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REVIEW

Effect of magnesium supplementation on glucose metabolism in people with or at risk of diabetes: a systematic review and meta-analysis of double-blind randomized controlled trials

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Although higher dietary intakes of magnesium (Mg) seem to correspond to lower diabetes incidence, research concerning Mg supplementation in people with or at risk of diabetes is limited. Thus, we aimed to investigate the effect of oral Mg supplementation on glucose and insulin-sensitivity parameters in participants with diabetes or at high risk of diabetes compared with placebo. A literature search in PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, was undertaken. Eligible studies were randomized controlled trials (RCTs) investigating the effect of oral Mg supplementation vs placebo in patients with diabetes or at high risk of diabetes. Standardized mean differences (SMD) and 95% confidence intervals (CIs) were used for summarizing outcomes with at least two studies; other outcomes were summarized descriptively. Eighteen RCTs (12 in people with diabetes and 6 in people at high risk of diabetes) were included. Compared with placebo ($n = 334$), Mg treatment ($n = 336$) reduced fasting plasma glucose (studies = 9; SMD = − 0.40; 95% CI: − 0.80 to − 0.00; $I^2 = 77\%$) in people with diabetes. In conditions in people at high risk of diabetes (Mg: 226; placebo = 227 participants), Mg supplementation significantly improved plasma glucose levels after a 2 h oral glucose tolerance test (three studies; SMD = − 0.35; 95% CI: − 0.62 to − 0.07; $I^2 = 0\%$) and demonstrated trend level reductions in HOMA-IR (homeostatic model assessment-insulin resistance; five studies; SMD = − 0.57; 95% CI: − 1.17 to 0.03; $I^2 = 88\%$). Mg supplementation appears to have a beneficial role and improves glucose parameters in people with diabetes and also improves insulin-sensitivity parameters in those at high risk of diabetes.

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INTRODUCTION

Magnesium (Mg) is the fourth most abundant cation in the body and has a pivotal role in many bodily functions and is involved in over 300 enzymatic reactions.[1]

Observational studies have demonstrated that low Mg intake and serum Mg deficit are associated with a higher risk of several cardiovascular and metabolic disease, including coronary artery disease,[2] hypertension[3] and metabolic syndrome.[4]

Similar evidence has emerged among people with diabetes. Among experimental models, Mg deficiency seems to be strongly related with insulin resistance through a number of potential pathways. Firstly, chronic Mg deficit appears to be associated with an impaired post-receptorial function with consequent reduced glucose utilization in the cells.[5,6] Moreover, Mg seems to be significantly involved in the insulin secretion from pancreatic beta-cells.[7] Insulin secretion, is in fact, started by a calcium influx that is inhibited by extracellular Mg. After binding of insulin to its receptor, tyrosine kinase is activated. The autophosphorylation of the receptor kinase and all protein kinases in the insulin signal transduction are dependent on Mg. Besides MgATP as substrate, protein tyrosine kinases are activated by a second Mg.[8] Finally, Mg deficiency might decrease the anti-oxidant barriers further contributing to an elevated insulin resistance. [5]

In humans, a large meta-analysis including over than 500 000 participants, found a significant decrease of the incidence of diabetes associated with higher Mg intake.[9] However, the number of people assuming the recommended daily allowance for Mg is low, suggesting that oral supplementation is often necessary for reaching the cutoff for the recommended daily allowance.[10]

Although several randomized, double-blind controlled trials (RCTs) have investigated the association between oral Mg supplementation and glucose metabolism parameters in people with diabetes, the RCTs to date have included a small numbers of participants. A systematic review and meta-analysis[11] with a search date of over 10 years ago attempted to overcome to these limitations; however, the review did not investigate any insulin-sensitivity marker changes, nor did it include any RCTs investigating Mg supplementation among conditions at higher risk of diabetes (for example, people who are overweight or have prediabetes). In addition, a number of new RCTs have investigated the influence of Mg supplementation and glucose parameters in diabetic people.

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Given the current state of the literature, we conducted an updated systematic review of RCTs investigating the effect of oral Mg supplementation on glucose and insulin-sensitivity parameters in participants with diabetes or at high risk of diabetes compared with placebo. We hypothesized that Mg supplementation would improve glucose and insulin outcomes in both populations.

MATERIALS AND METHODS

This systematic review adhered to the PRISMA statement[12] and followed a structured, but unpublished protocol.

Data sources and literature search strategy

Two investigators (CL and MS) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from database inception until 31 January 2016 for RCTs investigating the effect of oral Mg supplementation vs placebo in patients with diabetes or at higher risk of diabetes. In PubMed, the following search strategy was used: ('magnesium') AND ('diabet*' OR 'glucose' OR glycosylated hemoglobin OR 'insulin') AND ('clinical trial' OR 'randomized controlled trial' OR 'placebo'). Conference abstracts and reference lists of included articles were hand searched to identify and potential additional relevant articles. Any inconsistencies were resolved by consensus.

Study selection

Inclusion criteria for this meta-analysis were: (i) being a RCT; (ii) double-blind design; (iii) included diabetic participants or subjects at higher risk of diabetes; (iv) use of oral magnesium supplementation; (v) assessment of glucose metabolism or insulin-sensitivity parameters (see below); (vi) sufficient quality, as assessed by Jadad's scale[13] $\geqslant$ 3/5 points.

We considered diabetes if the diagnosis was made according to the criteria proposed by the American Diabetes Association, that is: fasting plasma glucose (FPG) $\geqslant$ 126 mg/dl (= 7.0 mmol/l), or 2-h PG $\geqslant$ 200 mg/dl (= 11.1 mmol/l) during oral glucose tolerance test (OGTT) with 75-g of glucose, or glycosylated hemoglobin (HbA1C $\geqslant$ 6.5% (= 48 mmol/mol), or random PG $\geqslant$ 200 mg/dl (= 11.1 mmol/l).[14]

Conditions at higher risk of diabetes were considered, obesity, overweight, metabolic syndrome, renal failure, family history of diabetes, prediabetes and so on. In case of divergence between the two investigators making the screening (CL and NV), a third reviewer expert in diabetes and metabolic disease (SFW) was contacted and a consensus among the three was reached.

Trials were excluded if: (i) did not include humans; (ii) used a control group taking other substances than placebo; (iii) investigated the effect of Mg supplementation on glucose/insulin-sensitivity parameters in healthy participants.

Data extraction

Two independent investigators (NV and BS) extracted key data from the included articles in a standardized Excel sheet and a third independent investigator (MS) checked these data. For each article, we extracted data about authors, year of publication, country, glucose metabolism/insulin-sensitivity end points, condition (for diabetes: type of diabetes; for conditions at higher risk of diabetes: obesity, overweight, metabolic syndrome, prediabetes, metabolically obese normal weight), study design (crossover or parallel), medications used for the treatment of diabetes, type of Mg used in the trial with daily dosage, follow-up duration (in weeks). Moreover, we extracted data by treating with Mg or placebo about mean age, body mass index (BMI), and number of women at baseline. When some information was missing, first and/or corresponding authors of the original article were contacted at least four times to obtain unpublished data.

Outcomes

The primary outcomes were parameters of glucose metabolism and insulin sensitivity.

Regarding the glucose metabolism, we included FPG, glycosylated hemoglobin (HbA1c), plasma glucose after the 2 h OGTT. Regarding the insulin sensitivity, we extracted data about fasting insulin levels or after 2 h OGTT, homeostatic model assessment-insulin resistance (HOMA-IR), C-peptide levels and quantitative insulin-sensitivity check index.

Assessment of study quality

Two authors (CL and MS) completed scoring using the Jadad's scale[13] for assessing the quality of the RCTs included. This quantifies the trial quality based on the description and appropriateness of randomization (2 points), blinding procedures (2 points) and description of withdrawals (1 point). A value < 3 (over a maximum of 5) usually indicates a low-quality study at high risk of bias.[15]

Data synthesis and statistical analysis

All analyses were performed using comprehensive meta-analysis 3 (http://www.meta-analysis.com). Outcomes with at least two studies were meta-analyzed, and in cases with less we described the data in a descriptive summary.

The primary analysis compared parameters of glucose metabolism or insulin sensitivity between participants treated with oral Mg supplementation vs placebo. We calculated the difference between the means of the treatment and placebo groups using the follow-up data through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model. [16]

Heterogeneity across studies was assessed by the I^2 metric and χ^2 statistics. Given significant heterogeneity ($I^2 \geqslant 50\%$, $P < 0.05$) and for outcomes having at least four studies (the minimum recommended number of studies for running a meta-regression analysis in comprehensive meta-analysis), we conducted a series of meta-regression analyses, according to continent (others (ref.) vs America), follow-up length, differences in baseline mean age, BMI and mean outcome investigated between Mg and placebo group.[17] For analyses regarding to conditions at higher risk of diabetes, also the condition investigated (categorized as overweight vs others) was explored as possible mediator of heterogeneity.

As the majority of the studies reported data on plasma/serum Mg, this parameter was considered when running a meta-regression analysis to examine if the differences in values of Mg at follow-up between treated and placebo could affect the glucose metabolism or insulin-sensitivity parameters at follow-up, independently from heterogeneity.

Publication bias was assessed by visually inspecting funnel plots and using the Begg–Mazumdar Kendall tau[18] and the Egger bias test.[17] Then, to account for publication bias, we used the trim-and-fill method, based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished (imputed) studies.[19]

For all analyses, a P-value < 0.05 was considered statistically significant.

RESULTS

Search results

Altogether, the search yielded 1195 non-duplicated articles. After excluding 1163 articles based on title/abstract review (predominantly because they were observational studies), 32 articles were retrieved for full text review. Finally, 18 RCTs (12 in people with diabetes[20–31] and 6 in people at high risk of diabetes[32–37]) were included (Figure 1).

Compared with a previous meta-analysis about this topic,[11] we excluded a study due to low quality (Jadad's score = 2)[38] and a further RCT as it used a comparison group consisting of people treated with vitamin C.[39]

Study and patient characteristics

Full descriptive details of the included studies are reported in Supplementary Table 1 (diabetes) and Supplementary Table 2 (high risk of diabetes).

Among the 12 studies included considering people with diabetes, the majority ($n = 10$)[21–28,30,31] considered type 2 diabetes, one was made among type 1 diabetic people[29] and 1 among pregnant women with gestational diabetes.[20] Nine RCTs had a parallel design, whereas 3 used a crossover design. The 12 studies followed-up 336 diabetic participants treated with Mg and 334 with placebo for a median of 12 weeks (range: 4–48).

The participants treated with Mg were on average 53.6 (vs 52.3 in placebo) years, had a mean BMI suggestive of overweight status and were prevalently women (53.0% vs 57.2% in Mg and placebo group, respectively). The supplementation with Mg was very different across the RCTs in terms of forms and dosages, as shown in Supplementary Table 1, with two studies using Mg oxide,[20,33] citrate[26,28] or chloride[24,31] and the other studies using pidolate,[27] aspartate,[22] idroxide,[29] lactate[28] or sulfate.[25]

All the studies except one[28] reported data on blood Mg levels, whereas three[21,22,25] reported data on urinary Mg as well as two[22,27] reported data on Mg within red blood cells.

The quality of the studies was generally high, as indicated by the Jadad's scale (Supplementary Table 1).

Six RCTs[32–37] investigated the effect of Mg in conditions at higher risk of diabetes. Three RCTs included overweight participants,[32,35,36] one among people with metabolic syndrome,[33] one prediabetes[34](defined as the presence of FPG between 100 and 126 mg/dl or plasma glucose after OGTT between 140 and 200 mg/dl) and one metabolically obese with normal weight subjects,[37] as shown in Supplementary Table 2. Five RCTs employed a parallel and only one a crossover design.

Altogether these studies followed-up 226 participants treated with Mg and 227 with placebo for a median of 14 (range: 4-24) weeks. The participants treated with Mg aged a mean of 40.5 years, had a mean BMI of 28.8 kg/m^2 and were prevalently males, whereas the participants treated with placebo had a mean age of 42.2 years with a mean BMI of 28.9 kg/m^2. Two RCTs used $MgCl_2$,[34,37] one chelate,[33] one oxide[35] and the other one aspartate hydrochloride.[36]

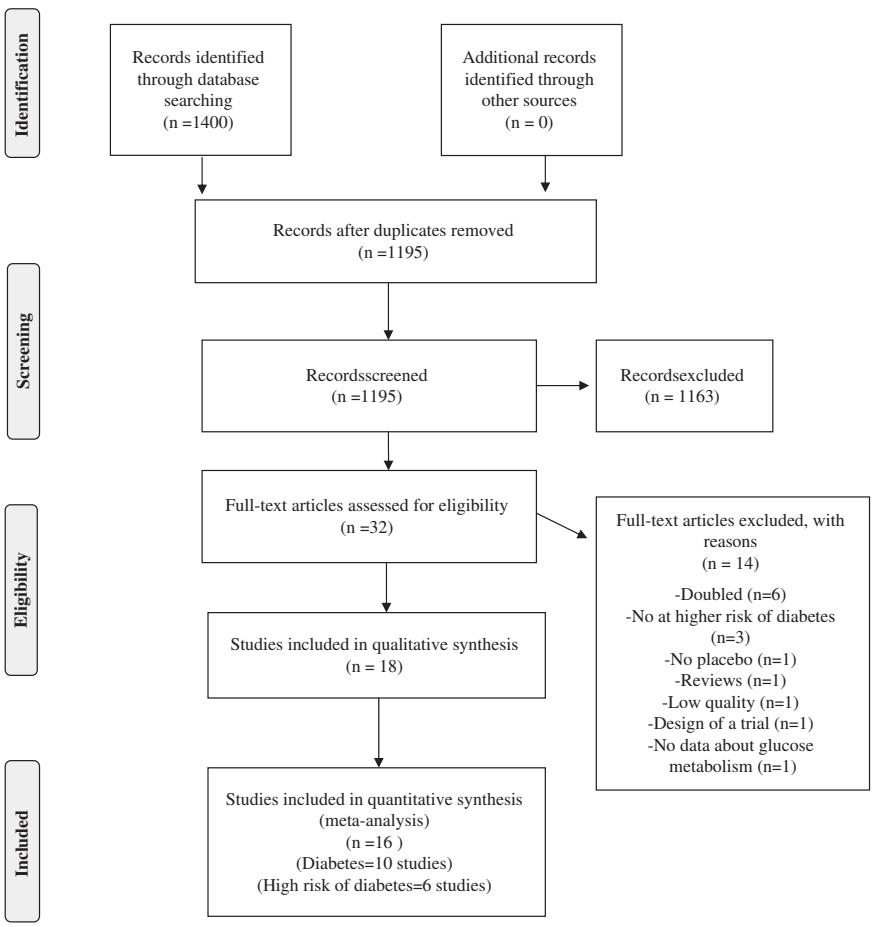

Figure 1. PRISMA flow-chart.

All the studies reported data on serum or plasma Mg,[32–37] whereas no one about urinary or other estimates of body Mg.

Also in these studies the quality seems to be high (Supplementary Table 2).

Meta-analysis of the effect of magnesium on glucose and insulin-sensitivity parameters

People with diabetes. As shown in Table 1, treatment with Mg reduced FPG at follow-up in 254 type 2 diabetic participants compared with 252 treated with placebo (studies = 9;[21–25,27,28,30,31] SMD = − 0.40; 95% CI: − 0.80 to − 0.00; $P = 0.049$; $I^2 = 77\%$; Supplementary Figure 1). Regarding to HbA1c levels, Mg supplementation was not able to improve this parameter in 250 type 2 diabetic people compared with 250 treated with placebo (8 studies,[21,22,25–28,30] SMD = − 0.11; 95% CI: − 0.32 to 0.09, $P = 0.26$), although this finding seems to be affected by missing studies (publication bias) as the result became significant after using the trim-and-fill analysis with three studies trimmed at the left of the mean (SMD = − 0.24; 95% CI: − 0.45 to − 0.04; Table 1). On the contrary, the supplementation with Mg was not able to improve fasting insulin or HOMA-IR levels in treated participants compared with placebo (Table 1).

No publication bias was evident with other tests among these outcomes, as also confirmed by the funnel plots reported in Supplementary Figure 2.

Among descriptive findings, a study in type 2 diabetic patients[25] reported a significant lower value of plasma glucose after a 2 h OGTT in those treated with Mg compared with placebo. Two studies reported data on other types of diabetes, namely diabetes in pregnancy[20] and type 1 diabetes.[29] In pregnant women,[20] oral supplementation with Mg for 6 weeks significantly improved FPG and insulin-sensitivity parameters compared with placebo, whereas in type 15 patients with type 1 diabetes treated with Mg vs 13 treated with placebo, no significant effect emerged on HbA1c levels.[29]

People at risk of diabetes. Table 2 summarizes the evidence of Mg supplementation compared with placebo on glucose and insulin-sensitivity parameters in subjects at higher risk of diabetes. Mg supplementation was able to significantly improve plasma glucose levels after a 2 h OGTT in three studies[34,36,37] (SMD = − 0.35; 95% CI: − 0.62 to − 0.07; $P = 0.01$; $I^2 = 0\%$; Supplementary Figure 3) and trend level significance across the HOMA-IR (five studies;[33–37] SMD = − 0.57; 95% CI: − 1.17 to 0.03; $P = 0.06$; $I^2 = 88\%$; Supplementary Figure 4). On the contrary, no effect was evident on FPG and fasting insulin levels (Table 2). No publication bias was evident for all these outcomes (Table 2; Supplementary Figure 5).

Among descriptive findings, Chacko *et al.*[32] reported no significant differences in HbA1c or C-peptide levels, similarly to another study[37] investigating serum insulin levels after 2 h OGTT.

Meta-regression analysis

Table 3 reports the meta-regression analysis taking as the exposure the differences in serum Mg between treated with oral supplementation and placebo at follow-up and the parameters of glucose and insulin-sensitivity metabolism as the outcomes. Higher differences in serum/plasma Mg at follow-up between treated and placebo groups were associated with lower HbA1c levels in type 2 diabetes (beta = − 3.96; 95% CI: − 7.18 to − 0.20, $P = 0.04$; $R^2 = 0.93$; Supplementary Figure 6a) as well as with FPG (beta = − 4.07; 95% CI: − 5.76 to − 2.38, $P < 0.0001$; $R^2 = 0.91$; Supplementary Figure 6b) and HOMA-IR (beta = − 3.82; 95% CI: − 5.48 to − 1.09, $P = 0.003$; $R^2 = 0.67$; Supplementary Figure 6c) in people at higher risk of diabetes.

Supplementary Table 3 shows the meta-regression analysis for the outcomes resulted heterogeneous ($I^2 \geqslant 50\%$) and having at

Table 1. Meta-analysis of eligible studies about type 2 diabetic people with publication bias assessment

Analysis	*Number of studies*	*Number participants*			*Meta-analysis*			*Heterogeneity (I^2)*	*Publication bias*		
		Mg	*PLC*	*SMD*	*95% CI*		P-*value*		*Egger bias and* P-*value*	*Trim and fill (95% CI)*	*Classic fail safe* N
FPG	9	254	252	**− 0.37**	**− 0.74**	**− 0.00**	**0.049**	74	− 4.24; 0.14	Unchanged	21
HbA1c	8	250	250	− 0.11	− 0.32	0.09	0.26	20	4.00; 0.71	**− 0.24 (0.45 to − 0.04)**	0
Insulin	4	121	92	0.45	− 0.13	1.03	0.12	72	1.36; 0.83	Unchanged	5
HOMA-IR	4	148	81	− 0.52	− 1.17	0.14	0.12	80	− 1.84; 0.84	Unchanged	9

Abbreviations: CI, confidence intervals; FPG, fasting plasma glucose; HbA1c, glycosilated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; Mg, magnesium; PLC, placebo; SMD, standardized mean difference. Bold values represent significant results (as *P*-value < 0.05).

Table 2. Meta-analysis of eligible studies about people at higher risk of diabetes with publication bias assessment

Analysis	*Number of studies*	*Number participants*			*Meta-analysis*			*Heterogeneity (I^2)*	*Publication bias*		
		Mg	*PLC*	*SMD*	*95% CI*		P-*value*		*Egger bias and* P-*value*	*Trim and fill (95% CI)*	*Classic fail safe* N
FPG	6	226	227	− 0.52	− 1.21	0.17	0.14	91	− 1.53; 0.79	Unchanged	33
2 h OGTT	3	108	102	**− 0.35**	**− 0.62**	**-0.07**	**0.01**	0	1.38; 0.15	− 0.41 (− 0.64 to − 0.18)	2
Insulin	6	226	227	− 0.20	− 0.47	0.08	0.17	49	− 3.38; 0.06	0.03 (− 0.26; 0.32)	0
HOMA-IR	5	213	214	− 0.57	− 1.17	0.03	0.06	88	− 6.74; 0.17	Unchanged	22

Abbreviations: CI, confidence intervals; FPG, fasting plasma glucose; HbA1c, glycosilated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; Mg, magnesium; OGTT, oral glucose tolerance test; PLC, placebo; SMD, standardized mean difference. Bold values represent significant results (as *P*-value < 0.05).

Table 3. Association between serum Mg differences at follow-up (treated vs placebo) and glucose metabolism outcomes in diabetic and at higher risk of diabetes participants

Outcome	*Beta (95% CI)*	P-*value*	R^2
Diabetes			
FPG	1.96 (−2.95; 6.42)	0.39	0.05
HbA1c	**−3.96 (−7.18; −0.20)**	**0.04**	**0.93**
Insulin		Only 3 studies	
HOMA-IR	1.19 (−6.69; 9.07)	0.77	0.00
Higher risk of diabetes			
FPG	**−4.07 (−5.76; −2.38)**	**< 0.0001**	**0.91**
2 h OGTT		Only 3 studies	
Insulin	−0.93 (−2.49; 0.64)	0.25	0.11
HOMA-IR	**−3.82 (−5.48; −1.09)**	**0.003**	**0.67**

Abbreviations: CI, confidence intervals; FPG, fasting plasma glucose; HbA1c, glycosilated hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; Mg, magnesium; OGTT, oral glucose tolerance test; PLC, placebo; SMD, standardized mean difference. All the analyses were run using a meta-regression analysis with the difference between treated and placebo group of serum/plasma Mg at follow-up. Bold values represent significant results (as *P*-value < 0.05).

least four studies. Continent in which the study was performed, follow-up duration, differences in mean age, BMI or in mean outcome parameter at baseline between Mg and placebo treated were not able to moderate our results.

Compliance and adverse effects

In trials reporting the number of allocated participants and those finishing the study, we observed that 88% of the allocated participants with diabetes and treated with Mg vs 78% treated with placebo finished the study, without any difference between the groups ($P = 0.58$). Among participants with higher risk of diabetes, these figures were 93% and 91%, respectively ($P = 0.87$).

As previously reported by Song *et al.*[11] no severe side effects (for example, death, onset of cardiovascular diseases) emerged in both groups. This trend was confirmed in the RCTs among diabetic people published after 2006[refs 20,25,30] and among at higher risk of diabetes[32–37] included in our meta-analysis. The most common side effects observed were of gastrointestinal nature (particularly diarrhea).

DISCUSSION

In this meta-analysis including RCTs comparing oral Mg supplementation vs placebo, we demonstrated that Mg supplementation significantly improves FPG levels in type 2 diabetic patients. In patients at higher risk of diabetes, oral Mg supplementation decreased plasma glucose after 2 h OGTT and marginally HOMA-IR. Altogether, these findings suggest a positive role of Mg supplementation in glucose metabolism, although the evidence is characterized by high heterogeneity, which was only partially explained in our meta-regression analyses. Moreover, our paper has demonstrated that in both people with and at risk of diabetes, Mg supplementation is well tolerated and without significant adverse effects. Given our findings, Mg supplementation is attracting interest in the treatment of diabetes and as prevention for diabetes in those at higher risk.

Observational studies have demonstrated that people with diabetes appear to have lower Mg levels than healthy counterparts,[40,41] which might be attributed to a higher urinary excretion due to glycosuria and/or lower Mg intake through diet.[42] Our meta-analysis supports a role of Mg supplementation in improving glucose parameters for type 2 diabetic patients, although Mg supplementation seems to poorly improve insulin-sensitivity markers and insulin secretion. The reasons are unknown and merit further specific research.

On the contrary, in patients at higher risk of diabetes, oral Mg supplementation was able to improve plasma glucose after 2 h OGTT and HOMA-IR suggesting a role of Mg in improving insulin secretion in these patients. It is likely that in these patients with a reserve in insulin, Mg is able to stimulate insulin secretion and consequently improve HOMA-IR and plasma glucose after OGTT.

Previous data from observational studies have demonstrated that people without diabetes who have higher intakes of Mg are at reduced risk of diabetes.[9] Our data confirm that oral Mg supplementation can improve some outcomes in this population and overcomes limitations associated with observational data. Taken together, our findings suggest that diets with a higher intake of Mg or the supplementation with Mg should be encouraged in people at higher risk of diabetes.

Another important finding from our work is that blood Mg at follow-up significantly correlated with improvement in glucose in diabetic and insulin sensitivity in people at higher risk of diabetes, respectively. Altogether our results suggest that Mg supplementation is able to improve glucose and insulin-sensitivity parameters only if serum or plasma Mg is raised sufficiently. This finding is in agreement with studies reporting that Mg supplementation is more efficacious in hypomagnesemia than in normal serum Mg levels.[26,37] Unfortunately, due to the limited studies for urinary and intracellular estimates, we were not able to assess whether these markers might correlate with glucose metabolism, but this could be of importance since the best marker of Mg status in human beings is still discussed.[43]

The findings of our meta-analysis should be interpreted within its limitations. First, the trials included in our investigation, although of high quality, included a few participants each one and the follow-up period is relatively short time frame to observe improvements in glucose metabolism parameters requiring longer time. Second, dosage and types of Mg used largely varied across studies and these factors probably contributed to the heterogeneity found in almost all outcomes included. Third, the evidence is mainly limited to type 2 diabetes and future studies are needed to understand if Mg supplementation might have a role in other types of diabetes.

Conversely, among the strengths of our work, we can consider that we are the first to explore the role of Mg supplementation in conditions at higher risk of diabetes, which could be of importance for the prevention of type 2 diabetes in these subjects. Moreover, we also investigated the effect of Mg on insulin-sensitivity markers. Although these data are contrasting between diabetic and non-diabetic participants, these findings could be of importance for better understanding the pathways in which Mg is involved in glucose metabolism.

In conclusion, our meta-analysis suggests a beneficial role of Mg supplementation compared to placebo in improving glucose parameters in diabetic patients and insulin-sensitivity parameters in those at higher risk of diabetes. Future larger studies are however needed to confirm our findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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