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Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials

Y. Song*†‡, K. He§, E. B. Levitan*†, J. E. Manson*† and S. Liu*†

*Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, †Department of Epidemiology, ‡Department of Nutrition, Harvard School of Public Health, Boston, MA and §Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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Abstract

Aims The aim of this study was to assess the evidence on the effect of oral magnesium supplementation on glycaemic control in patients with Type 2 diabetes.

Methods We searched the electronic databases of MEDLINE, EMBASE and the Cochrane Controlled Trials Register up to January 2005. We identified nine randomized double-blind controlled trials with a total of 370 patients with Type 2 diabetes and of duration 4–16 weeks. The median dose of oral magnesium supplementation was 15 mmol/day (360 mg/day) in the treatment groups. The primary outcome was glycaemic control, as measured by glycated haemoglobin (HbA_{1c}) or fasting blood glucose levels; the secondary outcomes included body mass index, blood pressure (BP) and lipids. Using a random-effects model, we calculated the weighted mean differences (WMD) and 95% confidence interval (CI).

Results After a median duration of 12 weeks, the weighted mean post-intervention fasting glucose was significantly lower in the treatment groups compared with the placebo groups [–0.56 mmol/l (95% CI, –1.10 to –0.01); *P* for heterogeneity = 0.02]. The difference in post-intervention HbA_{1c} between magnesium supplementation groups and control groups was not significant [–0.31% (95% CI, –0.81 to 0.19); *P* for heterogeneity = 0.10]. Neither systolic nor diastolic BP was significantly changed. Magnesium supplementation increased on high-density lipoprotein (HDL) cholesterol levels [0.08 mmol/l (95% CI, 0.03 to 0.14); *P* for heterogeneity = 0.36] but had no effect on total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride.

Conclusions Oral magnesium supplementation for 4–16 weeks may be effective in reducing plasma fasting glucose levels and raising HDL cholesterol in patients with Type 2 diabetes, although the long-term benefits and safety of magnesium treatment on glycaemic control remain to be determined.

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Keywords controlled trials, glycaemic control, HbA_{1c} levels, magnesium supplementation, meta-analysis

Abbreviations BP, blood pressure; CI, confidence interval; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIDDM, non-insulin dependent diabetes mellitus; RR, relative risk; WMD, weighted mean differences

Correspondence to: Yiqing Song, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215, USA. E-mail: ysong@hsph.harvard.edu

Introduction

Hypomagnesaemia occurs frequently in diabetic patients, especially those with poor glycaemic control [1]. Increased magnesium intake may improve insulin secretion and action [2,3], dyslipidaemia [4,5], and endothelial dysfunction [6], and decrease thrombotic tendency [7] and vascular contractility [2,7,8]. Whether magnesium supplementation has a clinically beneficial effect on glycaemic control in diabetes, however, is a matter of debate.

Over 20 human metabolic studies and clinical trials have examined the possible effects of magnesium supplementation in diabetic patients and yielded apparently conflicting results [9–20]. Among all published randomized double-blind clinical trials, some [13,17,18,20], but not all [9,14–16,19] of them showed beneficial effects by oral magnesium supplementation on glycaemic control among patients with Type 2 diabetes. Oral magnesium supplementation has been shown to be effective in raising serum or plasma magnesium levels regardless of formulation or dose [9–20]. Although the randomized double-blind controlled trial design is the best approach to examine a cause–effect relation, almost all published trials included small numbers of participants. Furthermore, differences in study population, duration of diabetes, glycaemic treatment and intervention periods, coupled with the fact that different magnesium doses and forms were used, may explain the inconsistent results from previous trials.

To provide a comprehensive and quantitative synthesis of evidence from all randomized double-blind controlled trials, we therefore performed a formal meta-analysis to evaluate the effect of oral magnesium supplementation on glycaemic control in patients with Type 2 diabetes.

Patients and methods

Study selection

We searched the literature for all reports of randomized controlled trials that evaluated the effects of oral magnesium supplementation on glycaemic parameters and/or lipids in patients with Type 2 diabetes. All relevant clinical trials were identified from MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (1966 to January 2005). We used search terms 'magnesium', 'magnesium supplementation', and 'magnesium supplements' in combination with 'diabetes', 'Type 2 diabetes', 'glycaemic control', and 'non-insulin dependent diabetes (NIDDM)'. No language restrictions were applied. We also performed a manual search of references using bibliographies from retrieved articles and recent reviews.

Two of our investigators (YS and KH) independently performed the literature search, study selection, quality assessment and data extraction. Discrepancies were resolved by group discussion. To be included, studies had to meet the following five criteria: (i) randomly assigning treatment and a control; (ii) double-blind design; (iii) placebo or alternative treatment used as control group; (iv) oral magnesium supplements; (v) measurements for glycated haemoglobin (HbA_{1c}), fasting glucose levels, lipids, blood pressure, or blood, urine or erythrocyte magnesium levels. The quality of randomized trials was assessed using the 5-point scale developed by Jadad *et al.* [21], which quantifies the trial quality based on the description and appropriateness of randomization and blinding procedures, and description of withdrawals.

Data extraction

Following the QUORUM guidelines [22], we used a standardized reporting form to independently abstract data from each included study. The data we collected included the first author's name, year of publication, country of origin, mean of patients' age, mean duration of diabetes, diabetic treatment, sample size, sex proportion, the number of randomized groups, duration of treatment, magnesium formulation and dosage. We extracted baseline and post-intervention means and SDs for the magnesium treatment and control groups. We preferred to extract the data from intention-to-treat analyses if trials explicitly stated the analyses were by intention to treat. When results were not presented in the published paper, attempts were made to obtain additional data by directly contacting seven lead authors, but we failed to obtain responses from all. One study had two magnesium treatment groups; the high-dose group was selected [13].

Statistical analyses

All statistical analyses were performed using the STATA statistical software (Version 7.0, STATA Corporation, College Station, TX, USA). The primary analysis was to compare oral magnesium supplementation with placebo for the outcome of glycaemic control, as measured by HbA_{1c} or fasting blood glucose, which included whole blood, plasma or serum glucose levels. The secondary analysis was to evaluate the effects of oral magnesium supplementation on high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, triglyceride, systolic and diastolic blood pressure, body mass index (BMI), plasma calcium, and plasma, serum, erythrocyte, or urine magnesium levels. We calculated the difference between the means of the treatment and placebo groups at the end of the intervention. Each mean difference was weighted according to the inverse of its pooled variance. Then we calculated the weighted mean difference (WMD) and 95% confidence interval (CI) to pool the results for each continuous outcome using random-effects models [23]. Between-study heterogeneity was tested using the χ^2 statistic.

We assessed publication bias primarily using a Begg's modified funnel plot, in which the relative risk (RR) was plotted on a logarithmic scale against its corresponding standard error for each study. In the absence of publication bias, one would expect studies of all sizes to be scattered equally above and below the line showing the pooled estimate of log RR [24]. Power for formal tests for publication bias was generally low because of the small number of studies included for each outcome.

We also used a meta-regression analysis to examine the dose–response relation between blood magnesium and magnesium supplementation. The mean difference in end-of-study plasma or serum magnesium levels from individual trials was regressed on the corresponding value for magnesium dosage in elemental magnesium (mmol/day).

Results

Characteristics of all included randomized controlled trials

Of the 21 trials identified, nine randomized controlled trials met the inclusion criteria (Table 1). We did not identify any unpublished trials or non-English language trials. Figure 1 describes the study selection process that led to the final nine trials in this meta-analysis. Of the nine trials, five were parallel design and four used cross-over design with a washout period of 2–4 weeks. Eight trials used placebo as control group and only one used vitamin C treatment as a comparison group [16]. The median Jadad score for trial quality was 4 (range 2–5). The number of participants ranged from 8 to 93 (median 54). The range of treatment period was from 4 to 16 weeks (median 12 weeks). A total of 370 participants were enrolled in these nine trials evaluating oral magnesium supplementation [median dose for elemental magnesium: 15 mmol/day (360 mg/day)] as an adjunct to conventional treatment with diet and/or medication for Type 2 diabetes. The subjects were generally of similar age (range 54–73 and median 61 years) and BMI (range 25–32, median 28 kg/m^2). Diabetes treatment included diet alone, oral glucose-lowering drugs or insulin. In most of the trials, treatment was with diet or oral glucose-lowering medication.

Effect of magnesium on glycaemic control

Oral magnesium supplementation did not significantly reduce HbA_{1c} levels compared with placebo. Figure 2(a) shows the WMD and 95% CI of HbA_{1c} for each trial comparing magnesium treatment with the placebo group using a random-effects model. There was no evidence for the presence of significant

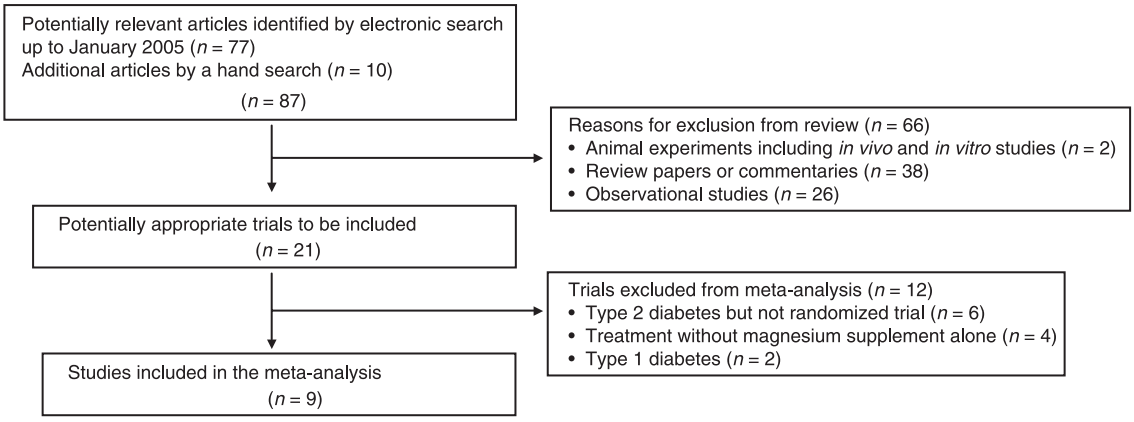

Figure 1 Flow chart of study selection.

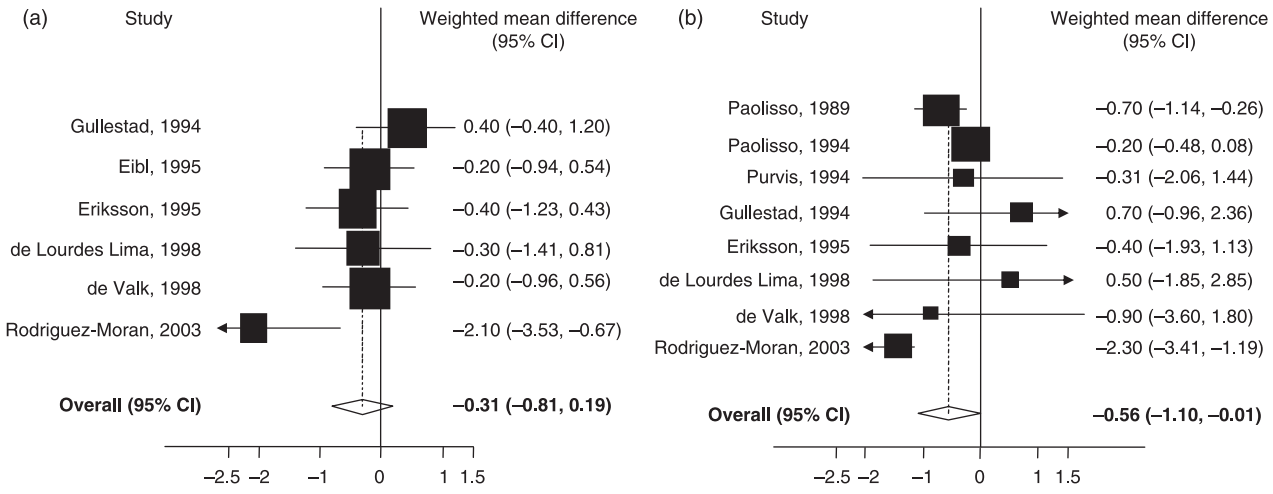

Figure 2 Weighted mean differences (95% CI) for plasma HbA_{1c} (a) and fasting glucose levels (b) after oral magnesium supplementation based on the data available from controlled clinical trials. Squares indicate the mean difference in each study. The size of the square is proportional to the per cent weight of each trial in the weighted mean difference; horizontal line represents the 95% CI. Studies are ordered by the publication year. The weighted mean difference and its 95% CI are indicated by the open diamond.

Table 1 Characteristics of nine randomized, double-blind, placebo-controlled clinical trials testing oral magnesium supplements as an adjunctive therapy for glycaemic control in patients with Type 2 diabetes

Source, country and year	No. of patients (placebo/ treatment)*	Study design	Age (years)	Women (%)	Duration of diabetes (years)	Diabetic treatment	Magnesium dosage	Follow-up (weeks)	Quality*	Endpoint measures
Paolisso *et al*., Italy, 1989 [17]	8/8	Crossover	72.2	37.5	11.5	Diet	Magnesium pidolate 2 g/day (7.0 mmol/day)	4	2	Euglycaemic–hyperinsulinaemic glucose clamp
Paolisso *et al*., Italy, 1994 [18]	9/9	Crossover	73	44.4	7.9	Diet	Magnesium pidolate 4.5 g/day (15.8 mmol/day)	4	3	Euglycaemic–hyperinsulinaemic glucose clamp
Gullestad *et al*., Norway, 1994 [9]	29/25	Parallel	64	NA	9.95	Diet (n = 11), oral agents (n = 19) and insulin (n = 24)	Magnesium lactate–citrate 15 mmol/day	16	4	Fasting glucose, HbA_{1c}, lipid profile, renal function, blood pressure and muscle strength
Purvis *et al*., USA, 1994 [19]	28/28	Crossover	53.8	85.7	NA	Diet and/or oral agents	Magnesium chloride 384 g/day (1.9 mmol/day)	6	5	Blood pressure, serum glucose, LDL, HDL and total cholesterol, triglyceride
Eibl *et al*., Norway, 1995 [15]	20/18	Parallel	58.3	50.5	6.8	Diet and oral agents	Magnesium citrate 30 mmol/day	12	4	HbA_{1c}, blood pressure, serum glucose, LDL, HDL and total cholesterol, triglyceride
Eriksson *et al*., Finland, 1995 [16]	27/27	Crossover	61	NA	10	Diet, oral agents and insulin	Magnesium 600 mg/day (24.7 mmol/day)	13 (90 days)	3	Fasting glucose, HbA_{1c}, blood pressure, LDL, HDL and total cholesterol, triglyceride
de Loudres Lima *et al*., Brazil, 1998 [13]	54/39	Parallel	53.7	77.4	7.2	Diet and/or oral agents	Magnesium oxide 41.4 mmol/day	4 (30 days)	4	Fasting glucose, HbA_{1c} and fructosamine
de Valk *et al*., the Netherlands, 1998 [14]	25/25	Parallel	62.5	44	15.6	Oral medication and insulin use	Magnesium–aspartate–HCl 15 mmol/day	12	4	Fasting glucose, HbA_{1c}, blood pressure, LDL, HDL and total cholesterol, triglyceride
Rodriguez-Moran *et al*., Mexico, 2003 [20]	31/32	Parallel	56.9	NA	9.1	Diet, exercise and oral agents	Magnesium chloride 2.5 g/day (12.8 mmol/day)	16	5	Homeostasis model assessment for insulin resistance, fasting glucose, HbA_{1c}, blood pressure, LDL, HDL and total cholesterol, triglyceride

*The 5-point Jadad Score based on the description of randomization, double blinding and withdrawals.
NA, not available.

heterogeneity among six trials ($\chi^2_5 = 9.13$; $P = 0.10$ for heterogeneity). The pooled WMD in HbA_{1c} between patients receiving magnesium treatment and those in the control group was –0.31% (95% CI, –0.81, 0.19; $P = 0.22$). Restricting the analysis to five trials with a duration ≥ 12 weeks yielded similar results [–0.33% (95% CI, –0.92 to 0.26); $P = 0.27$; P for heterogeneity = 0.06]. However, the effect of magnesium supplementation on fasting glucose was discernable and the WMD and 95% CI for fasting glucose was –0.56 mmol/l (95% CI, –1.10, –0.01; $P = 0.03$) (Fig. 2b) with a significant heterogeneity ($\chi^2_7 = 17.4$; $P = 0.02$ for heterogeneity). One trial showed a much larger effect than the others and contributed to most of the significant heterogeneity [20]. After excluding this trial from the meta-analysis, the between-study heterogeneity was no longer statistically significant, but the effect of magnesium on fasting glucose remained significant (WMD = –0.32 mmol/l; 95% CI: –0.55 to –0.09; $P < 0.001$; heterogeneity: $\chi^2_6 = 5.7$; $P = 0.46$).

The Begg's funnel plot showed data points scattered across the horizontal line (representing the pooled WMD), indicating no evidence of publication bias for meta-analyses of HbA_{1c} and fasting glucose levels (not shown).

Effect of magnesium on lipids, BP, weight (BMI) and plasma calcium

Table 2 presents the WMD and 95% CIs for the effects of oral magnesium supplementation on lipid profiles, and blood pressure as well as BMI and plasma calcium levels. Overall, compared with placebo, magnesium intake increased HDL cholesterol levels [0.08 mmol/l (95% CI: 0.03–0.14; P for heterogeneity = 0.36)]. However, the meta-analysis showed no significant effects on other parameters for different magnesium doses among patients with Type 2 diabetes.

Effect of magnesium on blood, erythrocyte or urinary magnesium levels

Overall, plasma or serum magnesium levels in the treatment group were significantly higher than that in the control group (WMD = 0.06 mmol/l; 95% CI: 0.04–0.08 mmol/l; P for heterogeneity = 0.60), regardless of different formulation and dosage used in these trials [13–20]. Our meta-regression analysis showed that on average each 10 mmol/day (243 mg/day) increase in supplemental magnesium was related to an 0.0052 mmol/l increase of blood magnesium levels, but there was no significant linear trend (P for trend = 0.66). Figure 3 shows the empirical relationship between magnesium treatment

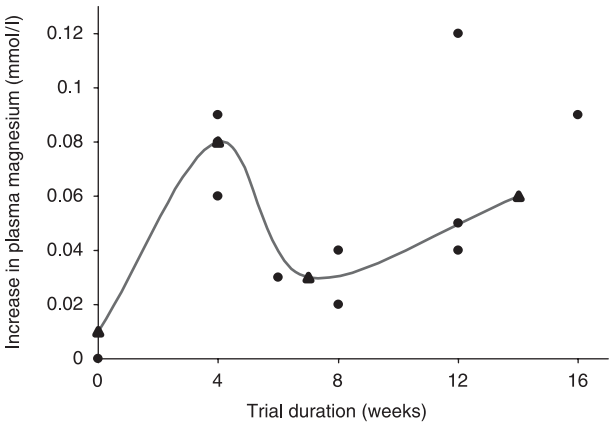

Figure 3 Trial data on mean changes in plasma magnesium levels (mmol/l) after magnesium treatment vs. placebo from 4 to 16 weeks. The smooth curve represents weighted mean differences at baseline, 4, 6–8 and 12–16 weeks comparing the magnesium treatment groups with placebo groups. The median doses of magnesium were 15, 12.5 and 20 mmol/day at 4, 6–8 and 12–16 weeks, respectively.

Table 2 Change in metabolic parameters in Type 2 diabetic patients in the magnesium treatment group compared with those in the control group

Metabolic parameters	No. of studies (placebo/treatment)	Weighted mean difference (WMD; 95% CI)	*P*-value for WMD	*P* for heterogeneity
Weight				
BMI (kg/m^2)	3 (112/98)	–0.21 (–1.77, 1.35)	0.72	0.85
Blood pressure (BP)				
Systolic BP (mmHg)	4 (120/117)	2.38 (–3.55, 8.31)	0.55	0.36
Diastolic BP (mmHg)	4 (120/117)	0.28 (–3.10, 3.65)	0.60	0.68
Lipids				
Total cholesterol (mmol/l)	5 (140/135)	–0.02 (–0.30, 0.26)	0.91	0.34
HDL cholesterol (mmol/l)	5 (140/135)	0.08 (0.03, 0.15)	0.001	0.36
LDL cholesterol (mmol/l)	3 (84/83)	–0.09 (–0.47, 0.28)	0.60	0.88
Triglyderides (mmol/l)	5 (140/135)	–0.06 (–0.35, 0.23)	0.48	0.94
Plasma calcium (mmol/l)	2 (56/57)	0.00 (–0.06, 0.06)	0.98	0.37
Magnesium status				
Blood magnesium (mmol/l)	8 (203/186)	0.06 (0.04, 0.08)	< 0.001	0.60
Erythrocyte magnesium (mmol/l)	4 (71/70)	0.16 (–0.09, 0.41)	0.24	< 0.0001
Urinary magnesium (mmol/24 h)	5 (159/142)	1.21 (0.93, 1.48)	< 0.001	0.48

and the time course of response in blood magnesium levels based on information from seven trials. Blood magnesium levels in diabetic patients increased abruptly at 4 weeks after oral magnesium treatment and then decreased over 4–8 weeks after treatment. However, after 12 weeks or more, there was still a trend toward an increase in blood magnesium.

Additionally, oral magnesium supplementation for 4–16 weeks significantly predicted an increase in urinary magnesium levels (Table 2) [13–16,19]. The increase in erythrocyte magnesium levels was not significant [14,17–19].

Adverse effects on diabetic patients

Six of the included trials reported on the presence or absence of adverse events among participants receiving oral magnesium supplements [13–15,18–20]. However, the small numbers of participants in these trials do not allow us to rule out rare side-effects. No severe adverse effects, such as cardiovascular events or deaths, were reported. Two trials showed that treatment with magnesium at doses up to 15.8 mmol/day and for periods as long as 4–12 weeks did not result in any adverse effects [14,18]. Overall, the most common side-effects were gastrointestinal symptoms, including mild abdominal pain (8.7%), diarrhoea (6.7%) and nausea (2.9%) among diabetic patients in the magnesium treatment group.

Discussion

In this meta-analysis of randomized double-blind controlled trials, we found that oral magnesium supplementation for 4–16 weeks may be effective in reducing plasma glucose levels and raising HDL cholesterol in Type 2 diabetic patients. However, we showed little evidence for an effect of magnesium supplementation on long-term glycaemic control as indicated by HbA_{1c} levels as well as weight control or blood pressure.

Magnesium supplements have been advocated as an attractive option for improving glycaemic control in diabetic patients because of their relative safety and affordability. However, there is limited empirical data to evaluate whether magnesium supplements should or should not be recommended to patients with diabetes. Almost all individual published trials were underpowered and used different doses and formulations of magnesium supplements. Given inconsistent results from previous trials, our meta-analysis increased statistical power for testing the hypothesis whether overall magnesium intake from various supplements exerts any beneficial effect on glycaemic control or metabolic parameters in patients with Type 2 diabetes.

Magnesium supplementation has many *in vivo* and *in vitro* beneficial effects on insulin sensitivity, lipid profiles, platelet aggregation and blood pressure [2,25]. Our findings tend to support the notion that oral magnesium supplementation may help maintain magnesium homeostasis in the human body and thereby exert a beneficial effect on fasting glucose and HDL cholesterol in patients with Type 2 diabetes. Our results showed no discernable effect of magnesium supplementation on long-term glycaemic control as reflected by HbA_{1c} levels. This is consistent with current evidence for measuring HbA_{1c} as an index of overall glycaemic control over the preceding 3–4 months [26]. Given most of the studies were short-term trials (≤ 12 weeks), our results may underestimate the true effect of magnesium supplementation on long-term glycaemic response. Although a single measurement of fasting glucose levels is a less accurate and stable indicator of glycaemic control than HbA_{1c}, our results for the effect of magnesium intake on fasting glucose levels may be an indication of favourable effects on glucose homeostasis in diabetic patients.

Current American Diabetes Association (ADA) nutrition guidelines recommend the use of magnesium supplements for people with diabetes mellitus who have low serum magnesium levels [27]. Our results clearly show that magnesium supplementation significantly increases plasma or serum or erythrocyte magnesium levels and thereby can normalize hypomagnesaemia in diabetes. Nevertheless, it should be noted that serum or plasma magnesium measurements are poor indicators for total body magnesium status. An accurate assessment of intracellular magnesium status is needed to reliably reflect the normalization of hypomagnesaemia after magnesium replenishment. In addition, optimal dosage to replenish magnesium deficiency and long-term safety of magnesium therapy, particularly at high doses, should also be evaluated in future studies, although there were no major adverse effects reported for different doses and forms of magnesium supplements in the included trials.

The present study has several limitations that merit discussion. First, our analyses are based on a small number of trials with short-term follow-up periods, so it is possible that a small-to-moderate effect in long-term glycaemic control, as reflected by HbA_{1c} levels, was undetectable. Second, magnesium formulation and dosage varied across individual studies. These differences might have contributed to differential results and lead to difficulties in estimating the true effect by treatment with high doses of magnesium supplement. Nevertheless, the likelihood of this bias should be small because most studies provided the data on blood magnesium levels and found a significant increase in blood magnesium levels after magnesium treatment from 1 to 3 months. Finally, publication bias is a concern, although we attempted to retrieve all relevant trial data. It is conceivable that positive findings were more likely to be published. However, the fact that half of the trials reported null findings suggested that substantial publication bias as a result of selective non-publication of negative trials is unlikely. Additionally, we cannot completely exclude the possibility that changes in treatment for diabetes in either treatment or placebo groups for all the trials included may affect the explanation for our observed differences between treatment and placebo groups, especially when relevant information was unavailable and sample size for each arm was small.

To evaluate the sufficiency of statistical power in future randomized trials [28], we calculated the necessary sample size to achieve 80% power for detecting a modest effect on HbA_{1c} suggested by our pooled estimate. Assuming a change in HbA_{1c}

from baseline of –0.31% with an SD of 3.29%, 1769 participants per treatment group would be needed using a two-sided test at a 5% significance level. Given the overall proportion of drop-out being 16%, the target sample size is finalized at 2052 participants to achieve at least 80% power to detect a significant difference for the primary outcome and at least two major secondary outcomes. To achieve stable diabetes treatment and optimal glycaemic control, we suggest that trial duration should be at least 4 months and magnesium supplementation should provide elemental magnesium > 15 mmol daily (360 mg/day).

In conclusion, our meta-analysis suggests that oral magnesium supplementation as adjunct therapy for 4–16 weeks may be effective in reducing plasma glucose levels and raising HDL cholesterol in patients with Type 2 diabetes. However, additional large-scale and long-term controlled trials in diabetic patients with hypomagnesaemia are warranted to assess the efficacy of magnesium supplementation.

Competing interests

None declared.

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