Review

Magnesium Intake, Insulin Resistance, and Type 2 Diabetes

Yiqing Song, MD, ScD;[1]* Qi Dai, MD, PhD;[2] Ka He, MD, MPH, ScD[3]

[1] *Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*
[2] *Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center,Vanderbilt University School of Medicine, Nashville, TN*
[3] *Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, IN*

Magnesium is one of essential minerals abundant in whole grains, green leafy vegetables, legumes, and nuts. Accumulating evidence suggests that adequate magnesium intake is important in maintaining glucose and insulin homeostasis and thereby in protecting against the development of type 2 diabetes. Observational evidence, primarily from cross-sectional studies, has shown that low dietary magnesium intake are inversely related to glucose intolerance and/or insulin resistance. Results from prospective studies of magnesium intake and risk of incident type 2 diabetes have been generally consistent; however, there are as yet no clinical trials examining the efficacy of magnesium supplementation or consumption of major magnesium-rich foods on the primary prevention of type 2 diabetes. The efficacy of oral magnesium supplementation as adjunct therapy in improving glycemic control among non-diabetic or diabetic patients has been suggested in some small randomized clinical trials. In addition, recent evidence from human population data suggested that common variants of two genes (ion channel transient receptor potential membrane melastatin 6 and 7, TRPM6 and TRPM7) critical for magnesium homeostasis may confer a susceptibility to type 2 diabetes in individuals with inadequate magnesium intake, although further replication in large-scale studies is warranted. This presentation provides an overview of the current evidence linking magnesium intake to insulin resistance and type 2 diabetes from observational studies to intervention trials.

[N A J Med Sci. 2013;6(1):9-15. **DOI:** *10.7156/najms.2013.0601009]*

Key Words: *magnesium intake, insulin resistance, type 2 diabetes*

INTRODUCTION

Magnesium is an essential mineral with several dietary sources including whole grains, green leafy vegetables, legumes, and nuts. National survey data indicate that dietary magnesium intake is inadequate in the US general population, particularly among adolescent girls, adult women, and the elderly.[1,2] Adequate magnesium intake is believed to be important in maintaining magnesium status in the human body.[3] Homeostasis of magnesium is tightly regulated and depends on the balance between intestinal absorption and renal excretion. Emerging evidence has indicated a genetic basis for magnesium metabolism in human. Cross-sectional evidence has shown that magnesium intake correlates significantly with features of the metabolic syndrome (or insulin resistance syndrome), including adiposity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, and low HDL cholesterol and hypertension.[4,5] The metabolic syndrome, defined as a cluster of metabolic abnormalities including obesity, hyperglycemia, hypertension, and dyslipidemia, is now reaching epidemic proportions worldwide and may reflect a common underlying pathophysiology related to insulin resistance. In prospective observational studies, dietary magnesium intake has been inversely associated with the incidence of the metabolic syndrome[6] and associated chronic diseases including type 2 DM,[7-9] cardiovascular disease,[10-12] hypertension,[13,14] and colorectal cancer.[15,16]

Received 11/16/2012; Revised 01/04/2013; Accepted 01/23/2013
***Corresponding Author:** Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue East, Boston, MA 02215. (Email: ysong3@rics.bwh.harvard.edu)

MAGNESIUM INTAKE AND INSULIN/GLUCOSE HOMEOSTASIS

Magnesium may play a role in glucose homeostasis, insulin action in peripheral tissues, and pancreatic insulin secretion.[3,17] Although the exact mechanisms are not well-understood, several mechanisms have been proposed (**Figure 1**). First, magnesium functions as a cofactor for several enzymes critical for glucose metabolism utilizing high-energy phosphate bonds.[3] Diminished levels of magnesium were observed to decrease tyrosine kinase activity at insulin receptors[18] and to increase intracellular calcium levels,[17] leading to an impairment in insulin signaling. Thus, intracellular magnesium levels have been hypothesized to be important for maintaining insulin sensitivity in skeletal muscle or adipose tissue.[17,19] Additionally, intracellular magnesium levels may also influence glucose-stimulated insulin secretion in pancreatic β-cells through altered cellular ion metabolism,[17] oxidative stress,[20] endothelial function, and the proinflammatory response.[21,22]

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.[23,24] Several epidemiologic studies have also found an association between dietary magnesium intake and insulin homeostasis.[4,9,23,25] Several short-term metabolic studies and small randomized trials have also specifically examined the efficacy of magnesium supplementation in improving insulin sensitivity among nondiabetic individuals, although evidence remains inconclusive.[26,27,28] Specifically, two randomized double-blind placebo-controlled trials found that magnesium supplementation improved both insulin secretion and insulin action among nondiabetic participants.[27,28] 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.[28] In another randomized double-blind placebo-controlled trial, among 60 apparently healthy participants who had low serum magnesium concentrations, magnesium treatment (2.5 g/day magnesium chloride [12.5 mmol]) 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 the homeostasis model analysis for insulin resistance (HOMA-IR) (4.6±2.8 to 2.6±1.1, $p<0.0001$).[27] We recently completed a 4-week randomized controlled crossover trial of Mg citrate supplementation (500 mg elemental Mg daily) among 14 overweight individuals (BMI $\geq$ 25 kg/m^2) and observed that Mg treatment significantly decreased fasting C-peptide concentrations (Change: -0.4 ng/mL after Mg vs. +0.05 ng/mL after placebo) and fasting insulin (-2.2 mcU/mL vs. 0.0 mcU/mL). We also observed down regulation of several genes related to metabolic and inflammatory pathways including C1q and tumor necrosis factor related protein 9 (C1qthf9) and pro-platelet basic protein (chemokine (C-X-C) motif) ligand (PPBP). Our results from urine proteomic profiling showed a number of proteins significantly altered expression in response to Mg treatment.[29] These findings indicate that among overweight or obese individuals Mg supplementation for four weeks may improve insulin and glucose homeostasis and may lead to systemic changes in gene and protein expression that warrant further investigation in larger trials.

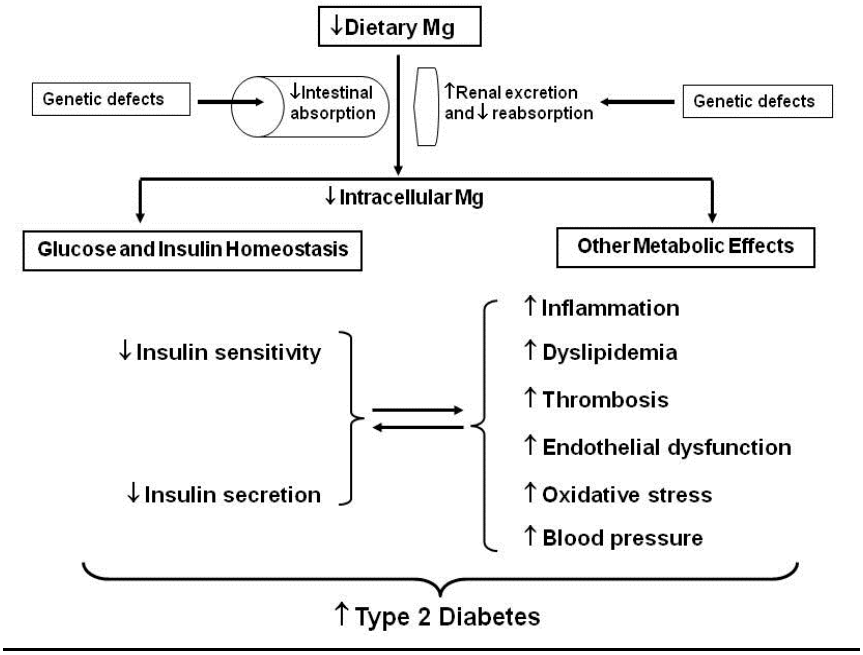

Figure 1. Potential mechanisms underlying the relation between magnesium intake and type 2 diabetes Magnesium Intake and the Development of Type 2 Diabetes.

Accumulating evidence based on animal models and from epidemiological studies supports a potentially important role of magnesium in the development of type 2 diabetes. Magnesium supplementation has been observed to prevent fructose-induced insulin resistance[30] and to delay the onset of spontaneous type 2 diabetes in rat models.[31]

In earlier clinical studies, hypomagnesemia was shown to be frequent among patients with diabetes, especially those with poor metabolic control.[17] Several cross-sectional studies have documented an inverse association between plasma or erythrocyte magnesium levels and fasting insulin levels in both diabetic patients and apparently healthy individuals.[4,9,23,24] Other cross-sectional studies have also shown an inverse association between serum or plasma concentrations of magnesium and prevalence of type 2 diabetes, suggesting a potential role of magnesium status in the pathogenesis of type 2 diabetes.[19,23,32] However, the evidence from cross-sectional studies cannot imply any causal relation between hypomagnesemia and type 2 diabetes.

Table 1. Prospective data on the relationship between dietary magnesium intake and incident type 2 diabetes.

Study	Population (cases/total)	Follow-up, years	Multivariate RR (95% confidence interval) (highest vs. lowest) and p for trend[a]
Nurses' Health Study[7,46]	4085/85060	18	0.66 (0.60-0.73), p<0.001
Health Professionals Follow-up Study [8]	1333/42872	12	0.67 (0.56-0.80, p<0.001
Atherosclerosis Risk in Communities Study [32]	1106/11896	6	0.95 (0.52-1.74) for Blacks, p=0.47 0.80 (0.56-1.14) for Whites, p=0.49
Iowa Women's Health Study [47]	1141/35988	6	0.67 (0.55-0.82) P=0.0003
Women's Health Study [9]	918/39345	6	BMI>=25: 0.77 (0.61-0.98) p=0.02 BMI<25: 1.77 (0.95-3.32) p=0.29
Melbourne Collaborative Cohort Study[50]	365/31641	4	0.62 (0.43-0.90) per 500 mg/day magnesium increase
Black Women's Health Study[49]	1964/41186	8	0.69 (0.59-0.81), P trend <0.0001
The European Prospective Investigation Into Cancer and Nutrition (EPIC)–Potsdam study[48]	844/25067	7	0.99 (0.78-1.26), P, NA

Meta-analysis	Year	Studies	No. of cases/total	Summary RR (95% CI)
Larsson SC, Wolk A. [51]	2007	7	10,912/286,668	0.85 (95% CI, 0.79–0.92) per 100 mg/day increase).
Schulze MB, et al.[48]	2007	8	8,459/228,997	0.77 (0.72-0.84)
Dong JY, et al. [52]	2011	13	24,516/ 536,318	0.78 (0.73–0.84)

RR: relative risk; NA: not available; No.: number.
a: Multivariate-adjusted RR represented those comparing the highest category with the lowest category of magnesium intake; p for trend indicated the linear trend across quartiles or quintiles of magnesium intake.

A large body of data from clinical case studies and cross-sectional studies provided further evidence for the correlation between blood magnesium levels and type 2 diabetes.[23,33-40] Hypomagnesemia is common among patients with diabetes, especially those with poor metabolic control.[35,39,41] Polyuria caused by 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 diabetes.[42,43] Inadequate intake of dietary magnesium in diabetic patients may also cause hypomagnesemia.[44] 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.

Results from prospective studies of magnesium intake and risk of type 2 diabetes have been generally consistent and parallel the findings from metabolic studies showing the role of adequate magnesium intake in maintaining insulin sensitivity in both healthy and diabetic participants.[19,45] **Table 1** summarizes prospective evidence for the association between dietary magnesium intake and risk of developing type 2 diabetes as well as previous meta-analyses of prospective cohort studies. Previous reports from the Nurses' Health Study,[7,46] the Iowa Women's Health Study,[47] the Health Professionals Follow-up Study,[8] the European Prospective Investigation Into Cancer and Nutrition(EPIC)-Postdam Study,[48] the Black Women's Health Study,[49] and the Melbourne Collaborative Cohort Study[50] all indicated an inverse association between magnesium intake and risk of incident type 2 diabetes, although such an association was not found in the ARIC study with relatively small number of incident cases.[32] An earlier meta-analysis of 7 prospective studies involving 271,869 participants and 9,792 cases showed a reduced diabetes risk with higher magnesium intake (RR for extreme categories, 0.77 [95% CI, 0.72-0.84]).[48] Another independent meta-analysis of 8 prospective cohort studies included 286 668 participants and 10 912 cases and found an inverse relation between magnesium intake and risk of type 2 diabetes; the overall relative risk for a 100 mg/day increase in magnesium intake was 0.85 (95% CI, 0.79–0.92). Results were similar for intake of dietary magnesium (RR, 0.86; 95% CI, 0.77–0.95) and total magnesium (RR, 0.83; 95% CI, 0.77–0.89).[51] Recently, an updated meta-analysis of 13 prospective cohort studies involving 536,318 participants and 24,516 cases confirmed a significant inverse association between magnesium intake and risk of type 2 diabetes (relative risk [RR] 0.78 [95% CI

0.73–0.84]).[52] This meta-analysis also showed that magnesium intake is significantly inversely associated with risk of type 2 diabetes in a dose-response manner. The summary RR of type 2 diabetes for every 100 mg/day increment in magnesium intake was 0.86 (95% CI 0.82–0.89).[52] Thus, the evidence from prospective cohort studies is strongly supportive of the role of magnesium intake in the development of type 2 diabetes.

There are as yet no clinical trials examining the efficacy of magnesium supplementation or consumption of major magnesium-rich foods on the primary prevention of type 2 diabetes. 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.[53-56] Nine randomized controlled trials of oral magnesium supplementation have assessed diabetes-related phenotypes (e.g., glycemic control, or insulin sensitivity) among patients with type 2 diabetes.[45,53,57-63] 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.[45,60,61,63] 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 diabetes.[53,57-59,62] 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 different magnesium doses and formulations used, have led to difficulties in interpreting the potential benefits of oral magnesium supplementation for patients with type 2 diabetes. Oral magnesium supplementation as adjunct therapy may be effective in improving glycemic control among type 2 diabetes 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.[45,53,57-63] 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.

POTENTIAL MODIFYING EFFECTS OF GENETIC VARIANTS ON THE ASSOCIATION OF MAGNESIUM INTAKE WITH TYPE 2 DIABETES

To enhance our understanding of the epidemiology of magnesium-type 2 diabetes relation, it has become increasingly important to consider molecular and genetic variations in the homeostatic regulation of magnesium metabolism and their roles in the etiology of type 2 diabetes.

Magnesium homeostasis in the human body is tightly regulated and may involve the as-yet unidentified mechanism underlying the balance between intestinal absorption and renal excretion. Growing evidence suggests that many genes are involved in magnesium uptake, distribution, and metabolism in the human body. Of them, ion channel transient receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7) play a central role in magnesium homeostasis, which is critical for maintaining glucose and insulin metabolism. TRPM6 is a magnesium-permeable channel protein primarily expressed in intestinal epithelia and kidney tubules that may play an important role in intestinal and renal magnesium handling.[64,65] Several loss-of-function mutations in TRPM6 have been identified among patients with autosomal-recessive familial hypomagnesemia with secondary hypocalcemia.[64-66] TRPM7 is ubiquitously expressed in various tissues or cell lines[67,68] and may be part of a magnesium sensing and/or uptake mechanism underlying cellular magnesium homeostasis.[67,68] Furthermore, a magnesium-deficient diet was shown to upregulate TRPM6 mRNA expression in mice.[69] Low serum magnesium levels caused by TRPM6 mutations among HSH patients can be ameliorated by oral supplementation of high doses of magnesium, indicating a potential gene-diet interaction on magnesium homeostasis.[70] However, it is unclear whether common genetic variation in TRPM6 and TRPM7 contributes to risk of type 2 diabetes. We conducted a nested case-control study of 359 incident diabetes cases and 359 matched controls in the Women's Health Study.[71] On the basis of the publicly accessible dataset, we focused on common SNPs including intronic SNPs, synonymous SNPs, and nonsynonymous SNPs to characterize genetic variation spanning the TRPM6 gene, including at least 30 kb upstream and downstream of the coding regions. We analyzed 20 haplotype-tagging single nucleotide polymorphisms (SNPs) in TRPM6 and 5 common SNPs in TRPM7 for their association with diabetes risk. Overall, there was no robust and significant association between any single SNP and diabetes risk. Our haplotype analyses suggested a significant risk of type 2 diabetes among carriers of both the rare alleles from two nonsynomous SNPs in TRPM6 (Val1393Ile in exon 29 [rs3750425] and Lys1584Glu in exon 30 [rs2274924]) when their magnesium intake was lower than 250 mg per day.[71] Compared with non-carriers, women who were homozygous carriers of the haplotype 1393Ile-1584Glu had an increased risk of type 2 diabetes (OR, 4.92, 95% CI, 1.05-23.0) only when they had low magnesium intake (<250 mg/day). Our results provide suggestive evidence that two common non-synonymous TRPM6 coding region variants, Ile1393Val and Lys1584Glu polymorphisms, might confer susceptibility to type 2 diabetes in women with low magnesium intake.[71] However, we cannot rule out the possibility that they may lead to changes in protein conformation and thus reduce TRPM6 channel activity. If our finding is replicated in future studies, it will suggest that common genetic variation in the TRPM6 locus known to harbor severe mutations causing monogenic magnesium deficiency confers a modest susceptibility to the risk of type 2 diabetes in a small subgroup of the general population. Given a limited number of SNPs (n=5) across TRPM7 (128

kb),[71] it is likely that TRPM7, as a housekeeping gene regulating cellular magnesium metabolism, may truly have limited genetic variability. Biologically, TRPM7 is ubiquitously expressed and its constitutive activation is required for cellular survival.

Several other candidate genes involved in magnesium bioavailability in the human body may also affects the risk of type 2 diabetes, but the relative importance of each gene involved in magnesium metabolism pathways has not yet been clarified. Future studies in this area will have to address both the genetic and magnesium status (dietary or biochemical marker of magnesium) to unravel the relative importance of common genetic variation in each candidate gene for diabetes risk.

POTENTIAL MODIFYING EFFECTS OF CALCIUM TO MAGNESIUM INTAKE RATIO ON THE ASSOCIATION OF MAGNESIUM INTAKE WITH TYPE 2 DIABETES

Calcium and magnesium have similar chemical properties and share the same homeostatic regulating system including gut absorption and kidney reabsorption to maintain a normal balance of calcium (Ca) and magnesium (Mg).[72-74] Furthermore, the changes in blood or colon lumen concentrations for Ca^{2+} and Mg^{2+} are monitored by the same receptor, the calcium-sensing receptor (CaSR).[72-74] Once the calcium or magnesium concentration is high, CaSR could respond to it even if the concentration of magnesium or calcium, respectively, is low, resulting in the simultaneous depression of the (re)absorption process for both calcium and magnesium.[73-76] Thus, in clinics, hypomagnesemia is commonly linked to secondary hypocalciuria[66]. Previous studies also showed that changes in the dietary calcium /magnesium balance affected systemic inflammation responses in animal models.[77,78] In addition to inflammation, Mg^{2+} and Ca^{2+} may potentially antagonize each other in many other physiologic activities,[72,75,76] such as oxidative stress and insulin resistance, DNA repair, cell differentiation and proliferation, apoptosis, and angiogenesis,[72,75,76] which may also be involved in development of cancer, type 2 diabetes, cardiovascular diseases and many other diseases.

In 2007, we reported that total magnesium intake from both dietary and supplemental source was associated with a significantly reduced risk of colorectal adenoma.[74] The inverse associations with both total intakes of calcium or magnesium may primarily appear among those with calcium/magnesium intake ratio was below 2.78.[74] In a recent paper based on the analysis of a large clinical trial, calcium treatment reduced risk of colorectal adenoma recurrence only among those with baseline dietary calcium/magnesium ratio less than or equal to 2.63.[73,74] Moreover, the effect of calcium treatment did not significantly differ by baseline intake of calcium or magnesium alone.[73,79] We also found high serum calcium/magnesium ratio was statistically associated with an increased risk of high-grade prostate cancer even after adjusting for both serum calcium and magnesium,[80] indicating that the balance between calcium and magnesium may affect risk or pathogenesis of diseases other than colorectal cancer or adenoma. Future studies are necessary to examine whether the association between intake of magnesium and risk of type 2 diabetes may be modified by calcium to magnesium intake ratio.

IMPLICATIONS AND FUTURE RESEARCH

Magnesium is one of the most promising nutritional factor for prevention of type 2 diabetes. Despite a century of research on potential health effects of magnesium, there has been a longstanding debate over the inconsistent results of dietary or supplemental magnesium against diabetes from observational studies. Of note, 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. 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. While 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 chronic diseases such as type 2 diabetes 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-conducted secondary prevention trials are warranted to unravel the efficacy and safety of magnesium supplements. In addition, emerging evidence has suggested that several genetic factors play central roles in magnesium metabolism in the human body. It has become increasingly important to consider molecular and genetic variations in the homeostatic regulation of magnesium metabolism and their roles in the etiology of type 2 diabetes. Of note, the application of microarray technology in randomized-controlled setting will not only enable us to analyze the expression levels of thousands of genes simultaneously, but also afford us the opportunity to gain important insight into the molecular mechanism for complex biological systems of inflammation, insulin resistance, and metabolic abnormalities in response to magnesium supplementation.

In summary, available 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 recommendations for primary prevention of type 2 diabetes by consuming foods rich in magnesium such as vegetables, whole grains, legumes, and nuts.

CONFLICT OF INTEREST
None.

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