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The effects of oral magnesium supplementation on glycaemic control in patients with type 2 diabetes: a systematic review and dose–response meta-analysis of controlled clinical trials

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Abstract

The current systematic review and meta-analysis were conducted to evaluate the effects of oral Mg supplementation on glycaemic control in type 2 diabetes mellitus (T2DM) patients. Related articles were found by searching the PubMed, SCOPUS, Embase and Web of Science databases (from inception to 30 February 2020). A one-stage robust error meta-regression model based on inverse variance weighted least squares regression and cluster robust error variances was used for the dose–response analysis between Mg supplementation and duration of intervention and glycaemic control factors. Eighteen eligible randomised clinical trials were included in our final analysis. The dose–response testing indicated that the estimated mean difference in HbA1c at 500 mg/d was −0·73 % (95 % CI: −1·25, −0·22) suggesting modest improvement in HbA1c with strong evidence (*P* value: 0·004). And in fasting blood sugar (FBS) at 360 mg/d was −7·11 mg/dl (95 % CI: −14·03, −0·19) suggesting minimal amelioration in FBS with weak evidence (*P* value: 0·092) against the model hypothesis at this sample size. The estimated mean difference in FBS and HbA1c at 24 weeks was −15·58 mg/dl (95 % CI: −24·67, −6·49) and −0·48 (95 % CI: −0·77, −0·19), respectively, suggesting modest improvement in FBS (*P* value: 0·034) and HbA1c (*P* value: 0·001) with strong evidence against the model hypothesis at this sample size. Oral Mg supplementation could have an effect on glycaemic control in T2DM patients. However, the clinical trials so far are not sufficient to make guidelines for clinical practice.

Key words: **Magnesium supplementation: Glycaemic control: Type 2 diabetes: Meta-analysis**

Diabetes is a well-known public health issue with an increasing prevalence worldwide. The scientific community has estimated that 592 million people will be diagnosed with diabetes by 2030[1]. In type 2 diabetes mellitus (T2DM), raised blood sugar levels known as hyperglycaemia[2,3] can lead to various chronic complications, including CVD, kidney disease, retinopathy, neuropathy and amputation[2–4]. Patients with diabetes are three times more likely to be hospitalised than healthy subjects. Higher risk of early death and shorter life expectancy have been observed in T2DM patients[5,6]. One of the essential goals in the treatment of T2DM is the control of glycaemic parameters[7].

Abbreviations: FBS, fasting blood sugar; HOMA-IR, homeostatic model assessment, of insulin resistance; RCT, randomised clinical trials; T2DM, type 2 diabetes mellitus.

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Mg is one of the most crucial micronutrient for humans, having a vital role in countless body reactions, including insulin secretion and activity, blood sugar regulation and in the energy and carbohydrates' metabolism[8,9]. Mg deficiency has been reported in 25 % to 38 % of diabetic patients[10]. However, Kurstjens *et al.*[11] reported that the prevalence of hypo-magnesemia in cohorts of diabetes patients was between 11 % and 65 % of patients. Low intracellular and extracellular Mg levels, known as hypo-magnesemia, can derive due to reduced Mg intake or elevated Mg losses in poorly controlled diabetes[12,13]. Hypo-magnesemia is linked to insulin resistance, decreased pancreatic insulin release, altered cellular glucose transport, impaired glucose tolerance and more rapid decline in kidney function[14–17]. Hence, hypo-magnesemia in diabetes patients leading to faster progression of diabetes and risk of end-stage kidney disease, CVD, nephropathy, retinopathy and foot ulcers[14–17].

Previously, Song *et al.* 2006[15,18] performed a systematic meta-analysis review on nine randomised clinical trials (RCT) to evaluate the efficacy of oral Mg supplementation on glycaemic control, lipids, blood pressure or Mg levels in patients with T2DM compared to the control group. The findings reported that Mg supplements were associated with a significant reduction in fasting blood sugar (FBS) but not HbA1c. However, several RCT[8,19–27] have been added to the literature, and the former results need to update.

Until now, the results of the studies on the efficacy of Mg supplementation on glycaemic control in T2DM patients are still inconsistent. Some studies have demonstrated that Mg supplementation is associated with improved glycaemic control and could prevent chronic complications of diabetes[20,28]. Although, other studies have not demonstrated such results[22]. These clinical trials individually cannot provide a clear answer whether Mg affects the glycaemic control of T2DM patients, and any previous meta-analysis needs to update. For this reason, in this study, we performed a systematic review and meta-analysis of the RCT to assess the effect of oral Mg supplementation on glycaemic control in T2DM patients.

Methods

Literature search and selection

This systematic review and meta-analysis were conducted based on the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis[29]. A systematic literature search was performed by the PubMed, SCOPUS, Web of Science, Google Scholar and Embase databases up to 30 February 2020. The systematic search was carried out using the following medical subject heading terms, in abstracts and keywords without language or date limitations. This was conducted using the following search terms (('Type 2 diabetes' OR T2DM OR diabetes) AND (Intervention OR 'Intervention Study' OR 'Intervention Studies' OR 'controlled trial' OR randomized OR randomized OR random OR randomly OR placebo OR 'clinical trial' OR Trial OR 'randomized controlled trial' OR 'randomized clinical trial' OR RCT OR blinded OR 'double blind' OR 'double blinded' OR trial OR 'clinical trial' OR trials OR 'Pragmatic Clinical Trial' OR 'Cross-Over Studies' OR 'Cross-Over' OR 'Cross-Over Study' OR parallel OR 'parallel study' OR 'parallel trial')). Electronic database systematic searches were completed along with reference list and citation hand searches. The research process was conducted by two authors (OM and SM) separately and in duplicate. Any disagreement was resolved through discussion with a third researcher (MM).

Eligibility criteria

Two investigators selected eligible articles separately by reading titles, abstracts and, whenever required, the full text of the publications. All human RCT (either parallel or cross-over designs) reported the effects of Mg supplementation on glycaemic parameters, particularly FBS, fasting insulin, the homoeostatic model assessment of insulin resistance (HOMA-IR) and HbA1c were considered. Studies were excluded if they had one or more of the following characteristics: (i) non-RCT, (ii) RCT with treatment duration < 2 weeks, (iii) studies without a control group for oral Mg supplementation and (iv) insufficient data. To keep away from overlapping, we included studies with larger participants. Disagreements regarding the study selection process were resolved by face-to-face discussion.

Data extraction

The following data were extracted from the full text of the eligible studies using a pre-designed abstraction form: (i) first author's name, (ii) year of the publication, (iii) location of the study, (iv) sample sizes of the Mg and control groups, (v) type and dose of the Mg supplementation and placebo, (vi) study duration and (vii) age, gender and BMI. In cases of lack of relevant data, we contacted the corresponding authors via e-mail to provide their help. The process of data extraction was undertaken independently by two investigators (OA and SM) to minimise potential errors. If there was a disagreement, it was resolved by consensus.

Study quality assessment

We used the Cochrane Collaboration's tools for quality assessment of studies to perform a systematic assessment of bias[30]. This tool separates a judgement about the risk of bias from a description of the support for that judgement for a series of items covering different bias domains. Two researchers (OA and SM) independently evaluated the methods and the quality of the eligible studies using Cochrane Collaboration's tools, covered the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting and (7) other possible sources of bias. For each item in the tool, the assessment of the risk of bias is in two parts. The support for judgement provides a succinct-free text description or summary of the relevant trial characteristic on which judgements of risk of bias are based and aims to ensure transparency in how judgements are reached[30]. The first part was a further classification: low risk (L), high risk (H) and unclear risk (U) of bias. Then, according to the guidelines, the general quality of each study was considered as good (low risk for more than two cases), fair (low risk for two cases) or weak (low risk for less than two cases)[30].

Meta-analysis of data

To analyse the effect size for FBS, fasting insulin, HOMA-IR and HbA1c, the mean difference and its standard deviation for both intervention and control groups, as the comparison group, were extracted. We considered mg/dl, μIU/ml and percentage as units of FBS, fasting insulin and HbA1c, respectively. Also, for those studies that reported different units, we converted them with valid methods.

A one-stage robust error meta-regression model based on inverse variance weighted least squares regression and cluster robust error variances was used for the dose–response analysis between Mg supplementation and duration of intervention and glycaemic control factors[31]. Statistical analysis was conducted using STATA, version 11.2 (Stata Corp). The statistical significant value was defined as P values $< 0{\cdot}05$.

Results

Selection and identification of studies

Out of the initial 1986 published studies obtained by electronic and hand search, 713 were duplicates, 1273 were screened according to our inclusion criteria. Then, after excluded animal, review and unrelated studies, we assessed twenty-one RCT, of which three studies did not meet the desired criteria. Finally, eighteen eligible RCT (Fig. 1) were included in our final analysis[8,10,15,19–28,32–36].

Characteristics of studies

The main characteristics of the included studies in this meta-analysis are described in Table 1. Overall, fifty effect sizes (seven effect sizes for HOMA-IR, eighteen effect sizes for FBS, nine effect sizes for fasting insulin, and sixteen effect sizes for HbA1c) were extracted from eighteen RCT, including 1097 participants, out of which 571 participants were in the Mg group, and 526 were the control group. Most RCT[8,10,15,19–21,23–28,33–36] adopted a parallel design except for two studies that used a crossover setting[22,32]. The mean age of participants in these studies ranged from 25·5 ± 6·5 to 72·2 ± 2·0 years. These studies were published between the year 1989 and 2019. The RCT were conducted in Iran[23,24,26–28], Mexico[19,20], Australia[15,35], Italy[21,32,33], Netherlands[21,32,33], Norway[34], India[8] and Brazil[10]. The dose of the oral elemental Mg given in these studies ranged from 36·49 to 500 mg/d, and all of the included

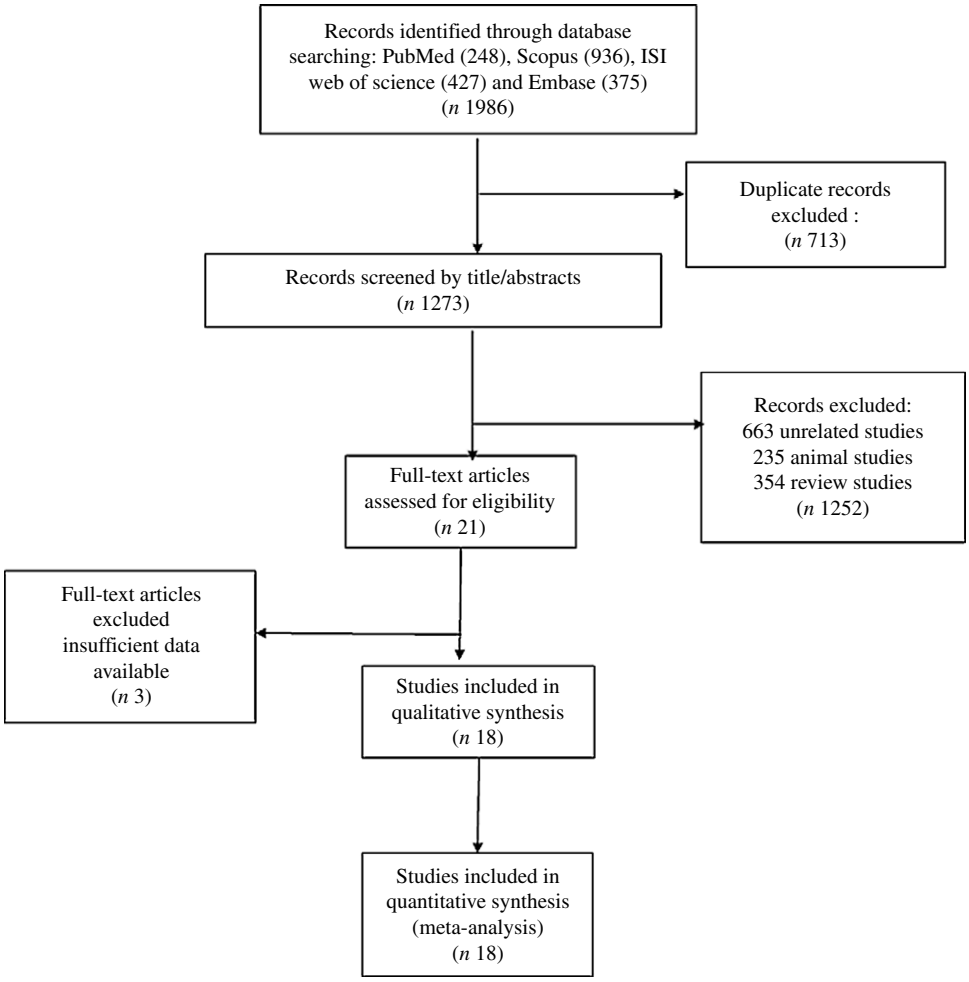

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Table 1. Characteristic of included studies in meta-analysis of included studies in meta-analysis

						IG		CG		IG		CG		Intervention		Sample size				
Study	Country	Study design	Participant	Sex	Trial duration control status	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Magnesium type	Magnesium elemental dose	IG	CG	Glycemic control status	Having/not having chronic complications	Antihypertensive
Paolisso et al. 1989[32]	Italy	Cross over (R,DB, PC)	T2DM	F/M	4	72·2	2·0	72·2	2·0	NR		NR		Magnesium pidolate	360 mg	8	8	NR	Obesity	NO
Gullestad, 1994[34]	Norway	Parallel (R,DB, PC)	T2DM	F/M	16	NR		NR		25·4	3·7	25·3	4·1	Magnesium lactate	15 mmol (36·49 mg)	25	29	NR	NO	NR
Corica et al. 1994[33]	Italy	Parallel (R/PC)	T2DM	F/M	4	63	5	61	3	24·8	0·7	24·4	0·4	Magnesium Pidolate	16·2 mmol (39·41 mg)	26	17	NR	NO	NO
Eibl et al. 1995[35]	Australia	Parallel (R/DB/PC)	T2DM Patients with Hypomagnesaemia	F/M	12	63	8	54	1·5	27·5	3·2	29·3	5	Magnesium citrate	30 mom (72·99 mg)	18	20	NR	NR	NO
De Val et al. 1998[36]	Netherlands	Parallel (R/DB/PC)	T2DM	F/M	12	63	8·2	62	7·3	28·7	5·35	27·1	4·46	Magnesium-aspartate-Hall	(36·49 mg)	25	25	NR	NO	NO
De Lima et al. 1998 [10]	Brazil	Parallel (R/DB/PC)	T2DM Patients with Hypomagnesaemia	F/M	4	G1:55·4 ± 10·2 G2:51·2 ± 11		55·5	8·3	G1:25·3 ± 8 G2:25·5 ± 6·5		25·5	6·5	Magnesium oxide	Group 1:20·7 mom (50·36 mg) Group 2:41·4 mom (100·72 mg)	G1:35 G2:39	54	Poor controlled	NR	NR
Rodriguez-Moran et al. 2003 [15]	Australia	Parallel (R/DB/PC)	T2DM Patients with Hypomagnesaemia	F/M	16	59·7	8·3	54·1	9·6	27·6	9·1	28·6	4·2	Magnesium chloride	450 mg	32	31	NR	NR	NO
Barragan-Rodríguez et al. 2008 [19]	Mexico	Parallel (R/C)	T2DM Patients with Hypomagnesaemia	F/M	12	69	5·9	66·4	6·1	NR		NR		Magnesium chloride	450 mg	12	9	NR	Depression	NR
Guerrero-Romero et al. 2009 [20]	Mexico	Parallel R/DB/PC	T2DM Patients with Hypomagnesaemia	F/M	16	58·9	8·5	60·5	9·4	29·9	5·2	29	5·1	Magnesium chloride	450 mg	40	39	NR	NR	NO
Barba Gallo et al. 2010 [21]	Italy	Parallel C	T2DM Patients with Hypomagnesemia	F/M	4	71	4·9	71·2	4·9	27·9	1·5	28·1	1·6	Magnesium pidolate	368 mg	30	30	NR	Hypertensive	NR
Solati et al. 2013[23]	Iran	Parallel R/DB/PC	T2DM	F/M	12	46·76	9	50·15	6·93	26·19	2·86	26·89	5·23	Magnesium sulphate	300 mg	25	22	NR	Hypertensive	NR
Navarrete-Cortes et al. 2014[22] NO	México	Cross over R/DB/PC	T2DM	F/M	12	52·84	8·42	52·84	8·42	30·55	5·72	30·55	5·72	Magnesium lactate	360 mg	56	56	62·5 %	uncontrolled	NO
Singh et al. 2015[8]	India	Parallel C	T2DM Patients with Hypomagnesemia	F/M	16	NR		NR		NR		NR		Magnesium chloride tablet	300 mg	60	60	NR	NO	NR
Razzaghi et al. 2018[24]	Iran	Parallel R/DB/PC	T2DM with grade 3 diabetic foot ulcer	F/M	12	60·1	11·1	59	10·1	28·2	5·2	26·2	4·1	Magnesium oxide	250 mg	35	35	NR	Diabetic foot ulcer	NR
Talari et al. 2019[28]	Iran	Parallel R/DB/PC	Diabetic hemodialysis patients	F/M	24	58·8	10·1	61·8	10·2	27·2	5·6	26·1	4·5	Magnesium oxide	250 mg	27	27	NR	Hemodialysis	NR
Sadeghian et al. 2019[27]	Iran	Parallel R/DB/PC	T2DM	F/M	12	41·2	8·8	42·8	8·4	31·2	5·5	30·9	4·4	Magnesium oxide	250 mg	40	40	NR	Nephropathy	NR
Rashvand et al. 2019[26]	Iran	Parallel R/DB/PC	T2DM	F/M	8	49·89	7·83	48·23	14·2	29·69	3·24	29·34	3·71	Magnesium oxide	500 mg	18	19	NR	NO	NR
Elderawi et al. 2019[25]	Gaza	Parallel R/C	T2DM	F/M	12	51·15		51·55		29·02		30		Magnesium tablets (oxide, gluconate, lactate)	250 mg	20	20	NR	NO	NO

R, randomised; C, controlled; PC, placebo-controlled; DB, double blind; T2DM, type 2 diabetes mellitus; F, female; M, male; IG, intervention group; CG, control group; NR, not reported.

studies were used Mg as intervention. The duration of intervention also varied from 4 to 24 weeks among the studies. Based on Cochrane scores, five studies were classified as fair- or weak-quality studies[8,21,25,33,35], and the rest were good-quality studies[10,15,19,20,22–24,26–28,32,34,36]. The result of the quality assessment is reported in Table 2.

Non-linear dose–response meta-analysis

The estimated mean difference in HbA1c at 500 mg/d was −0·73 % (95 % CI: −1·25, −0·22) suggesting modest improvement in HbA1c with strong evidence (*P* value: 0·004). And in FBS at 360 mg/d was −7·11 mg/dl (95 % CI: −14·03, −0·19) suggesting minimal amelioration in FBS with weak evidence (*P* value: 0·092) against the model hypothesis at this sample size (Fig. 2(a)–(d)). The estimated mean difference in FBS and HbA1c at 24 weeks was −15·58 mg/dl (95 % CI: −24·67, −6·49) and −0·48 (95 % CI: −0·77, −0·19), respectively, suggesting modest improvement in FBS (*P* value: 0·034) and HbA1c (*P* value: 0·001) with strong evidence against the model hypothesis at this sample size (Fig. 3(a)–(d)) (Table 3).

Discussion

Diabetes is associated with an elevated risk for CVD[37,38]. Multiple laboratory tests are recommended to diagnose, manage, monitor and follow-up during the treatment of diabetic patients. These include plasma glucose, HbA1c, insulin[39,40] and HOMA-IR[41].

This condition comes with great costs for both the individual and society. Therefore, therapeutic strategies, including a range of dietary, supplements have been developed to improve the glycaemic control[3,42,43]. Among dietary supplements, Mg has aroused curiosity among the scientific community. It might be because it is a crucial enzymatic cofactor in the various biological functions such as glucose metabolism and insulin signalling[44].

Existing evidence diverges on the possible effects of oral Mg supplementation in the clinical management of glycaemic parameters. Therefore, the purpose of this review is to critically assess the scientific evidence regarding the efficacy of oral Mg supplementation on the glycaemic control in T2DM patients.

The present meta-analysis of eighteen RCT indicated that the increment of Mg intakes led to a more significant benefit in FBS and HbA1c. The same benefits were observed in FBS when oral Mg supplement was provided in the long term.

In 2017, a meta-analysis was conducted to evaluate the effect of oral Mg supplementation on T2DM-associated cardiovascular risk factors[45]. There appears to be suggestive evidence of the benefit of oral Mg supplementation on the fasting plasma glucose level. A beneficial effect was observed in diabetic participants with hypomagnesemia[45]. Another meta-analysis that assessed the effects of Mg supplementation on insulin sensitivity and glucose control in diabetic and non-diabetic individuals indicated a significant effect on the HOMA-IR index but not on plasma glucose, HbA1c and insulin levels. However, Mg supplementation intake for more than 4 months can improve the HOMA-IR index and fasting glucose in diabetic or non-diabetic individuals[46]. Another meta-analysis with the goal of reviewing the effect of Mg supplementation on glucose metabolism in people with or at risk of diabetes revealed Mg supplementation could reduce fasting plasma glucose in people with diabetes and improve plasma glucose levels after a 2 h oral glucose tolerance test and the HOMA-IR index[47]. Since the mentioned meta-analysis provides a snapshot of knowledge at the time of

Table 2. Quality assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	General quality
Paolisso et al. 1989[32]	L	U	L	U	L	H	H	Good
Gullestad, 1994[34]	L	U	L	U	L	H	H	Good
Corica et al. 1994[33]	L	U	H	H	L	H	H	Fair
Eibl et al. 1995[35]	L	U	L	U	H	H	H	Fair
De Valk et al. 1998[36]	L	U	L	U	L	H	H	Good
De Lima et al. 1998[10]	L	U	L	U	L	H	H	Good
Rodriguez-Moran et al. 2003[15]	L	L	L	U	L	L	H	Good
Barragan-Rodríguez et al. 2008[19]	L	L	H	H	L	H	H	Good
Guerrero-Romero et al. 2009[20]	L	L	L	U	L	H	H	Good
Barbagallo et al. 2010[21]	U	H	H	H	L	H	H	Weak
Solati et al. 2013[23]	L	L	L	U	L	L	H	Good
Navarrete-Cortes et al. 2014[22]	L	L	L	U	L	L	H	Good
Singh et al. 2015[8]	U	H	H	H	L	H	H	Weak
Razzaghi et al. 2018[24]	L	U	L	U	L	L	H	Good
Talari et al. 2019[28]	L	L	L	U	L	L	L	Good
Sadeghian et al. 2019[27]	L	L	L	U	L	L	L	Good
Rashvand et al. 2019[26]	L	L	L	U	L	L	L	Good
Elderawi et al. 2019[25]	L	U	H	H	L	H	H	Fair

L, low-risk of bias; H, high-risk of bias; U, unclear-risk of bias.

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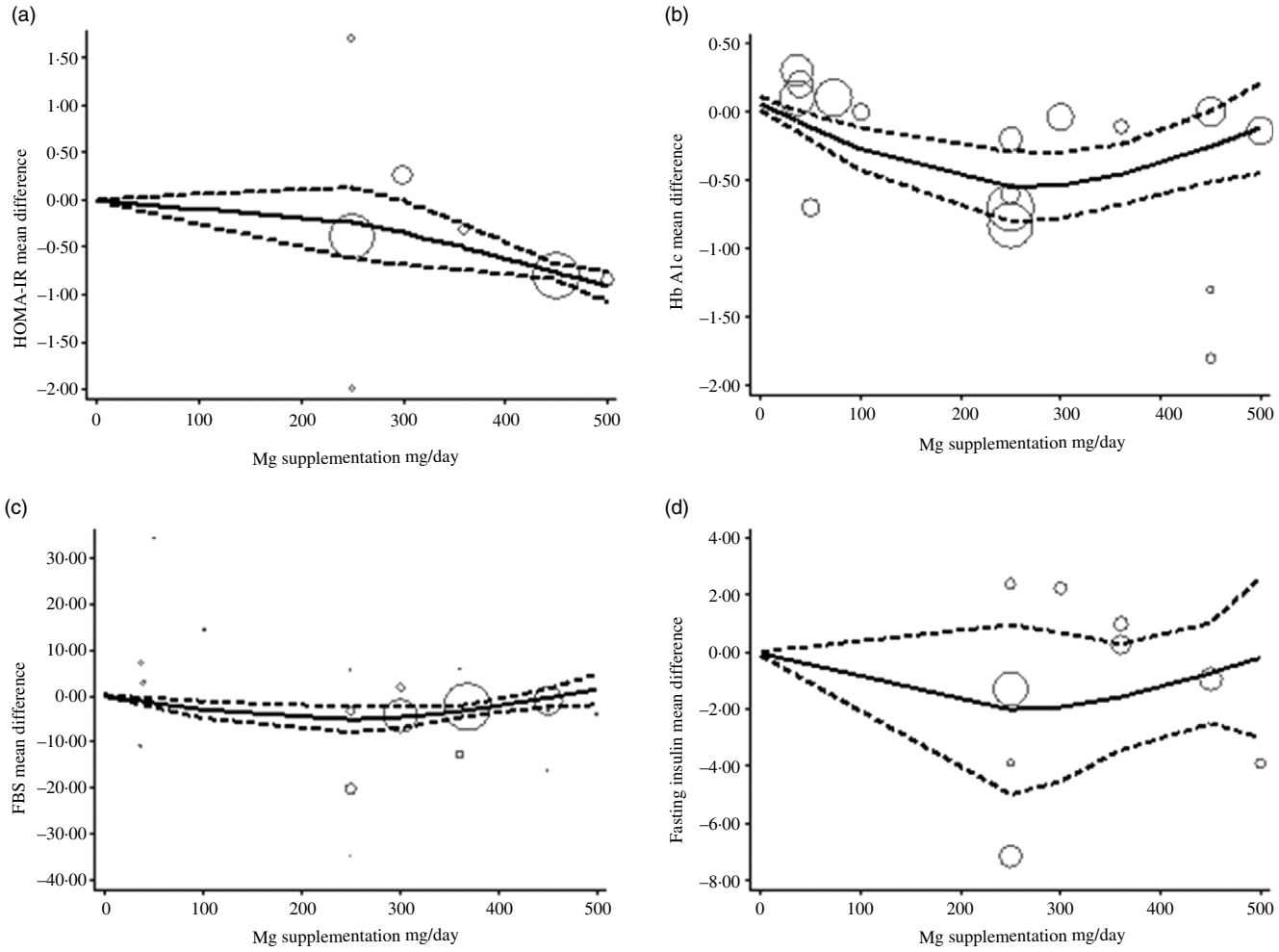

Fig. 2. The solid lines represent the estimate non-linear dose–response for magnesium supplementation on; (a) homoeostatic model assessment of insulin resistance (HOMA-IR); (b) HbA1c; (c) fasting blood sugar (FBS); and (d) Fasting insulin. The dashed lines represent 95 % CI.

incorporating of data from studies identified during the latest search, newly identified studies can change the conclusion of those reviews. So, we aimed to include all of the controlled and clinical trials to summarise current findings on the effect of oral Mg supplementation on glycaemic control in T2DM patients. Results from such investigations can produce evidence with greater clarity in the applicability of oral Mg supplementation on glycaemic control in T2DM patients and enable health professionals to make specific recommendations for incorporating Mg supplementation into the habitual diets in this context.

Due to the divergence in all mentioned meta-analysis, some points should be taken into account. In our analysis, most of the participants presented normo-magnesemia. Hence, the possible beneficial effect of oral Mg supplementation might be minimised in this population. Oral Mg supplementation in individuals with hypo-magnesemia can be more efficient than others[48]. Also, the most common approach for evaluating Mg status is serum Mg concentration as a non-invasive, feasible and inexpensive test. But serum Mg concentration is kept under tight control, and also it has a little correlation with total body Mg concentrations in tissues. Thus, it is not a sensitive evaluation except for severe deficiency. In addition, there are individuals, in particular those with a subtle chronic Mg deficiency whose serum Mg levels are within the reference range but still may have a deficit in total body Mg. And vice versa: some people, though very few, have low serum Mg levels but a physiological Mg body content[49].

Another possible explanation for the mentioned divergence in findings may be that, although the Mg serum can increase during a period of supplementation, the complete equilibrium in intracellular levels and observe beneficial effects may be obtained during a more extended period of intervention[50]. Although serum Mg levels might reflect the dietary Mg intake, we should keep in mind that in T2DM patients there is a wide range of non-dietary factors such as serum Ca:Mg ratio and anti-hypertensive drugs including diuretics affect Mg homoeostasis[51]. Furthermore, since the homoeostasis of the Mg is strictly regulated by the renal function[52], there could be a possible favourite effect of oral Mg supplementation patients with impaired renal function.

Other points that could modify the response of the glycaemic parameters to oral Mg supplementation are different formulations/salts of the Mg, which could be responsible for different bioavailability of the Mg and heterogeneity in the results. Bias in the results can also be introduced as a result of factors affecting the glycaemic control. These factors often manifest differently among the racial and ethnic groups and

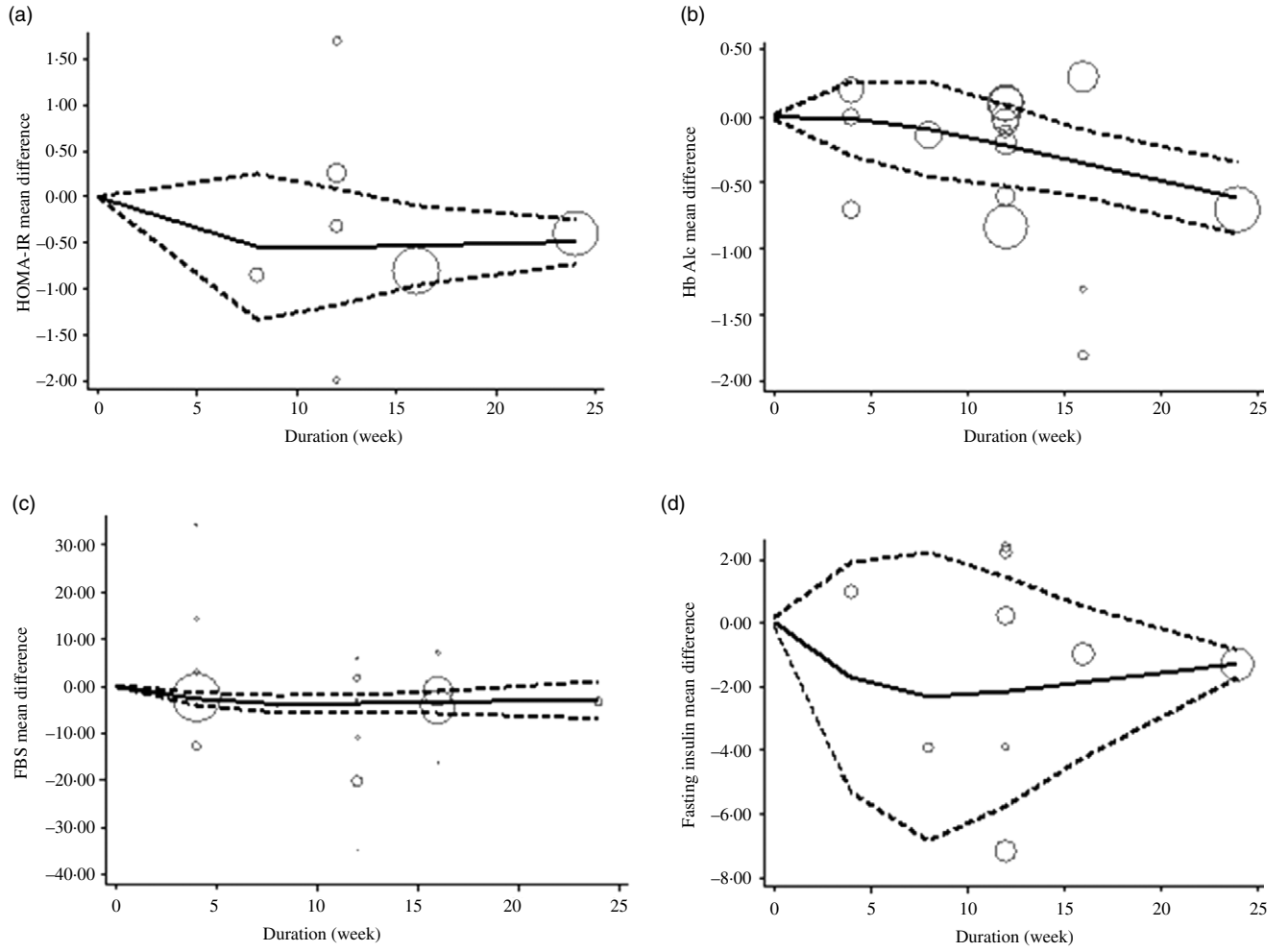

Fig. 3. The solid lines represent the estimate non-linear dose–response for duration of intervention on (a) HOMA-IR; (b) HbA1c; (c) fasting blood sugar (FBS) and (d) fasting insulin. The dashed lines represent 95 % CI.

Table 3. Non-linear dose–response meta-analysis

		Duration			Dose		
		Coefficiency	*P*	Optimum duration	Coefficiency	*P*	Optimum dose (mg/d)
FBS	Dose 1	−0·775	0·003	4–24	−0·032	0·004	36·49–368
	Dose 2	0·842	0·014		0·047	0·013	
HbA1c	Dose 1	0·0006	0·989	16–24	−0·003	0·001	72·98–360
	Dose 2	−0·033	0·547		0·004	0·005	
Insulin	Dose 1	−0·502	0·385	24	−0·011	0·275	–
	Dose 2	0·575	0·438		0·015	0·373	
HOMA-IR	Dose 1	−0·108	0·296	16–24	−0·0005	0·676	300–500
	Dose 2	0·113	0·392		−0·0017	0·371	

FBS, fasting blood sugar; HOMA-IR, Homoeostatic Model Assessment of Insulin Resistance.

can have individual variations across a person lifespan[53]. Differences in the various dietary compliance and energy intake[54], the gut microbiome[55], lifestyle factors and medications[56–58], glycaemic index and rate of the intestinal digestion and absorption of carbohydrate[59] and diversified used approaches for glycaemic control measurements[60] may also contribute to the different clinical response.

At last, any clinician who will interpret our results should bear in mind that some of the medical conditions such as end-stage renal disease or pregnancy and supplements and medications including vitamins E, Ribavirin and interferon-α, generally can present a falsely low HbA1C levels[61]. Variants of haemoglobin could also be considered as potential interferes that could affect the measurement of HbA1C[62].

Several mechanisms have been proposed for the favourite effects of Mg on glycaemic control. Mg is the main co-factor in all enzymes of glycolysis[44] and is also necessary to regulate of insulin signalling, in the phosphorylation of the insulin receptor kinase, in the post receptor action of insulin and in insulin-mediated cellular glucose uptake[44]. Another possible link between Mg deficiency and abnormal glycaemic control is reduced glucose utilisation in the cells, following the post-receptor insulin resistance, which can worsen the reduced insulin sensitivity[44]. On the other hand, the relation between Mg deficiency and reduced insulin sensitivity is the presence of oxidative stress and/or inflammation[63]. Oxidative stress is often increased in metabolic disorder such as T2DM, as a condition associated with Mg deficits[44,64].

The present meta-analysis has some limitations, such as high heterogeneity among the included studies. The pair-wise analysis was not applicable, while dose and duration differed across trials. Moreover, the effects of the confounding variables, including the genetic background and lifestyle factors, on the efficacy of oral Mg supplementation were ignored. Therefore, the results should be interpreted with caution.

The strength of the present study was that we provided the correct analysis in the homogenous populations against an analysis of the pooled individual data when the need for this method is obviated.

Safety

Although the positive effects of oral Mg supplementation on health have been reported, a particular concern about its administration in some medical condition, including chronic kidney disease and end-stage renal disease, should be considered[65,66]. Also, it might be unsafe for patients who take specific diuretics and heart medications[67].

Implications for practice

Although the current meta-analysis suggests that oral Mg supplementation might benefit the glycaemic control in T2DM patients, so far, the RCT are not sufficient for making robust guidelines for clinical practice.

Implications for research

Moving forward, there is a place for larger, longer, pragmatic clinical trials, which would be necessary to rely on simpler and less sensitive outcome measures. Another outcome to consider is whether any beneficial effects are maintained.

Conclusion

Oral Mg supplementation could have a beneficial effect on glycaemic control in T2DM patients. Yet, the clinical trials are not sufficient to make guidelines for clinical practice.

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O. A. and S. M. designed this study. O. A., S. M. and M. Z. contributed to the conduct of the search. O. A. and M. A. H. K. performed the statistical analysis and interpreted the results. M. M., S. N. and A. L. wrote the initial manuscript. S. M. and M. M. critically revised the manuscript and contributed to the subsequent drafts of the manuscript. All authors approved the final version of the manuscript.

The authors declare that they have no conflicts of interest.

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