

## Original Article



# The Effects of Magnesium Supplementation on Serum Magnesium and Calcium Concentration in Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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### Conflict of Interest

The authors declare that they have no  
competing interests.

### Author Contributions

Conceptualization: Zamani M, Haghighat  
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## ABSTRACT

The aim of this systematic review and meta-analysis was to summarize all the existing randomized controlled trials (RCTs) evidence and to evaluate the effects of magnesium supplementation on serum magnesium, calcium and urinary magnesium concentrations in patients with type 2 diabetes compared with the control. Two independent authors systematically searched online databases including Embase, Scopus, PubMed, and Web of Science from inception until 30th January 2022. RCTs complying with the inclusion criteria were included in this meta-analysis. The heterogeneity among the included studies was assessed using Cochran's Q test and I-square ( $I^2$ ) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size. Sixteen trials were included in this meta-analysis. Serum magnesium (mean difference, 0.15 mg/dL; 95% confidence interval [CI], 0.06 to 0.23;  $p = 0.001$ ) and urinary magnesium (WMD, 1.99 mg/dL; 95% CI, 0.36 to 3.62;  $p = 0.017$ ) concentrations were significantly increased after magnesium supplementation when compared with the control group. However, magnesium supplementation did not have any significant effect on serum calcium (WMD, -0.09 mg/dL; 95% CI, -0.27 to 0.08;  $p = 0.294$ ) level when compared with the control group. This meta-analysis demonstrated that magnesium supplementation significantly increased Serum magnesium levels which may have played an indirect role in improved clinical symptoms in patients with type 2 diabetes.

**Keywords:** Magnesium; Calcium; Diabetes; Meta-analysis; Clinical trials

## INTRODUCTION

Around the world, patients with diabetes or pre-diabetes are epidemically increasing [1]. Diabetes mellitus is one of the main causes of morbidity and mortality worldwide, the International Diabetes Federation approximates that the number of diabetics will increase

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to 592 million by 2035 [2]. Nowadays, 80% of the world's people with diabetes live in low- and middle-income countries [3]. Diabetes is also related to a host of life-threatening and likely disabling macro- and microvascular problems [4]. Most of the patients with diabetes have type-2 diabetes, marked by hyperglycemia, insulin resistance, and following cell failure [5]. While diabetes is induced by a mixture of hereditary and acquired aspects, diabetes prevalence has been ascribed to a growingly deficient diet and inactive lifestyle [1,6]. There is strong evidence that micronutrient deficiencies exacerbate diabetes, and that receiving certain foods, vitamins and minerals alleviates the complications of diabetes [7-11].

Magnesium deficiency, one of the nutritional factors related to diabetes, has been caused by urinary magnesium loss and insufficient intake. [12-14]. Magnesium is the second most plentiful intracellular cation that acts also as a cofactor in the glycolytic pathway [15]. Several studies have exhibited that magnesium deficiency is related to declined insulin sensitivity. Glucose disposal rate has been certainly related to the Fasting plasma magnesium levels [16,17]. In comparison with the normal population, patients with type 1 or type 2 diabetes had remarkably lower serum magnesium and higher urinary magnesium excretion [18]. Besides, there was an inverse association between the serum calcium and duration or age of diabetes mellitus [19]. Previous studies on the effect of magnesium supplementation on serum magnesium, calcium and urinary magnesium concentrations in diabetes have conflicting results [18,20-22]. Some studies have investigated magnesium supplementation in patients with type 2 diabetes increased plasma magnesium concentration and urinary magnesium excretion but decreased plasma calcium levels [18,20,21]. Meanwhile other studies did not support these claims [14,22]. To our knowledge, no meta-analysis has been done about this issue to date. Therefore, this study reviews data on magnesium supplementation and its effect on serum magnesium, calcium and urinary magnesium concentrations in patients with type 2 diabetes for the first time.

## MATERIALS AND METHODS

### Literature search and selection

This systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [23]. A systematic literature search was performed by the PubMed, Scopus, The Cochrane library, Web of Science and Embase databases up to 30th January 2022. The systematic search was carried out by medical subject headings (MeSH) terms, abstract and keywords without language and date limitations. This was conducted using the following search terms: (((magnesium) AND ("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 2 authors (SK and SM) separately and in duplicate. Any disagreements in this regard were resolved through discussion with the third researcher (OM).

### Eligibility criteria

Two researchers selected eligible articles separately by reading titles, abstracts and whenever required the full text of the articles. All human randomized controlled trials (RCTs) (either parallel or cross-over designs) which reported the effect of magnesium supplementation on serum magnesium, calcium, and urinary magnesium concentrations in patients with type 2 diabetes were considered. Following studies were excluded: 1) RCTs with treatment duration less than 2 weeks, 2) studies without any comparing control group. 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

Two investigators carried out data extraction from each qualified RCT independently (MZ, NH). Researchers extracted the first author's specification, publication year, location of the study, total sample size, type and dose of intervention and placebo, and study duration. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. The whole process of data extraction was undertaken independently by 2 investigators (MZ and NH) to minimize potential errors. If there was a disagreement, it was resolved by consensus.

### Quality assessment of studies

Based on the Cochrane Collaboration modified risk of bias tool, one independent reviewer (MZ) evaluated the qualified studies ( $n = 8$ ). This protocol assesses the risk of bias in RCTs in seven domains, including random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. As a result, domains were scored using terms such as "Low," "High," and "Unclear." Finally, the corresponding author solved any dissimilarity [24].

### Meta-analysis of data

To analyze the effect size for serum magnesium, calcium concentrations and magnesium urinary levels among patients with type 2 diabetes, the mean change and its standard deviation for intervention and control groups as comparison group were extracted. A random effects model was used to calculate weighted mean differences (WMDs) with 95% confidence intervals (CIs). Between-study heterogeneity was tested by Cochran's Q test and quantified by  $I^2$  statistic. A subgroup analysis according to duration of study ( $\leq 12$  or  $> 12$ ) and dose of intervention ( $\leq 300$  or  $> 300$ ) were conducted to detect potential sources of heterogeneity. Between subgroup heterogeneity was assessed using a fixed effect model. Begg's rank correlation test and Egger's regression asymmetry test were performed for detecting potential publication bias. Sensitivity analysis was conducted by removing each study one by one and recalculating the pooled evaluations. Statistical analysis was conducted using STATA, version 11.2 (StataCorp LCC, College Station, TX, USA). The statistical significant value was defined as  $p$  values  $< 0.05$ .

### Certainty assessment

The overall certainty of evidence across the studies was graded according to the guidelines of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. The quality of evidence could be classified into 4 categories according to the corresponding evaluation criteria: high, moderate, low, and very low [25].

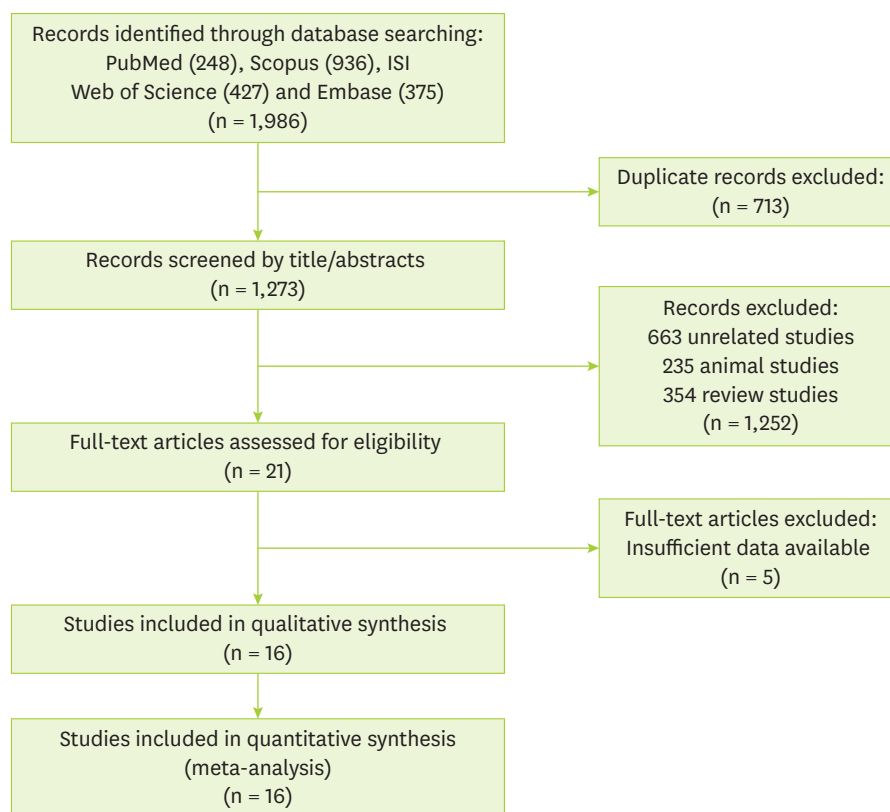
## RESULTS

### Selection and identification of studies

Out of the initial 1,986 articles that were obtained by electronic and hand search (713 duplicates) 1,273 were excluded because according to our inclusion criteria, they were unrelated to present meta-analysis. After reading the full text of the remaining 21 papers, 5 articles did not meet with the desired criteria. In total, 16 eligible RCTs were included in our final analysis [26-36]. A flow chart showing the systematic search and study selection process is shown in **Figure 1**.

### Characteristics of studies

The main characteristics of the included studies in the present meta-analysis are described in **Table 1**. Overall, 17 effect sizes were extracted from 16 RCTs which included a total of 1,060 subjects, out of which 538 subjects were in the magnesium group and 522 belonged to the control group. The mean age of participants in these studies ranged from  $46.76 \pm 9$  to  $71.2 \pm 4.9$  years. These studies were published between the year 1994 and 2019. The RCTs were conducted in Iran [31,33,34-36], Mexico [21,28], Australia [20,27,], Italy [26,29] and Netherlands [18], India [32], Brazil [14], and Palestine [22]. The dose of magnesium ranged from 36.49 to 500 mg/day and all included studies were used pure form of magnesium as intervention. The duration of intervention also varied from 4 to 24 weeks. Based on Cochrane scores, six studies were classified as high-quality studies (score = 3) [22,26-29,32], and other were low quality (score < 3), [14,18,20,21,30,31,33,34-36]. The result of the quality assessment is reported in the **Table 2**.



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

Table 1. Characteristic of included studies in meta-analysis

Author	Study year	Country	Study design	Participant	Sex	Trial duration (wk)	Means age (yr)		Means BMI (kg/m <sup>2</sup> )		Intervention	Sample size
							IG	CG	IG	CG		
Corica et al. [26]	1994	Italy	P	T2DM patients	F/M	4	63 ± 5	61 ± 3	24.8 ± 0.7	24.4 ± 0.4	Magnesium pidolate	IG: 26 CG: 17
Eibl et al. [27]	1995	Australia	R/DB/P	T2DM patients with hypomagnesemia	F/M	12	63 ± 8	54 ± 1.5	27.5 ± 3.2	29.3 ± 5	Magnesium citrate	18 20
de Valk et al. [18]	1998	Netherlands	R/DB/P	T2DM patients	F/M	12	63 ± 8.2	62 ± 7.3	28.7 ± 5.35	27.1 ± 4.46	Magnesium-aspartate-HCl	25 25
de Lima et al. [14]	1998	Brazil	R/DB/P	T2DM patients	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	G1: 35 G2: 39
Rodríguez-Morán and Guerrero-Romero [20]	2003	Australia	R/DB/P	T2DM with decreased serum magnesium levels < 0.74 mmol/L	F/M	16	59.7 ± 8.3	54.1 ± 9.6	27.6 ± 9.1	28.6 ± 4.2	Magnesium chloride	32 31
Barragán-Rodríguez et al. [28]	2008	Mexico	R/CO	Elderly with T2DM, hypomagnesemia and depression	F/M	12	69 ± 5.9	66.4 ± 6.1	NR	NR	Magnesium chloride	12 9
Guerrero-Romero and Rodríguez-Morán [21]	2009	Mexico	R/DB/P	Diabetic hypertensive adults with low serum mg	F/M	16	58.9 ± 8.5	60.5 ± 9.4	29.9 ± 5.2	29 ± 5.1	Magnesium chloride	40 39
Barbagallo et al. [29]	2010	Italy	CO	Elderly diabetic patients	F/M	4	71 ± 4.9	71.2 ± 4.9	27.9 ± 1.5	28.1 ± 1.6	Magnesium pidolate	30 30
Solati et al. [31]	2013	Iran	R/DB/P	T2DM patients	F/M	12	46.76 ± 9	50.15 ± 6.93	26.19 ± 2.86	26.89 ± 5.23	Magnesium sulfate	25 22
Navarrete-Cortes et al. [30]	2014	México	R/DB/P/CR	T2DM patients with normomagnesemia	F/M	12	52.84 ± 8.42	52.84 ± 8.42	30.55 ± 5.72	30.55 ± 5.72	Magnesium lactate	56 56
Singh et al. [32]	2015	India	CO	T2DM patients	NR	16	NR	NR	NR	NR	Magnesium chloride tablet	60 60
Razzaghi et al. [37]	2018	Iran	R/DB/P	Grade 3 DFU	F/M	12	60.1 ± 11.1	59 ± 10.1	28.2 ± 5.2	26.2 ± 4.1	Magnesium oxide	250 35
Talari et al. [36]	2019	Iran	R/DB/P	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 27
Sadeghian et al. [35]	2019	Iran	R/DB/P	Hypomagnesemic patients with T2M nephropathy	F/M	12	41.2 ± 8.8	42.8 ± 8.4	31.2 ± 5.5	30.9 ± 4.4	Magnesium oxide	250 40
Rashvand et al. [34]	2019	Iran	R/DB/P	T2DM patients	F/M	8	49.89 ± 7.83	48.23 ± 14.2	29.69 ± 3.24	29.34 ± 3.71	Magnesium oxide	500 18
ELDerawi et al. [22]	2019	Palestine	R/CO	T2DM patients	F/M	12	51.15	51.55	29.02	30	Magnesium tablets (oxide, gluconate, lactate)	250 20 20

IG, intervention group; CG, control group, DB, double-blinded; SB, single-blinded; P, placebo-controlled, C, controlled; R, randomized, NR, non-reported; F, female; M, male; BMI, body mass index; T2DM, type 2 diabetes; DFU, diabetic foot ulcer.

**Table 2.** Quality assessment

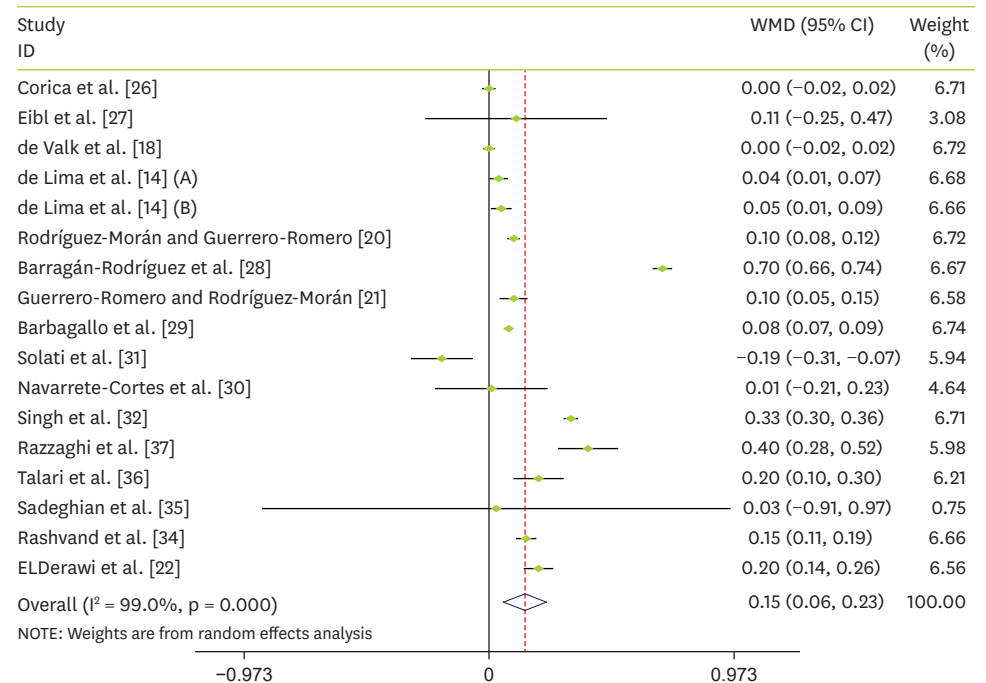
Study	Study year	Random sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Corica et al. [26]	1994	L	U	H	H	L	H	H
Eibl et al. [27]	1995	L	U	L	U	H	H	H
de Valk et al. [18]	1998	L	U	L	U	L	H	H
de Lima et al. [14]	1998	L	U	L	U	L	H	H
Rodríguez-Morán and Guerrero-Romero [20]	2003	L	L	L	U	L	L	H
Barragán-Rodríguez et al. [28]	2008	L	L	H	H	L	H	H
Guerrero-Romero and Rodríguez-Morán [21]	2009	L	L	L	U	L	H	H
Barbagallo et al. [29]	2010	U	H	H	H	L	H	H
Solati et al. [31]	2013	L	L	L	U	L	L	H
Navarrete-Cortes et al. [30]	2014	L	L	L	U	L	L	H
Singh et al. [32]	2015	U	H	H	H	L	H	H
Razzaghi et al. [33]	2018	L	U	L	U	L	L	H
Talari et al. [36]	2019	L	L	L	U	L	L	L
Sadeghian et al. [35]	2019	L	L	L	U	L	L	L
Rashvand et al. [34]	2019	L	L	L	U	L	L	L
ELDerawi et al. [22]	2019	L	U	H	H	L	H	H

L, low; H, high; U, unclear.

### Meta-analysis of data

#### Effects of magnesium supplementation on serum magnesium

Pooled analysis of 16 RCTs (17 treatment arms) showed that magnesium supplementation significantly increase serum magnesium concentrations (mean difference, 0.15 mg/dL; 95% CI, 0.06 to 0.23;  $p = 0.001$ ) among T2DM patients in comparison with control (**Figure 2**). A high heterogeneity was found among the studies ( $I^2 = 99.9\%$ ;  $p < 0.001$ ). For detecting the potential sources of heterogeneity, subgroup analysis was run based on dose of intervention and study duration (**Table 3**). Subgroup analysis did not show any differences between mentioned subgroups.



**Figure 2.** Forest plot detailing WMD and 95% CIs for the effect of magnesium supplementation on serum magnesium. WMD, weighted mean difference; CI, confidence interval.

**Table 3.** Subgroup analyses of magnesium supplementation on serum magnesium in patients with type 2 diabetes

Variables	No.	WMD (95%CI)	p within group	p heterogeneity	I <sup>2</sup>
Subgroup analyses of magnesium supplementation on serum mg level.					
Overall effect	17	0.14 (0.05 to 0.23)	0.001	< 0.001	99.0%
Trial duration (wk)					
≤ 12	13	0.13 (0.02 to 0.24)	0.017	< 0.001	99.1%
> 12	4	0.18 (0.04 to 0.32)	0.012	< 0.001	98.3%
Magnesium dose (mg)					
> 300	11	0.11 (0.01 to 0.21)	0.023	< 0.001	98.1%
≤ 300	6	0.19 (0.01 to 0.37)	0.032	< 0.001	99.5%

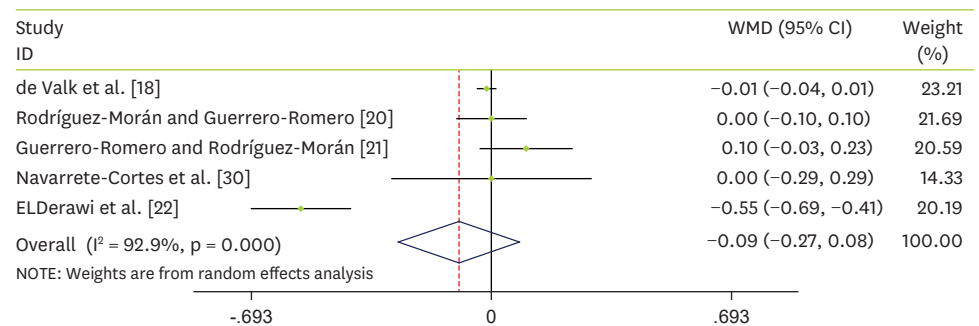
CI, confidence interval; WMD, weighted mean differences.

*Effect of magnesium supplementation on serum calcium*

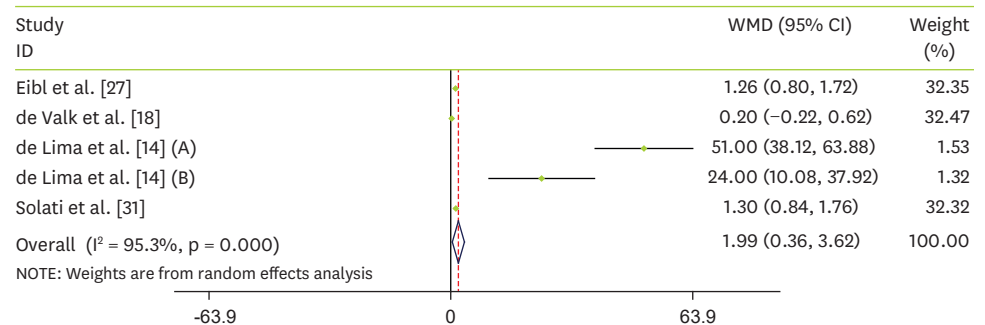
Forest plots summarizing the efficacy of magnesium supplementation on serum calcium levels are shown in **Figure 3**. Pooling 5 RCTs (5 treatment arms) together did not show significant change of serum calcium level (WMD, -0.09 mg/dL; 95% CI, -0.27 to 0.08; p = 0.294) among T2DM patients in comparison with control group (**Figure 3**). A high heterogeneity was found among the studies (I<sup>2</sup> = 92.9%; p = 0.004). We did not conduct subgroup analysis for effect of magnesium supplementation on urinary magnesium, because of the small number of studies.

*Effect of magnesium supplementation on urinary magnesium*

Forest plots summarizing the efficacy of magnesium supplementation on urinary magnesium are shown in **Figure 4**. Pooling 4 RCTs (5 treatment arms) together significant increase of magnesium urinary (WMD, 1.99 mg/dL; 95% CI, 0.36 to 3.62; p = 0.017) in T2DM patients in comparison with control group (**Figure 4**). A high heterogeneity was found among the



**Figure 3.** Forest plot detailing WMD and 95% CIs for the effect of magnesium supplementation on serum calcium. WMD, weighted mean difference; CI, confidence interval.



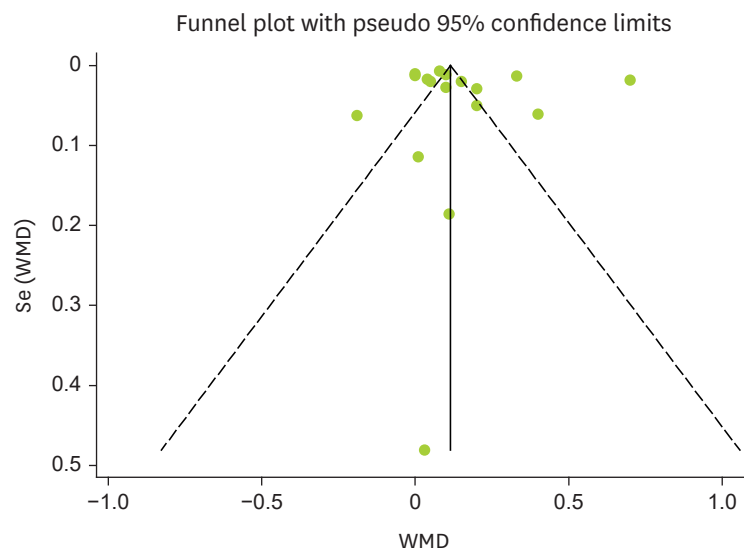
**Figure 4.** Forest plot detailing WMD and 95% CIs for the effect of magnesium supplementation on urinary magnesium. WMD, weighted mean difference; CI, confidence interval.



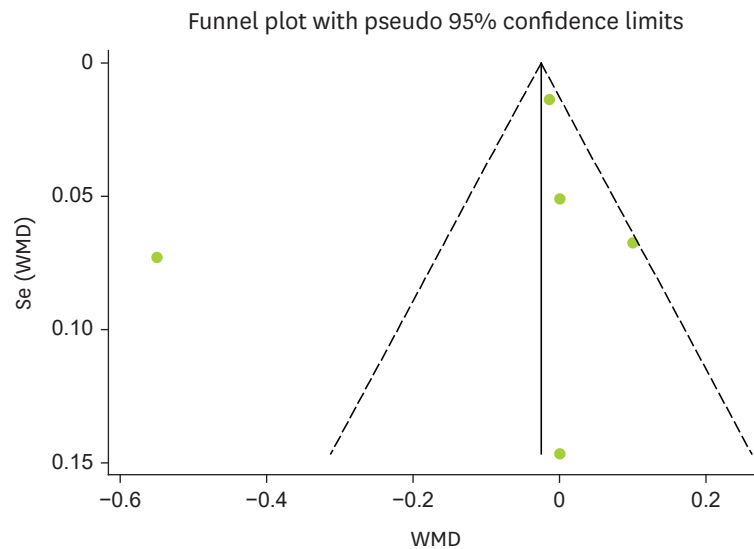
studies ( $I^2 = 95.3\%$ ;  $p < 0.001$ ). We did not conduct subgroup analysis for effect of magnesium supplementation on serum calcium, because of the small number of studies.

**Publication bias**

The sensitivity analysis demonstrated that assessed overall effect sizes for serum magnesium, calcium concentrations and magnesium urinary levels were not substantially changed after removing each article. Egger’s weighted regression tests and visual inspection of funnel plots were used to assess the publication bias. The result from the Egger’s test indicated no publication bias for studies examining the effect of magnesium supplementation on serum magnesium ( $p = 0.24$ ), serum calcium ( $p = 0.91$ ) and magnesium urinary levels ( $p = 0.051$ ). The results of funnel plots are shown in **Figures 5-7**.

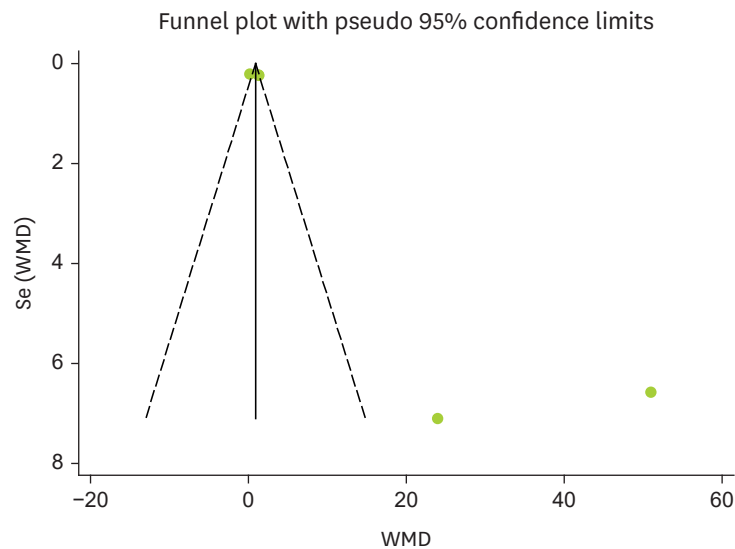


**Figure 5.** Funnel plot for the effect of magnesium supplementation on serum magnesium. WMD, weighted mean difference.



**Figure 6.** Funnel plot for the effect of magnesium supplementation on serum calcium. WMD, weighted mean difference.





**Figure 7.** Funnel plot for the effect of magnesium supplementation on urinary magnesium. WMD, weighted mean difference.

### GRADE assessment

Based on GRADE assessment, data for serum and urinary magnesium were low level of quality, due to serious limitation related with inconsistency, also, there was low quality of evidence for serum calcium, because of serious limitation about inconsistency and imprecision (Table 2).

## DISCUSSION

To our knowledge, this meta-analysis is the first to investigate the impact of magnesium supplementation on serum magnesium, calcium and urinary magnesium concentrations in patients with type 2 diabetes. From 16 eligible RCTs; our analysis shows that magnesium supplementation significantly rises serum magnesium and urinary magnesium concentrations but did not show significant changes in serum calcium level among T2DM patients in comparison with control group. In the human body, magnesium is a cofactor in several enzyme systems such as  $\text{Na}^+/\text{K}^+$ -ATPase, hexokinase, creatine kinase, protein kinase. Also, magnesium plays a role in signal transduction, protein synthesis, neuromuscular conduction, muscle and nerve transmission, blood glucose control, and blood pressure regulation [37-39]. Abnormal magnesium homeostasis can lead to metabolic disorders, such as diabetes [40]. Hypomagnesemia is a frequent condition in patients with T2DM [27]. Magnesium can influence insulin secretion and insulin signal transduction. An increase in serum magnesium could decrease insulin secretion as a result of an emptying in the intracellular calcium concentration in beta cells [41]. The first step in insulin secretion by  $\beta$ -cells is their intracellular uptake of glucose via glucose transporter 2. The tricarboxylic acid cycle and oxidative phosphorylation are glucose metabolic pathways. A lot of enzymes in these metabolic pathways require magnesium. Indeed, magnesium and ATP binding close ATP-sensitive  $\text{K}^+$  channels, leading to depolarization of the cell membrane. The depolarization opens voltage-sensitive calcium channels and induces calcium invasion [41]. Magnesium is mostly absorbed in the small bowel and the kidneys throw out it. Kidneys keep the plasma magnesium concentration in a normal range between 1.7 to 2.4 mg/dL [42].

Our findings were in agreement with previous clinical trials which proposed magnesium supplementation significantly increased serum magnesium levels [20-22,26,34,36,43] and urinary magnesium concentrations [14,30] but did not affect serum calcium levels [18,21,30].

In contrast, many clinical trials exhibited that magnesium supplementation did not affect serum magnesium levels [14,18,28,31,35]. Findings from a study revealed that in patients supplemented with magnesium, urinary magnesium increased significantly without plasma magnesium changes and this result may be due to an increment in ionized or intracellular magnesium. This study showed that magnesium supplementation did not improve serum magnesium levels and this result is in opposition to our results. It should be noted that differences between results might be attributed to the variable dietary stabilization phase and prescribed diet between studies [31]. A recent clinical trial showed a significant reduction in serum calcium levels and the Ca/Mg ratio, and a significant increase in serum magnesium levels after magnesium supplementation [22]. These results reveal the role of magnesium as a calcium antagonist because of the similarities between calcium and magnesium in chemical reactivity and charge [44,45]. The differences in the results of the previous studies, which exhibited the effectiveness of magnesium supplements on serum magnesium levels and urinary magnesium concentration, might be explained by the differences in the magnesium dosages and the duration of supplementation.

There are some limitations in this study. First, only 16 studies were included in this meta-analysis. Second, the heterogeneity of the included studies was significant. These could be because of differences between the doses of magnesium and duration of the interventions. Third, we only searched RCTs published in English, hence, possibly omitted important studies that appeared only in non-English journals. More high-quality trials with large sample size RCTs are suggested in the future.

## CONCLUSION

This meta-analysis demonstrated that magnesium supplementation significantly increased serum magnesium levels which may have played an indirect role in improved clinical symptoms in patients with type 2 diabetes.

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