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The Effects of Magnesium Supplementation on Blood Pressure and Obesity Measure Among Type 2 Diabetes Patient: a Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

In this study, we aimed to systematically review the literature to evaluate the effects of magnesium (Mg) supplementation on blood pressure (BP) and obesity measure among patients with type 2 diabetes mellitus (T2DM). Major electronic databases of Web of Science, the Cochrane library, PubMed, and Scopus were searched completely from the inception until 15 October 2019 to identify randomized clinical trials (RCTs) pertaining to the topic of interest. All outcomes were pooled using a random-effects model and expressed as weighted mean differences (WMD) with 95% confidential intervals (CI). Heterogeneity, sensitivity analysis, and publication bias were also assessed using standard methods. The pooled analysis of five RCTs showed that Mg supplementation did not affect body weight (WMD: − 0.01 kg, 95% CI: − 0.36 to 0.33), BMI (WMD: − 0.07, 95% CI: − 0.18 to 0.04), and waist circumference (WMD: 0.12, 95% CI: − 1.24 to 1.48) in T2DM patients compared to the control groups of the patients who received placebo. However, pooling seven RCTs together showed significant reduction of systolic blood pressure (WMD: − 5.78 mmHg, 95% CI: − 11.37 to − 0.19) and diastolic blood pressure (WMD: − 2.50 mmHg, 95% CI: − 4.58 to − 0.41) in T2DM patients. Furthermore, subgroup analysis by dose of intervention, intervention duration, and type of intervention suggested that Mg supplementation for > 12 weeks, in doses higher than 300 mg/day or inorganic forms, could significantly decrease both systolic and diastolic BP in T2DM patients. Based on the findings, Mg supplementation has beneficial effects on BP in type 2 diabetes patients independent of body weight status. However, further investigations are needed to provide more reliable evidences.

Keywords Magnesium supplementation · Blood pressure · Obesity · Type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a multi-systemic endocrine disorder characterized by hyperglycemia in which insulin is not produced in sufficient amounts or hepatocytes become resistant to insulin, which subsequently lead to impaired glucose control [1]. T2DM is known as one of the most prevalent endocrine disorders, and it is estimated by WHO (World Health Organization) that by the year 2030, at least 333 million people or 6.3% of the global population will be affected by T2DM [2, 3]. Prolonged hyperglycemia accompanied with pro-inflammatory conditions, disturbs normal oxidant-antioxidant balance, hence results in oxidative stress and injury in diabetes [4, 5]. Cardiovascular diseases (CVDs), as the leading cause of mortality worldwide, have been shown to be more prevalent among people with diabetes mellitus, and hypertension has been considered as the main risk factor for the development of those disorders [6]. Therefore, blood pressure (BP) management could potentially reduce the risk of stroke and mortality, especially among patients with T2DM [7]. In this regard, natural supplements have been considered widely as a safe tool to normalize BP along with other beneficial effects [8].

There are several studies indicating that magnesium (Mg) supplementation, as the fourth most abundant mineral in the body, might lower BP. It has been shown that Mg directly induces prostacyclin and nitric oxide formation [9], modulates vasodilation [10, 11], reduces vascular tone and reactivity [12], and has some antioxidant and anti-inflammatory properties [13, 14], which thereby can decrease BP. Moreover, in previous experimental studies, hypomagnesaemia has been proven to be associated with different pathophysiological features including hypertension [15, 16].

In the past years, many clinical trials have been conducted to examine the beneficial effects of Mg supplementation on BP; however, inconsistent results were obtained. Similarly, inconclusive results have also been reported by some systematic reviews carried out on several randomized controlled trials. In this regards, Burgess et al. found no significant benefit of Mg supplementation in patients with hypertension [17]. On the contrast, Dickinson et al. showed a small non-significant decrease in systolic blood pressure (SBP) (− 1.3 mm Hg) and a significant decrease in diastolic blood pressure (DBP) (− 2.2 mm Hg) in patients supplemented by Mg [18]. However, other meta-analyses showed no significant changes nor in SBP neither DBP after supplementation with Mg [19].

More recently, Verma et al. conducted a meta-analysis on 28 RCTs [20–38] to examine the effects of Mg on fasting blood glucose, lipid profile, and BP, compared with the control group in patients with T2DM or at high risk of developing T2DM (i.e., prediabetics, hypertensive, overweight, or obese). The authors found no significant changes in the BP among those diabetic patients who received Mg supplementation [39]. However, there are some gross errors in the mentioned study which should be corrected to provide a more accurate interpretation. In some studies included by Verma et al., initial or difference values (final-baseline) of the desired factors are not available, and only final values were reported [20]; some studies had no control group [21, 24]; some studies had only non-diabetic controls [22]; and some studies conducted on patients other than diabetics [23, 25–32]. Moreover, they did not perform subgroup analysis, despite significant heterogeneity for SBP. According to our knowledge, these errors could confound the true results of Mg effects on BP in patients with T2DM. Therefore, based on the aforementioned notes, in the current meta-analysis, we excluded 13 of those studies included by Verma et al. and added a recently published study [40], to more precisely examine the possible beneficial effects of Mg supplementation on BP in patients with T2DM.

Methods

Literature Search and Selection

The current systematic review and meta-analysis were conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [41]. A comprehensive and systematic literature searches were carried out through the Web of Science, the Cochrane library, PubMed, and Scopus databases from the inception until 15 October 2019. In the search strategy, we used medical subject heading (MeSHs), abstract, and keywords but not language and date restrictions. The following terms were used to systematically search the pertaining articles on the topic of interest: (("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")). In addition to electronic database searches, the reference lists of the included studies were also explored to find any possible relevant publication. All the searching and data extraction works were done in duplicate by two independent authors (OM and SM). Furthermore, any disagreement was resolved by the third researcher (RH).

Eligibility Criteria

The titles, abstracts, and the full text of the searched articles were examined by two authors separately to select the eligible publications for inclusion in this study. All human RCTs

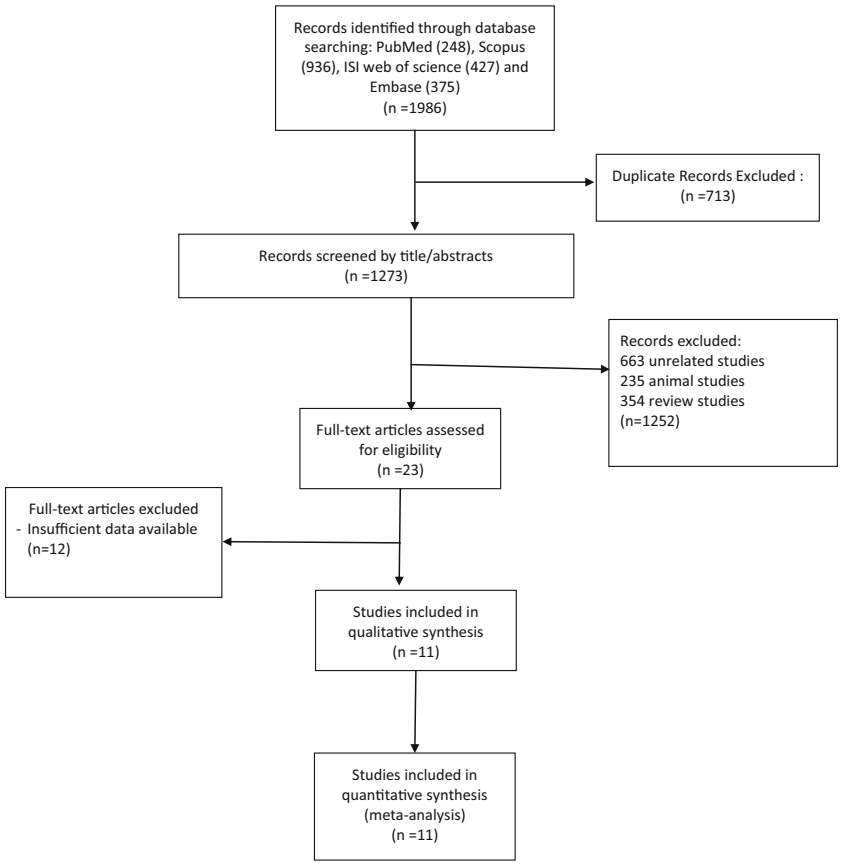

Fig. 1 Flowchart of study selection for inclusion trials in the systematic review

(either parallel or cross-over designs) which reported the effect of Mg supplementation on anthropometric or BP parameters were considered. Moreover, studies with the following features were excluded: (1) RCTs with treatment duration less than 2 weeks and (2) studies that lacked the necessary control groups. To keep away from overlapping, among studies that had same participants, we included studies with higher number of 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 included studies using a pre-designed abstraction form: 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. In cases of lack of relevant data, we contacted the corresponding authors via e-mail to get their help. The whole process of data extraction was undertaken independently by two investigators (OA and SK) to minimize potential errors. If there was a disagreement, it was resolved by consensus.

Quality Assessment of Studies

The quality of included studies was assessed using Cochrane Collaboration's tool [42]. The tool separates a judgment about the risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias. Two researchers (OA and SM) independently evaluated the methods and the quality of the eligible studies through Cochrane Collaboration's tools, which includes seven 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 sources of bias. For each item in the tool, the assessment of risk of bias is in two parts. The support for judgment provides a succinct free text description or summary of the relevant trial characteristic on which judgments of risk of bias are based and aims to ensure transparency in how judgments are reached [42]. Moreover, each scope was further classified into three classes: low risk, high risk, and unclear risk of bias. 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) [42].

Table 1 Characteristics of included studies

Authors)Ref)	Publication year	Country	Sample size (control/ intervention)	Age (years) (control/ intervention)	BMI (kg/m^2) (control/ intervention)	Duration (week)	Intervention/control (type and elemental magnesium dosage)	Diabetic medications or hypertensive medications	Outcomes
De Valk et al.	1998	Netherlands	25/25	63 ± 8.2/62 ± 7.3	28.7 ± 5.35/27.1 ± 4.46	12	Magnesium-aspartate-HCl (36.49 mg)/placebo	NR	SBP, DBP
Rodriguez-Moran et al.	2003	Australia	32/31	59.7 ± 8.3/54.1 ± 9.6	27.6 ± 9.1/28.6 ± 4.2	16	Magnesium chloride (450 mg)/placebo	NR	Bodyweight, BMI, SBP, DBP
Barragan-Rodríguez et al.	2008	Mexico	12/9	69 ± 5.9/66.4 ± 6.1	NR/NR	12	Magnesium chloride (450 mg)/placebo	NR	SBP, DBP
Guerrero-Romero et al.	2009	Mexico	40/39	58.9 ± 8.5/60.5 ± 9.4	29.9 ± 5.2/29 ± 5.1	16	Magnesium chloride (450 mg)/placebo	NR	BMI, SBP, DBP
Barbagallo et al.	2010	Italy	30/30	71 ± 4.9/71.2 ± 4.9	27.9 ± 1.5/28.1 ± 1.6	4	Magnesium pidolate (368 mg)/placebo	NR	SBP, DBP
Solati et al.	2013	Iran	25/22	46.76 ± 9/50.15 ± 6.93	26.19 ± 2.86/26.89 ± 5.23	12	Magnesium sulfate (300 mg)/placebo	Antihypertensive and antidiabetic treatment	BMI, SBP, DBP
Navarrete-Cortes et al.	2014	Mexico	56/56	52.84 ± 8.42/52.84 ± 8.42	30.55 ± 5.72/30.55 ± 5.72	12	Magnesium lactate (360 mg)/placebo	Antidiabetic treatment	Waist circumference, BMI
Razzaghi et al.	2018	Iran	35/35	60.1 ± 11.1/59 ± 10.1	28.2 ± 5.2/26.2 ± 4.1	12	Magnesium oxide (250 mg)/placebo	Antidiabetic treatment	Bodyweight, BMI
Talari et al.	2019	Iran	27/27	58.8 ± 10.1/61.8 ± 10.2	27.2 ± 5.6/26.1 ± 4.5	24	Magnesium oxide (250 mg)/placebo	NR	Bodyweight, BMI
Sadeghian et al.	2019	Iran	40/40	41.2 ± 8.8/42.8 ± 8.4	31.2 ± 5.5/30.9 ± 4.4	12	Magnesium oxide (250 mg)/placebo	Antidiabetic treatment	Waist circumference, Bodyweight, BMI
Rashvand et al.	2019	Iran	18/19	49.89 ± 7.83/48.23 ± 14.2	29.69 ± 3.24/29.34 ± 3.71	8	Magnesium oxide (500 mg)/placebo	Antidiabetic treatment	Waist circumference, Bodyweight, BMI, SBP, DBP

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *NR* not reported

Table 2 Quality assessment by Cochrane Collaboration's tool

Study	Random sequence generation	Allocation concealment	Blinding of participants' personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
De Valk et al.	L	H	H	H	L	L	H
Rodriguez-Moran et al.	L	L	L	U	L	L	H
Barragan-Rodríguez et al.	L	L	L	H	L	L	L
Guerrero-Romero et al.	L	L	L	U	L	H	H
Barbagallo et al.	H	H	L	H	L	L	H
Solati et al.	L	U	L	U	L	H	H
Navarrete-Cortes et al.	L	L	L	H	L	H	H
Razzaghi et al.	L	L	L	U	L	L	L
Talari et al.	L	L	L	U	L	L	L
Sadeghian et al.	L	L	L	U	L	L	L
Rashvand et al.	L	L	H	U	L	L	L

Meta-analysis of Data

To analyze the effect size for BP and anthropometric measures (weight, BMI, waist circumference), 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 based on the BMI (25–29.9 or ≥ 30), duration of study (≥ 12 or < 12), dose of intervention (≥ 300 or < 300), and type of intervention (organic or inorganic) was conducted to detect potential sources of heterogeneity. Between-subgroup heterogeneity was assessed using a fixed effect model. Sensitivity analysis was conducted by removing each study one by one and recalculating the pooled evaluations. Begg's rank correlation test and Egger's regression asymmetry test were performed for detecting potential publication bias. Statistical analysis was conducted using STATA, version 11.2 (Stata Corp, College Station, TX). The statistical significant value was defined as P values < 0.05.

Results

Selection and Identification of Studies

Out of the initial 1986 articles obtained by electronic and hand search, 713 were excluded due to duplication, and 1273 articles were further excluded based on inclusion criteria, since that they were unrelated to the topic of the present meta-analysis. After reading the full text of the remaining 23 papers, 12 studies were also excluded as these articles did not meet the predefined inclusion criteria. In total, 11 eligible RCTs with 11

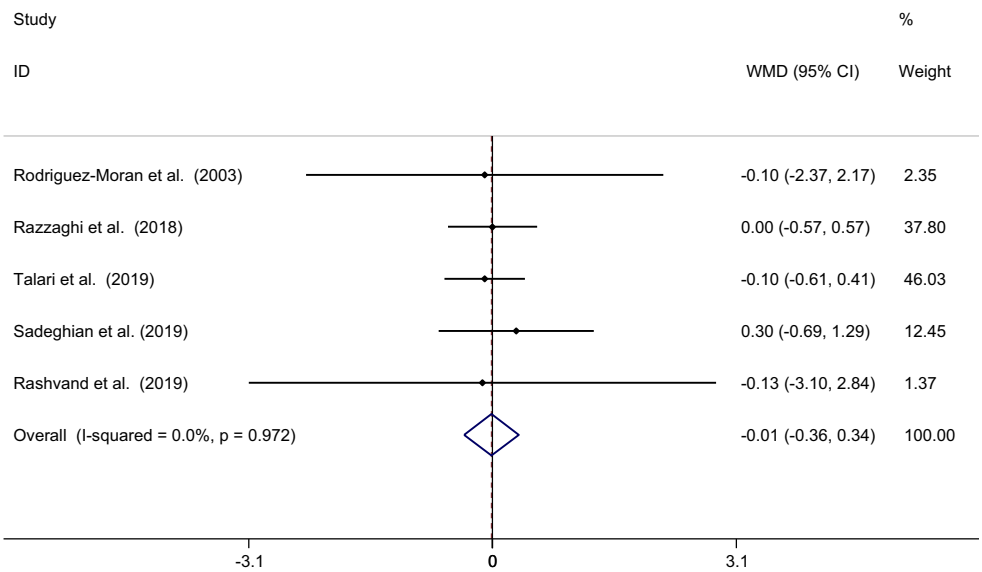

Fig. 2 Forest plot of the comparison of the effects of magnesium supplementation versus placebo on body weight

Table 3 The effects of magnesium on anthropometric measurements and blood pressure in patients with type 2 diabetes

Variables	Number of effect sizes	Weighted mean difference	CI 95%	*P* value	Heterogeneity	
					I^2 (%)	*P* value heterogeneity
Body weight	5	− 0.01	− 0.36, 0.33	0.943	0.0%	0.972
BMI	8	− 0.07	− 0.18, 0.04	0.241	0.0%	1.000
WC	3	0.12	− 1.24, 1.48	0.862	0.0%	0.465
SBP	7	− 5.78	− 11.37, − 0.19	*0.043*	77.0%	< 0.000
DBP	7	− 2.50	− 4.58, − 0.41	*0.019*	77.1%	< 0.000

BMI body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

treatment arms were included in the present meta-analysis [33–38, 40, 43–46]. Twelve studies were not included in the quantitative synthesis because it did not have a control group [21, 24], enrolled non-diabetic subjects in the control group [22], and conducted on non-diabetic volunteers [23, 25–32]. A flow chart describing the systematic search and study selection process is shown in Fig. 1.

Characteristics of Studies

The main characteristics of the included studies in the present meta-analysis are described in Table 1. Taken together, 12 effect sizes were extracted from the 11 RCTs which included a total of 673 subjects, out of which 358 subjects were in the Mg group and 315 belonged to the control group. The mean age of participants in these studies ranged from 41.2 ± 8.8 to 71.2 ± 4.9 years. All the studies were published between the years 1998 and 2019. The RCTs were conducted in Netherlands [33], Australia [34], Mexico [35, 36, 46], Italy [37], and Iran [38, 40, 43–45]. The dose of supplemental Mg ranged from 36.49 to 500 mg/day. Eight studies were used inorganic forms of Mg as intervention [34–36, 38, 40, 43–45] and three studies were used organic forms of Mg supplementation [33, 37, 46]. The duration of intervention also varied from 4 to 24 weeks between the studies. Among included studies, five studies reported that participants had taken antihypertensive or antidiabetic drugs [11, 40, 44–46] and the others did not report [30, 33, 35–37, 43].

According to Cochrane scores, three studies were classified as high-quality studies (score = 3), [33, 37, 46] and the others were considered as low-quality studies (score < 3) [34–36, 38, 40, 43–45]. The result of the quality assessment is reported in the Table 2.

Meta-analysis of Data

Effects of Mg on Anthropometric Measurements

The pooled analysis of 5 RCTs (5 treatment arms) showed that Mg supplementation did not affect body weight (MD: − 0.01 kg, 95% CI: − 0.36 to 0.33, I^2 = 0.0%) in T2DM patients compared to control groups (Fig. 2, Table 3). In same results,

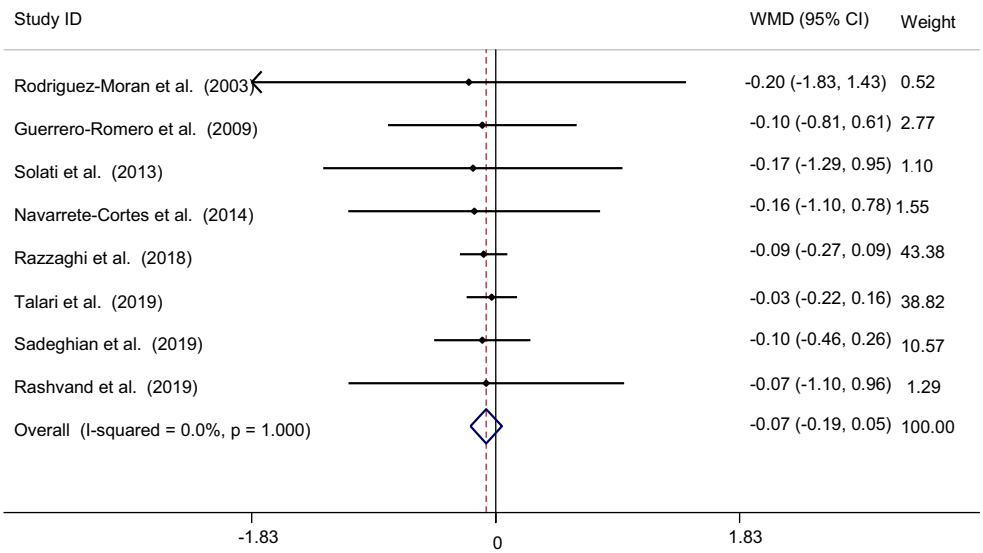

Fig. 3 Forest plot of the comparison of the effects of magnesium supplementation versus placebo on body mass index

Mg supplementation among T2DM patients had no effect on BMI (MD: − 0.07, 95% CI: − 0.18 to 0.04) and waist circumference (MD: 0.12, 95% CI: − 1.24 to 1.48) in comparison with placebo group (Figs. 3 and 4 and Table 3). Moreover, no significant effect of Mg supplementation on anthropometric measurements among T2DM patients was found according to the subgroup analyses based on BMI (25–29.9 or ≥ 30), duration of study (≥ 12 or < 12), and dose of intervention (≥ 300 or < 300) (Table 4).

Effect of Mg Supplementation on Blood Pressure

Forest plots summarizing the efficacy of Mg supplementation on SBP are shown in Fig. 5. Pooling seven RCTs (seven treatment arms) together showed significant reduction of SBP (WMD: − 5.78 mmHg, 95% CI: − 11.37 to − 0.19) in T2DM patients who received Mg (Fig. 5, Table 3). A high heterogeneity was found among the studies (I^2 = 77.0%, P < 0.001). Mg supplementation was found to have a significant effect on DBP (WMD: − 2.50 mmHg, 95% CI: − 4.58 to − 0.41) compared to that of placebo group (Fig. 6, Table 3). However, there was also high heterogeneity between the studies (I^2 = 71%, P < 0.001). To identify the potential sources of heterogeneity, subgroup analysis was run based on the duration of study (≥ 12 or < 12) and dose of intervention (≥ 300 or < 300). Subgroup analysis by dose of intervention suggested that < 300 mg Mg supplementation significantly decreased the SBP (WMD: 2.27 mmHg, 95% CI: − 3.18, − 1.35) and DBP (WMD: − 6.54 mmHg, 95% CI: − 12.07 to − 1.02) in T2DM patients but not ≥ 300 mg Mg intervention (Table 3). Furthermore, subgroup analysis according to the duration of study illustrated that Mg supplementation more than 12 weeks significantly decreased the DBP (WMD: − 10.50 mmHg, 95% CI: 20.70 to − 0.31) in patients with T2DM, but no changes were observed in interventions ≤ 12 weeks (Table 3). Ultimately, subgroup analysis based on type of intervention revealed that inorganic Mg supplementation significantly decreased the SBP (WMD: − 8.08 mmHg, 95% CI: − 13.29 to − 2.87) and DBP (WMD: − 3.77 mmHg, 95% CI: − 5.96 to − 1.58) among patients with T2DM, while organic Mg supplementation did not.

Publication Bias

Begg's rank correlation and Egger's weighted regression tests were conducted to detect the publication bias. The outcomes of Begg's and Egger's test showed no publication bias for body weight (P = 1.00, Begg's test and P = 0.69, Egger's test), waist circumference (P = 1.00, Begg's test and P = 0.42, Egger's test), BMI (P = 0.90, Begg's test and P = 0.051, Egger's test), SBP (P = 0.76, Begg's test and P = 0.79, Egger's test), and DBP (P = 1.00, Begg's test and P = 0.21, Egger's test).

Discussion

The aim of this meta-analysis was to investigate overall effects of Mg supplementation on anthropometric measurements and BP in individuals with T2DM. The results of the present study indicated that the supplementation with inorganic Mg could significantly reduce both SBP and DBP in individuals with T2DM compared to diabetic controls. The average reductions in BP due to Mg supplementation observed in the present study (SBP: 5.78 mmHg; DBP: 2.50 mmHg) might have relevant clinical effects on diabetic health. These findings also are supported by the other meta-analysis studies [18, 39, 47–51]. As previously mentioned based on subgroup analysis

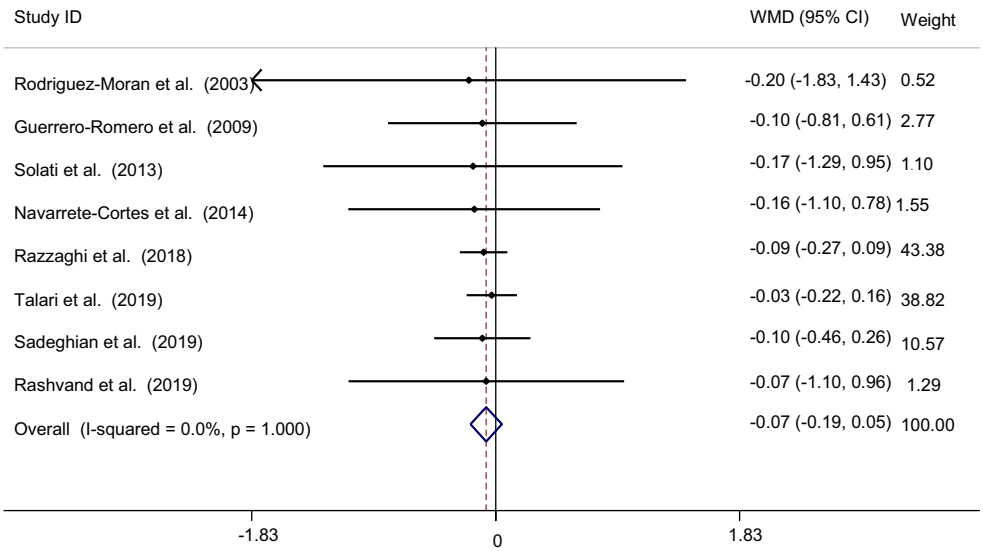

Fig. 4 Forest plot of the comparison of the effects of magnesium supplementation versus placebo on waist circumference

Table 4 Subgroup analyses of magnesium supplementation on anthropometric measurements and blood pressure in patients with type 2 diabetes

	NO	WMD (95%CI)	P within group	P heterogeneity	I^2 (%)
Subgroup analyses of magnesium supplementation on body weight.					
baseline BMI					
25–29.9	4	− 0.05 (− 0.42, 0.31)	0.763	0.995	0.0%
≤ 30	1	0.30 (− 0.68, 1.28)	0.551	–	–
Duration					
≥ 12	3	0.06 (− 0.41, 0.55)	0.780	0.867	0.0%
< 12	2	− 0.10 (− 0.60, 0.40)	0.695	1.000	0.0%
Dose					
≥ 300	3	− 0.00 (− 0.36, 0.34)	0.960	0.779	0.0%
< 300	2	− 0.11 (− 1.91, 1.69)	0.904	0.987	0.0%
Subgroup analyses of magnesium supplementation on BMI					
baseline BMI					
25–29.9	6	− 0.06 (− 0.19, 0.06)	0.308	0.998	0.0%
≤30	2	− 0.10 (− 0.44, 0.23)	0.532	0.907	0.0%
Duration					
≥12	5	− 0.09 (− 0.24, 0.06)	0.229	1.000	0.0%
< 12	3	− 0.03 (− 0.21, 0.14)	0.691	0.963	0.0%
Dose					
≥300	4	− 0.06 (− 0.18, 0.05)	0.277	0.964	0.0%
< 300	4	− 0.11 (− 0.59, 0.35)	0.628	0.999	0.0%
Subgroup analyses of magnesium supplementation on DBP					
Duration					
≥ 12	5	− 2.06 (− 4.54, 0.40)	0.102	< 0.000	83.2%
< 12	2	− 4.12 (− 9.12, 0.86)	0.105	0.153	51.0%
Dose					
≥ 300	2	− 1.16 (− 11.55, 9.22)	0.826	< 0.000	94.8%
< 300	5	− 2.27 (− 3.18, − 1.35)	*< 0.000*	0.420	0.0%
Type of intervention					
Organic	2	0.81 (− 5.32, 6.95)	0.795	0.005	87.6%
Inorganic	5	− 3.77 (− 5.96, − 1.58)	*0.001*	0.038	60.6%
Subgroup analyses of magnesium supplementation on SBP					
Duration					
≥ 12	5	− 3.58 (− 9.75, 2.59)	0.256	0.009	70.4%
< 12	2	− 10.50 (20.70, − 0.31)	*0.043*	0.023	80.5%
Dose					
≥ 300	2	− 4.77 (− 20.74, 11.19)	0.558	< 0.000	92.4%
< 300	5	− 6.54 (− 12.07, − 1.02)	*0.020*	0.034	61.7%
Type of intervention					
Organic	2	2.94 (− 2.17, 8.06)	0.259	0.701	0.0%
Inorganic	5	− 8.08 (− 13.29, − 2.87)	*0.002*	0.014	67.9%

BMI body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

results, a differential effect was also observed for dose of intervention and duration of study. In this regards, a significant beneficial effect was found in diabetic patients treated with Mg supplementation for > 12 weeks or those who received Mg ≥ 300 mg. In line with our result, a meta-analysis showed that 370-mg/day Mg supplementation could improve both SBP (3–4 mmHg) and DBP (2–3 mmHg) [49]. Similarly, Dibaba et al. in their meta-analysis showed that supplementation with elemental Mg, in doses ranging from 365 to 450 mg/day can reduce SBP by 4.18 mmHg and DBP by 2.27 mmHg [47]. On the contrast, our results regarding the beneficial effect of Mg supplementation on BP are different from those

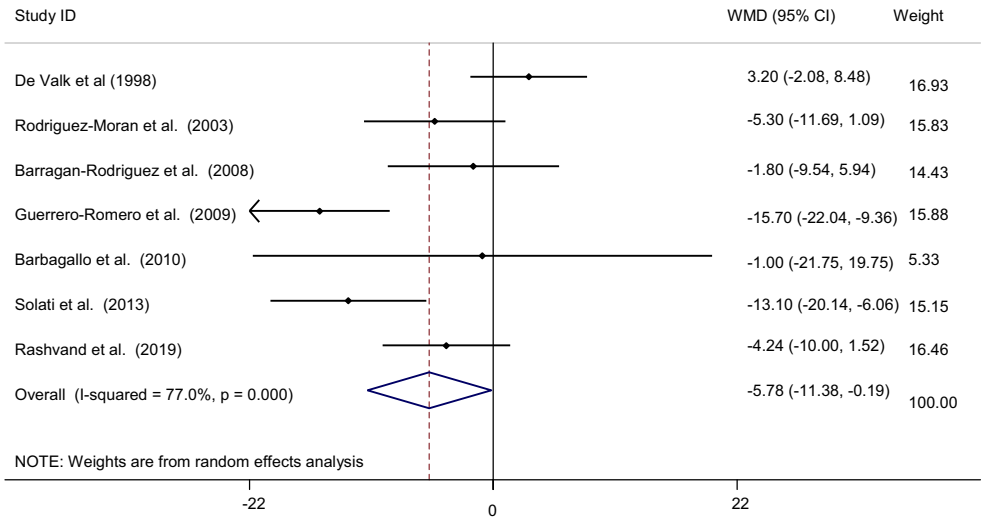

Fig. 5 Forest plot of the comparison of the effects of magnesium supplementation versus placebo on systolic blood pressure

reported by Song et al. [51]. This might be explained by a greater number of clinical studies being included in the present meta-analysis and by a greater median dose of oral Mg supplementation in the treatment groups. No beneficial effect of Mg supplementation was observed on anthropometric measurements. These findings are in accordance with those of Song et al. [51]. Moreover, some previous meta-analyses demonstrated that higher dose of Mg intake is associated with improved insulin sensitivity which is beneficial particularly for both overweight and obese individuals as well as diabetic patients [47, 48, 50]. Several studies have shown that some essential elements such as calcium, Mg, sodium, chromium, cobalt, iodine, iron, selenium, manganese, and zinc, but not potassium and copper, are at lower concentrations in T2DM patients which may play a role in disease pathogenesis [52]. Among the aforementioned micronutrients, Mg is the fourth most abundant mineral in the human body with 99% intracellular distribution [53]. This element is an essential cofactor of numerous enzymes including enzymes involved in glycolysis; therefore, it seems to be reasonable that in concentrations under the biological levels, different physiological processes including energy pathways might be dysregulated. The effects of Mg on hypertension have been linked to its interaction with calcium [47]. Moreover, there are evidences indicating that Mg might trigger membrane -Na + K + -ATPase in cardiac muscle cells to release intracellular sodium and calcium stores and thereby decreases the peripheral vascular resistance which subsequently reduces the blood hypertension [54]. In addition, Mg has been known to induce the release of nitric oxide (NO) and prostaglandin I2 from endothelial cells, as vasoactive mediators, and synergies with the antihypertensive medications [55]. The other possible mechanism by which Mg could reduce hypertension is its effects on the expression of osteopontin, matrix Gla protein, bone morphogenetic protein-7 (BMP-7), and receptor potential melastin 7 (TRPM7) which collectively reported to inhibit the vascular calcification [56].

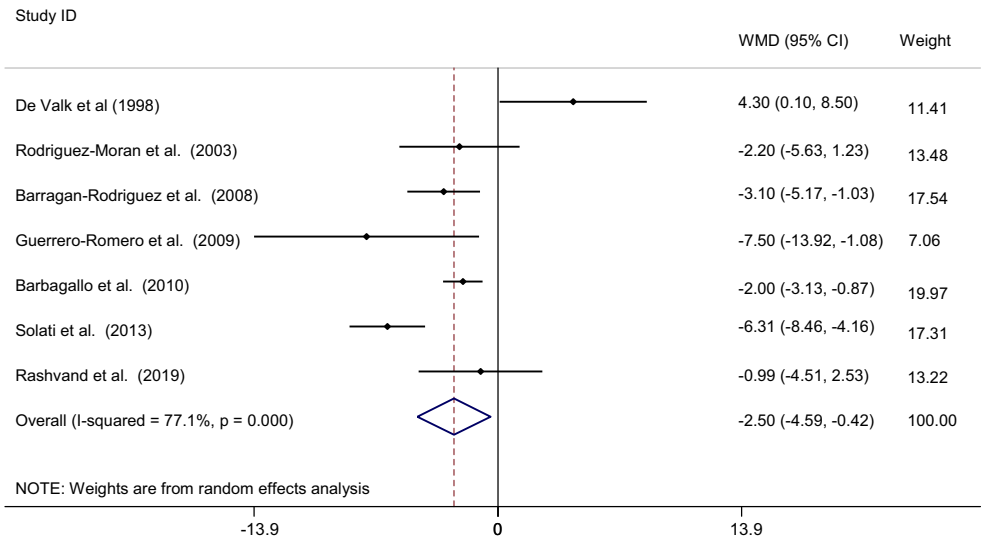

Fig. 6 Forest plot of the comparison of the effects of magnesium supplementation versus placebo on diastolic blood pressure

Furthermore, it has been demonstrated that Mg could change lipid profile of diabetic patients, improve insulin resistance and hyperglycemia, therefore improves the clinical conditions and reduce the hypertension and related organ damage. Previous studies documented that lifestyle interventions, such as Dietary Approaches to Stop Hypertension (DASH diet) and higher physical activity, are associated with clinically significant reductions in BP values among T2DM patients [57–59]. In this regard, a recent systematic review and meta-analysis revealed that adherence to DASH diet style significantly lowers SBP (− 6.19 mmHg, CI: − 9.43 to − 2.94), but does not affect DBP (− 4.47 mmHg, CI: − 13.29 to 4.34) in T2DM patients [60]. On the other hand, our results indicated that Mg supplementation could significantly reduce SBP (− 5.78 mmHg) and DBP (− 2.50 mmHg). Therefore, by putting these results together, it can be assumed that lifestyle modifications (such as adherence to DASH diet) along with the Mg supplementation may further improve BP control in T2DM patients.

Our study has some notable strengths which should be clarified. To the best of our knowledge, this is the first meta-analysis that considered the effect of Mg supplementation on body weight, BMI, waist circumference, and BP in T2DM patients. In addition, our results are comparatively more uniform than those reported by the previous studies, since that we included RCTs on T2DM patients supplemented with most inorganic Mg which further reduces the bias from bioavailability of Mg salts. We also evaluated the publication biases based on the results of Egger's test, and in exception to BMI, no evidence of publication bias was observed which makes our result more reliable. Of note, only five RCTs had assessed the effect of Mg supplementation on BMI; hence, more trials are warranted to determine any beneficial effect of Mg on BMI. However, there are also several limitations in the present meta-analysis. A major limitation is that most of the RCTs included in this study had not reported the baseline serum levels of Mg. Therefore, it would be beneficial if in the future clinical trials, the pre-intervention and post-intervention levels of plasma Mg be compared. Furthermore, since the Mg level is strictly regulated by renal function and the kidney failures and its disorders are very prevalent among type 2 diabetic patients [50], it would be rationale to address these confounding factors in the next trials. The final limitation was the evidence of heterogeneity across the studies, especially in their design and methodologies.

Conclusions

The findings of the present meta-analysis showed an overall reduction in SBP and DBP by Mg supplementation among T2DM patients. Although high heterogeneity was observed between the included RCTs, the effect of the intervention is still clear. Taken together, the findings of the present study indicated that Mg supplementation for > 12 weeks or in doses higher than 300 mg/day could significantly improve the BP in type 2 diabetic subjects. However, future large-scale, well-designed studies are warranted to provide more reliable evidences of the Mg supplementation benefit on BP among these patients.

Authors' Contributions Omid Asbaghi (OA) and Sajjad Moradi (SM) designed the research; OA and Sara Kashkooli conducted the research; OA and SM performed statistical analysis; SM, Behnoosh Boozari, and Ehsan Ghaedi wrote the paper; SM had primary responsibility for final content. Reza Hosseini contributed to the revision of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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