have related serum magnesium level to MetS and/or its components. In a cross-sectional population-based study, low serum magnesium levels were associated with elevated risk of MetS.^[58] In another cross-sectional study, low levels of serum ionized magnesium were associated with the MetS and serum magnesium level was inversely related to triglycerides and waist circumference. However, it remains controversial whether serum magnesium levels can reflect long-term magnesium intake or total magnesium status in the human body.^[86,87]

Magnesium intake has been observed to be associated with all features of the MetS. Song *et al.* first reported an inverse relation between dietary intake of magnesium and the prevalence of MetS among 11,686 apparently healthy American women in the Women's Health Study.^[48] Update to now, totally seven cross-sectional studies concerned on the relationship between dietary magnesium intake and the MetS,^[78,79,80-84] six of them indicated the inverse association between dietary magnesium intake and MetS.^[78,80-82,84] A recently meta-analysis of six cross-sectional studies concluded a significant reverse association between dietary magnesium intake and the risk of MetS (OR: 0.69; 95% CI: 0.59-0.81) comparing the highest quantile category with the lowest category.^[88] The prevalence of MetS would be reduced by 17% (OR: 0.83; 95% CI: 0.77-0.89) of the overall risk of having MetS for every 100-mg/day increment in magnesium intake.^[88] In this review, we performed a meta-analysis to characterize the dose-response relationship between dietary magnesium intake and the MetS based on seven cross-sectional studies and one prospective cohort study. The results indicated a significantly inverse relationship between magnesium intake and the MetS. A 100-mg daily increment in dietary intake of magnesium was related with a 7% reduction in the prevalence of MetS (95% CI: 0.90-0.96; P for trend < 0.0001). The quadratic polynomial spline analysis clearly showed a linear inverse association between magnesium and MetS across a range of magnesium intake from 180 to 588.2 mg/day [Figure 1].

Only one prospective study has been identified. In 2006, He *et al.* conducted a longitudinal study and prospectively

Table 1: Epidemiologic evidence for the relationship between dietary magnesium intake and the MetS

Author, year study Cohort	Participants	Age (range)	MetS definition	MetS proportion*	Magnesium categories and multivariate RR (95%CI)	Adjusted variables
Song <i>et al.</i> (2005), WHS ^[78]	14,719 US women (mostly Caucasian)	39-89	Modified NCEP ATP III criteria	Prevalence: 24.4%	Quintiles of dietary magnesium intake (mg/day) and ORs (95% CIs): Q1 (116-277): 1.00 (referent); Q2 (277-309): 0.89 (0.75-1.06); Q3 (309-341): 0.84 (0.70-1.02); Q4 (341-383): 0.78 (0.63-0.96); Q5 (383-837): 0.65 (0.52-0.83); (<i>P</i> for trend=0.0004). No significant associations with triglycerides	Age, smoking, exercise, total calorie, alcohol use, multivitamin use, parental history of myocardial infarction, dietary intakes of total fat, cholesterol, folate, glycemic load, and fiber
Bo <i>et al.</i> (2006), Italy ^[79]	1653 (male: 47.2%)	45-64	NCEP ATP III criteria	Prevalence: 23%	Quintiles of dietary magnesium intake (mg/day) and ORs (95% CIs): Q1 241.2 (38.6-278): 1.03 (0.62-1.70); Q2 308.2 (269.1-338.6): 0.86 (0.57-1.30); Q3 397.9 (337.5-1052.3): 1; (<i>P</i> value for trend 0.70). Not reported the association with individual MetS components	Age, gender, BMI, smoking status, alcohol intake, level of physical activity, dietary intake of total calories, the total percentage of fat and dietary intake of fiber
Ford <i>et al.</i> (2007), NHANES III ^[80]	7669 Americans (3799 women and 3870 men)	26-82	NCEP ATP III criteria	Prevalence: 25.6%	Quintiles of dietary magnesium intake (men and women, mg/day) and ORs (95% CIs): Q1 (men ≥221 and women ≤164): 1.00 (referent); Q2 (222-292 and 165-213): 0.84 (0.58-1.23); Q3 (293-376 and 214-263): 0.76 (0.54-1.07); Q4 (377-465 and 264-336): 0.62 (0.40-0.98); Q5 (≥466 and ≥337): 0.56 (0.34-0.92); (<i>P</i> for trend <0.0001). No significant associations with individual MetS components	Age, sex, race, education, smoking, CRP, alcohol use, physical activity, family history of early CHD, vitamin use, history of diabetes, fat, carbohydrate, fiber, total energy intake
Beydoun <i>et al.</i> (2008), USA ^[81]	4519 Americans	≥18	NCEP ATP III criteria	Prevalence: 25.8%	Continuous, per 100 mg/day magnesium intake. OR (95% CI): 0.83 (0.72-0.96) for every 100 mg/day increment of magnesium intake. NR	Gender, ethnicity, dietary group, e.g., calcium, phosphorus, daily products, fats
McKeown <i>et al.</i> (2008), USA ^[82]	535 Americans (179 men and 356 women)	≥60	NCEP ATP III criteria	Prevalence: 39.8%	Quartiles of dietary magnesium intake (mg/day) and ORs (95% CIs): Q1 (≤215.0): 1.00 (reference); Q2 (215.1-265.5): 0.74 (0.45-1.24); Q3 (265.6-332.4): 0.55 (0.32-0.97); Q4 (>332.4): 0.36 (0.19-0.69) (<i>P</i> for trend = 0.002). No significant associations with triglycerides and BP	Age, gender, race, education, marital status, smoking status, alcohol intake, exercise, BMI, total energy intake, percentage of energy from saturated fatty acid intake, lipid-lowering medication use and BP medication use
Huang <i>et al.</i> (2012) Taiwan ^[83]	210 Chinese (male: 46.7%)	≥65	NCEP ATP III and IDF criteria	Prevalence: 74.3%	Quartiles of dietary magnesium intake (mg/kg) and ORs (95% CIs): Q1 (<2.3): 1.00 (reference); Q2 (2.3-3.2): 2.10 (0.73-6.06); Q3 (3.3-4.4): 1.68 (0.60-4.70); Q4 (≥4.5): 0.49 (0.17-1.43) (<i>P</i> for trend = 0.153). Significant associations with BMI and circumference	Gender, age, physical activity, total energy intake, carbohydrate intake (% energy), protein intake (% energy), total fat intake (% energy), smoking status and alcohol intake
Al-Daghri <i>et al.</i> (2013) Saudi Arabia ^[84]	185 Arabian (87 men 98 women)	19-60	IDF criteria	Prevalence: 39%	Quintiles of dietary magnesium intake (mg/day) and ORs (95% CIs): Q1 (median: 183.0): 2.70 (1.00-7.20); Q2 (median: 299.0): 3.10 (1.10-8.60); Q3 (median: 417.5): 0.62 (0.24-1.60); Q4 (median: 588.2): 1.00 (referent); (not report the <i>P</i> value for trend). Not reported the association with individual MetS components	Age, BMI and physical activity
He <i>et al.</i> (2006), CARDIA ^[85] *	4637 (2363 Blacks and 2274 Whites)	18-30	NCEP ATP III criteria (including diabetic cases)	13% incidence for 15 years of follow-up	Quartiles of total magnesium intake (median, mg/day) and ORs (95% CIs): Q1 (median: 96): 1.00 (referent); Q2 (median: 121): 0.98 (0.79-1.21); Q3 (median: 147): 0.75 (0.59-0.96); Q4 (median: 191): 0.69 (0.52-0.91); (<i>P</i> for trend <0.01). No significant associations with BP and triglycerides	Age, gender, race, education, smoking, physical activity, family history of diabetes, alcohol intake, dietary intakes of fiber, polyunsaturated fat, saturated fat, total carbohydrates, total energy with additional adjustment for each component of the MetS at baseline

WHS: The Women's Health Study, NHANES III: Third National Health and Nutrition Examination Survey, MetS: The metabolic syndrome, CARDIA: The Coronary Artery Risk Development in Young Adults Study, NCEP ATP III: The National Cholesterol Education Program Adult Treatment Panel III, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, BP: Blood pressure, RR: Risk ratio, IDF: International Diabetes Federation, CRP: C-reactive protein, CHD: Coronary heart disease. *Only one prospective study was available

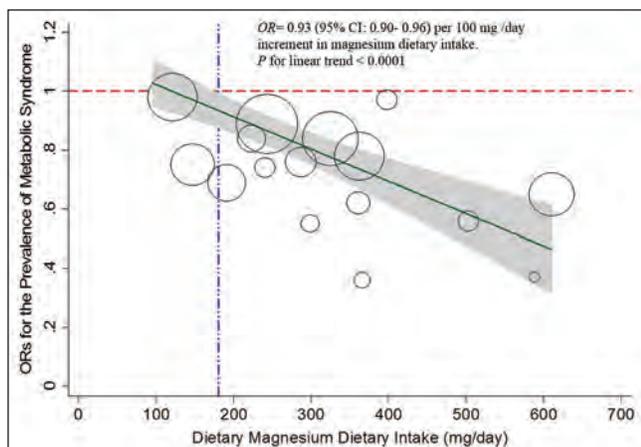


Figure 1: Dose-response relationship between dietary magnesium intake (ranged from 96 to 588.2 mg/day) and the prevalence of metabolic syndrome in five independent observational studies. The median Mg intake in the lowest quantile categories is 184 mg/day. The quadratic polynomial spline regression is used to model the relation shape, and 95% confidence intervals of the regression line are shown as the gray shaded region. Circles indicate odds ratio (OR) in each study. The circle size is proportional to the precision of the OR (inverse of the variance)

examined the relations between magnesium intake and incident MetS (defined by the Adult Treatment Panel III definition) in American young adults.^[85] They finally found that magnesium intake was inversely associated with the incidence of MetS (OR: 0.69; 95% CI: 0.52-0.91) for 15 years follow-up. All the data appeared to support the hypothesis that higher magnesium intake, predominantly from diet, may be beneficial for cardiometabolic health.

Future research implication

In summary, epidemiologic evidence suggests that high magnesium intake from diet or supplements may favorably affect a cluster of metabolic abnormalities including IR, hypertension, dyslipidemia, and overall MetS. However, there remain many important questions that require answers in future studies before we are able to obtain conclusive evidence.

First, 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 causal effect of any single nutrient on disease risk.

Second, much uncertainty exists regarding the validity of epidemiologic 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 MetS because of cost, logistical, and compliance issues. The evidence for the benefits of

magnesium supplementation in the secondary prevention of MetS-related chronic disease remains a matter of debate. It is obvious that future large well-conducted secondary prevention trials are warranted to unravel the efficacy and safety of magnesium supplements.

Third, there is evidence from intervention trials suggesting the relation between magnesium intake and these metabolic disorders that are not included in the MetS definition such as oxidative stress, microalbuminuria,^[89] and impaired fibrinolysis.^[90] It remains to be addressed whether or to what extent these abnormalities could be ameliorated by magnesium intake and contribute to the overall benefit of magnesium intake.

Fourth, extracellular magnesium levels are under tight homeostatic regulation in the human body. Thus, normal levels of serum magnesium are within a narrow range and do not correlate well with total magnesium status or with intracellular magnesium pool.^[86,87] However, serum magnesium concentrations are still the most commonly used metric to define magnesium deficiency in humans. From a mechanistic perspective, there is a 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. 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.

Fifth, the precise mechanisms underlying magnesium metabolism are far from clear. Recent genetic studies about links between a mitochondrial mutation, TRPM6 (an ion channel kinase of the “transient receptor potential” gene family) mutations, and hypomagnesemia had shed light on the underlying molecular basis for magnesium metabolism and helped identify genetic variants in modifying the metabolic effects of magnesium intake.^[91-93] However, there are few population data available on common genetic susceptibility to magnesium deficiency in the general population.

Finally, we believe that the application of microarray technology in randomized-controlled setting will technically help us to analyze the expression levels of thousands of genes simultaneously, and afford us the opportunity to gain important insight into the molecular mechanism for complex biological systems of metabolic abnormalities in response to magnesium supplementation.

CONCLUSION

In summary, available evidences suggest that higher intake of magnesium may contribute to a reduction in the risk of MetS through its potential benefits on the individual components of MetS. In the lack of reliable data from large longitudinal studies and well-designed RCTs, collective evidence from epidemiological studies regarding the potential benefits of magnesium intake is consistent with prevailing dietary recommendations for primary prevention of metabolic diseases by consuming rich magnesium foods.

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