Article

Oral Magnesium Supplementation for Treating Glucose Metabolism Parameters in People with or at Risk of Diabetes: A Systematic Review and Meta-Analysis of Double-Blind Randomized Controlled Trials

Nicola Veronese [1,*], Ligia J. Dominguez [1,2], Damiano Pizzol [3], Jacopo Demurtas [4,5], Lee Smith [6] and Mario Barbagallo [1]

1   Geriatrics Section, Department of Internal Medicine, University of Palermo, 90127 Palermo, Italy; ligia.dominguez@unipa.it (L.J.D.); mario.barbagallo@unipa.it (M.B.)
2   School of Medicine, Kore University of Enna, 94100 Enna, Italy
3   Italian Agency for Development Cooperation-Khartoum, Sudan Street 33, Khartoum 21111, Sudan; damianopizzol8@gmail.com
4   Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, 41124 Modena, Italy; eritrox7@gmail.com
5   Primary Care Department USL Toscana Sud Est-Grosseto, 58100 Grosseto, Italy
6   Centre for Health, Performance, and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK; lee.smith@aru.ac.uk
*   Correspondence: nicola.veronese@unipa.it

Abstract: There is a large and growing body of literature focusing on the use of oral magnesium (Mg) supplementation for improving glucose metabolism in people with or at risk of diabetes. We therefore 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 a placebo. Several databases were searched investigating the effect of oral Mg supplementation vs placebo in patients with diabetes or conditions at high risk of diabetes. Data were reported as standardized mean differences (SMDs) with their 95% confidence intervals (CIs) using follow-up data of glucose and insulin-sensitivity parameters. Compared with placebo, Mg supplementation reduced fasting plasma glucose in people with diabetes. In people at high risk of diabetes, Mg supplementation significantly improved plasma glucose per se, and after a 2 h oral glucose tolerance test. Furthermore, Mg supplementation demonstrated an improvement in insulin sensitivity markers. In conclusion, Mg supplementation appears to have a beneficial role and improves glucose parameters in people with diabetes. Moreover, our work indicates that Mg supplementation may improve insulin-sensitivity parameters in those at high risk of diabetes.

Keywords: magnesium; diabetes; glucose; meta-analysis

1. Introduction

The literature regarding the health benefits of magnesium (Mg) is exponentially increasing [1]. Recent literature has reported that Mg, involved in more than 300 enzymatic reactions [2], has a wide spectrum of action in cardiovascular [3,4], pregnancy [5], gastrointestinal [6], in infectious [7] and metabolic diseases [8], such as diabetes.

In a previous systematic review and meta-analysis, it was reported that Mg supplementation, compared to placebo, improves several glucose and insulin-sensitivity parameters in people affected by diabetes or have conditions (such as obesity) that put them at increased risk of developing diabetes [9]. In a large meta-analysis including more than 500,000 participants it was found that higher Mg intake is associated with a significant decrease in the incidence of diabetes [10], supported by evidence with a low risk of bias [1]. Unfortunately, the proportion of people meeting the recommended daily allowance (RDA) for Mg is still

low. Therefore, in some high risk populations (such as diabetes, older people and pregnant women), oral supplementation is often necessary [11].

Regarding diabetes, several randomized, double-blind controlled trials (RCTs) have investigated the effect of oral Mg supplementation on glucose metabolism parameters. However, these RCTs have an important limitation since they only include a small number of participants [9], as highlighted in a previous systematic review and meta-analysis regarding this topic [12].

Given this background, we conducted a 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 a placebo. It is hypothesized that Mg supplementation would improve glucose and insulin outcomes in those with diabetes and in those with conditions that put them at a high risk of developing diabetes.

2. Materials and Methods

This systematic review adhered to the PRISMA statement [13] and followed a pre-planned, but unpublished protocol that can be requested by contacting the corresponding author.

2.1. Data Sources and Searches

Two investigators (NV and DP) independently conducted a literature search using several databases including PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restriction, from 31 January 2016 until 26 October 2021, including RCTs investigating the effect of oral Mg vs. placebo in patients with diabetes or at high risk of developing diabetes. In a previous meta-analysis of the present group literature on this topic was screened up to 31 January 2016.

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'), adapting the search according to the database. Conference abstracts and reference lists of included articles were hand searched to identify any potential additional relevant articles. Any inconsistencies were resolved by consensus, with a senior author participating in the first meta-analysis on this topic [9].

2.2. Study Selection

Inclusion criteria for this meta-analysis were: (i) being an RCT; (ii) double-blind design; (iii) participants with diabetes or subjects at high risk of developing diabetes included; (iv) use of oral magnesium supplementation; (v) assessment of glucose metabolism or insulin sensitivity parameters (see below for further details); (vi) sufficient quality, as assessed by Jadad's scale [14] $\geq$ 3/5 points. We considered it diabetes when the diagnosis was made according to the criteria proposed by the American Diabetes Association, i.e.,: fasting plasma glucose (FPG) $\geq$ 126 mg/dl (=7.0 mmol/L), or 2 h PG $\geq$ 200 mg/dL (=11.1 mmol/L) during oral glucose tolerance test (OGTT) with 75 g of glucose, or glycosylated hemoglobin (HbA1C $\geq$ 6.5% (=48 mmol/mol), or random PG $\geq$ 200 mg/dL (=11.1 mmol/L). [15] Several conditions were considered as placing people at high risk of diabetes, including obesity/overweight, metabolic syndrome, renal failure, family history of diabetes, prediabetes, and others. In the case of disagreement between the two reviewers, a third senior reviewer with expertise in diabetes and metabolic disease (LD) was involved and a consensus among the three reviewers was reached. RCTs were excluded if they: (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.

2.3. Data Extraction

Two independent investigators (JD and DP) extracted key data from the included articles in a standardized Excel spread sheet and a third independent investigator (NV)

checked these data. For each article, we extracted data on authors, year of publication, country, glucose metabolism/insulin-sensitivity end points, condition, study design (crossover or parallel), medications used for the treatment of diabetes, type of Mg used in the trial with daily dosage, and follow-up duration (in weeks). Moreover, we extracted data on treatment with Mg or placebo, mean age, body mass index (BMI), and number of women at baseline. When information was missing, first and/or corresponding authors of the original article were contacted at least four times to obtain unpublished data.

2.4. Outcomes

The primary outcomes were parameters of glucose metabolism and insulin sensitivity. Regarding glucose metabolism, we included FPG, glycosylated hemoglobin (HbA1c), plasma glucose after the 2 h OGTT. Regarding insulin sensitivity, we extracted data on fasting insulin levels or after 2 h OGTT, homeostatic model assessment-insulin resistance (HOMA-IR).

2.5. Quality Assessment

Two authors (JD and DP) completed scoring using the Jadad's scale [14] 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 of 3 (over a maximum of 5) usually indicates a low-quality study at high risk of bias [16].

2.6. Data Synthesis and Analysis

All analyses were performed using STATA version 14.0 (StataCorp). Outcomes with at least two studies were meta-analyzed; outcomes with less than two studies, i.e., not suitable to be included in meta-analyses were excluded.

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 follow-up data through standardized mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model [17]. Heterogeneity across studies was assessed by the I^2 metric and χ^2 statistics. In case of significant heterogeneity ($I^2 \geq 50\%$, $p < 0.05$) and for outcomes having at least four studies, we conducted a series of meta-regression analyses using as moderators the continent in which the study was performed (categorized as America vs. others), follow-up length, differences in baseline mean age, BMI and mean outcome investigated between Mg and the placebo group [18]. For analyses regarding conditions that included people at high risk of diabetes, the condition investigated (categorized as overweight vs. others) was also explored as a possible mediator of heterogeneity.

As most of the studies reported data on plasma/serum Mg, this parameter was considered when running meta-regression analysis to examine if differences in values of Mg at follow-up between treated and placebo groups 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 [19] and the Egger bias test [18]. Then, to account for publication bias, the trim-and-fill method was employed, 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, adjustment for the potential effect of unpublished (trimmed) studies is employed [20].

For all analyses, a p-value less than 0.05 was considered statistically significant.

3. Results
3.1. Search Results

As shown in Figure 1, among 1606 records initially screened, 48 were retrieved as full texts. Compared to the previous meta-analysis regarding this topic, nine new RCTs

were available (three in people with diabetes and six at high risk of diabetes), but one RCT, published in 2019 in diabetic patients, was retracted [21]. Moreover, another study published in 2015 in gestational diabetes was retracted [22], leaving 25 RCTs eligible for the present systematic review and meta-analysis [23–47].
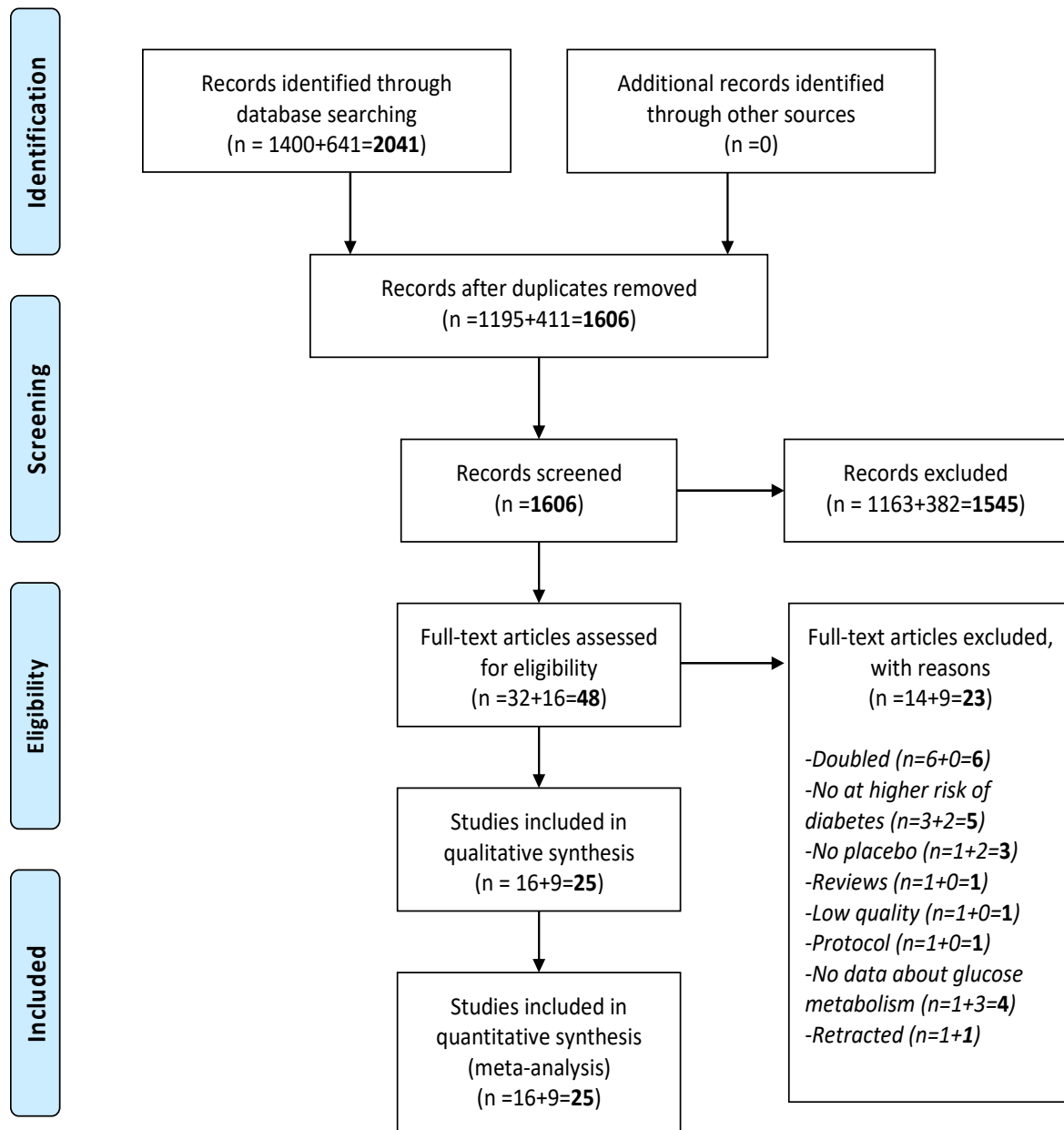

Figure 1. PRISMA flow-chart.

3.2. Study and Patient Characteristics

Full details regarding descriptive findings are reported in Supplementary Table S1 (for people with diabetes) and Supplementary Table S2 (high risk of diabetes).

Among the 13 studies including people with diabetes [23,26,31,34–43], the majority (n = 11) focused on type 2 diabetes, one among pregnant women, one was made among type 1 diabetic people. Ten RCTs had a parallel design, whilst three used a crossover design. The 13 studies followed-up 361 diabetic participants treated with Mg compared to 359 with placebo for a median of 12 weeks (range: 4–48). The participants treated with Mg were on average 50.6 (vs 49.9 in placebo) years, had a mean BMI suggestive of overweight status

and were predominantly women. Full details regarding the type of Mg supplementation are reported in Supplementary Table S1, with Mg oxide being the most used. The quality of the studies was generally high, as indicated by the Jadad's scale (Supplementary Table S1).

Twelve RCTs [24,25,27–30,32,33,44–47] investigated the effect of Mg in conditions that put people at high risk of developing diabetes. Five RCTs included participants being overweight, two among people with metabolic syndrome, two prediabetes (defined as the presence of FPG between 100 and 126 mg/dL or plasma glucose after OGTT between 140 and 200 mg/dL), two in women having polycystic metabolic syndrome, and one metabolically obese with normal weight subjects, fully reported in Supplementary Table S2. Eleven RCTs employed a parallel and only one a crossover design.

Altogether these studies followed up 477 participants treated with Mg and 480 with placebo for a median of 14 (range: 4–24) weeks. The participants treated with Mg had a mean age of 42.5 years, a mean BMI of 28.8 kg/m^2 and were predominantly males; the participants treated with placebo had a mean age of 45.6 years with a mean BMI of 28.9 kg/m^2. Among the formulations available, similarly to the RCTs included diabetic patients, Mg oxide was the most used form (Supplementary Table S2).

3.3. Meta-Analysis of the Effect of Magnesium on Glucose and Insulin-Sensitivity Parameters

3.3.1. People with Diabetes

As shown in Table 1, treatment with Mg significantly reduced FPG at follow-up in 325 participants with diabetes compared to 331 taking placebo (n = 11 studies; SMD = −0.426; 95%CI: −0.782 to −0.07; p = 0.02), this finding was characterized by a high heterogeneity (I^2 = 79.0%) (Supplementary Figure S1). Regarding HbA1c levels, Mg supplementation did not improve this parameter in 301 participants compared to 307 participants taking placebo (n = 10 studies; SMD = −0.134; 95%CI: −0.409 to 0.141; p = 0.34; I^2 = 63.7%). On the contrary, there was no evidence that Mg supplementation was able to improve fasting insulin or HOMA-IR compared to placebo in four studies including 153 people taking Mg and 149 taking placebo.

Table 1. Meta-analysis of eligible studies in diabetes and in conditions at high risk of diabetes.

Diabetes									
Analysis	**Number of Studies**	**Number of Participants**		**Meta-Analysis**			**Heterogeneity (I^2)**	**Publication Bias**		
		Mg	**Placebo**	**SMD**	**95% CI**	**p-Value**		**Egger's Bias and p-Value**	**Trim and Fill (95%CI)**	**Classic Fail Safe N**
FPG	11	325	331	−0.426	−0.782; −0.07	0.02	79.0%	−5.84; p = 0.02	Unchanged	65
HbA1c	10	301	307	−0.134	−0.409; 0.141	0.34	63.7%	5.02; p = 0.06	−0.25 (−0.52; 0.03) [2 L]	6
Insulin	4	153	149	0.596	−0.576; 1.767	0.32	96.0%	−0.16; p = 0.99	Unchanged	4
HOMA-IR	4	153	149	−0.169	−0.656; 0.319	0.50	76.9%	−3.98; p = 0.63	Unchanged	4
High risk of diabetes										
FPG	12	482	485	−0.344	−0.655; −0.03	<0.0001	81.2%	1.18; p = 0.63	−0.565 (−0.860; −0.271) [4 L]	71
2hOGTT	3	105	105	−0.35	−0.62; −0.07	0.01	0%	1.38; p = 0.15	−0.41 (−0.64 to −0.18) [2 L]	2
HbA1c	2	70	74	−0.275	−1.032; 0.481	0.48	69.3%		Only two studies	
Insulin	9	296	296	−0.059	−0.234; 0.116	0.51	11.0%	−2.17; p = 0.09	Unchanged	0
HOMA-IR	9	340	344	−0.234	−0.443; −0.025	0.028	43.2%	−0.57; p = 0.77	Unchanged	15

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.

3.3.2. People at High Risk of Diabetes

Table 1 reports the data regarding the effect of Mg, compared to placebo on glucose and insulin-sensitivity parameters. Overall, Mg supplementation significantly improved FPG in 482 subjects at high risk of diabetes compared to 485 randomized to placebo (11 RCTs; SMD = −0.344; 95%CI: −0.655 to −0.03; p < 0.0001; I^2 = 81.2%) (Supplementary Figure S2). After trimming 4 studies at the left of the mean, these results remained statistically significant (SMD = −0.565; 95%CI: −0.860 to −0.271).

Similarly, Mg significantly improved 2hOGTT in 3 studies involving 210 participants (SMD = −0.35; 95%CI: −0.62 to −0.07; I^2 = 0%). Finally, compared to placebo, Mg significantly decreases HOMA-IR in 9 studies (340 Mg vs. 344 placebo) (SMD = −0.234; 95%CI: −0.443 to −0.025; *p* = 0.028; I^2 = 43.2%) (Supplementary Figure S3), whilst no effect was observed on HbA1c or serum insulin levels (Table 1).

3.4. Meta-Regression Analysis

Figure 2 reports the meta-regression analysis in people at high risk of diabetes using as the exposure the differences in serum Mg between the treated and placebo groups at the follow-up evaluation and the parameters of glucose or insulin-sensitivity metabolism as outcomes. No significant associations were found between differences in serum Mg and differences in FPG in people affected by diabetes.
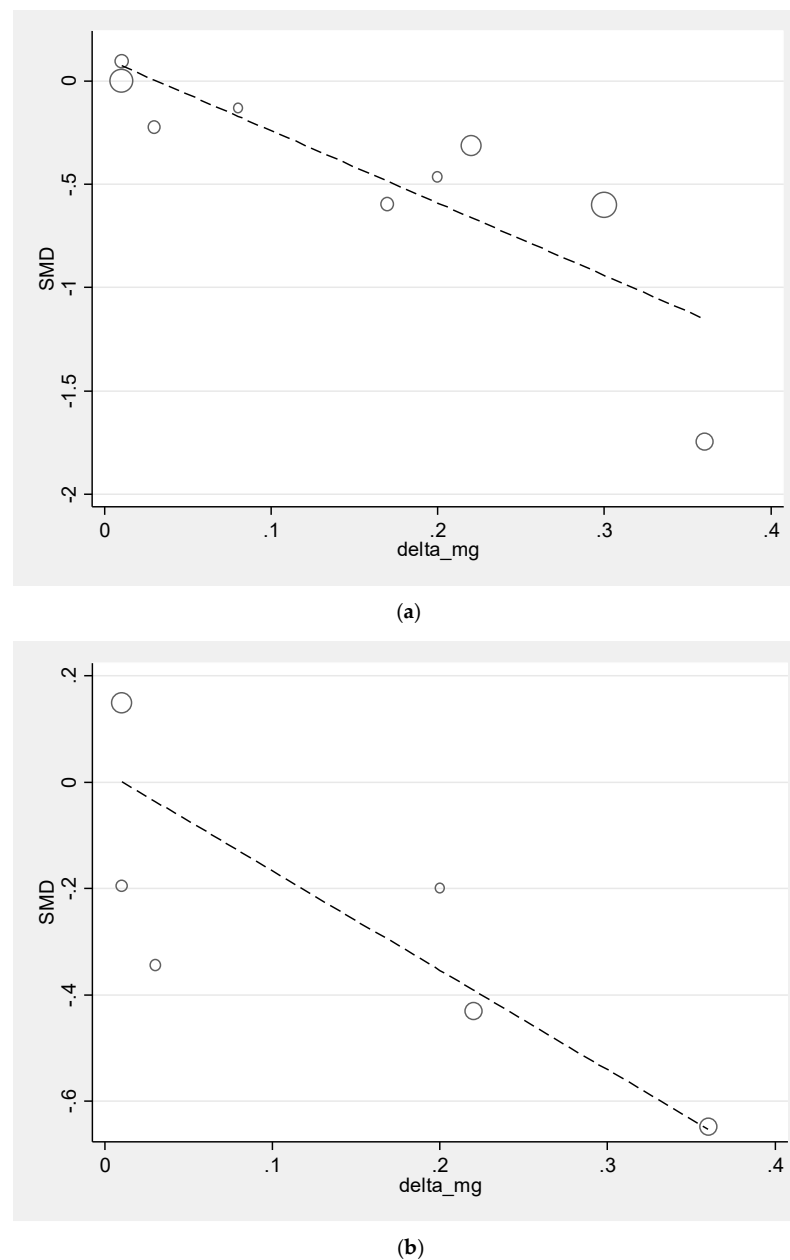

(**a**)

(**b**)

Figure 2. Meta-regression analysis of changes of serum magnesium at follow-up (treated vs. placebo) and (**a**) fasting plasma glucose and(**b**) HOMA-IR.

As shown in Figure 2a, higher differences in serum Mg between the treated and placebo groups at follow-up were associated with higher differences in FPG (beta = −3.50; 95% CI: −5.77 to −1.23; *p* = 0.008; R^2 = 71.7%) and HOMA-IR (beta = −1.87; 95% CI: −3.69 to −0.13; *p* = 0.04; R^2 = 100%) (Figure 2b) in participants at high risk of diabetes. On the contrary, as in the previous meta-analysis [9] regarding Mg supplementation on glucose and insulin sensitivity parameters, 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 moderated the present results.

3.5. Compliance and Adverse Effects

In trials reporting the number of allocated participants and those finishing the study, we observed that 82% of the allocated participants with diabetes and treated with Mg vs. 75% treated with placebo finished the study, without any difference between the groups (*p* = 0.55). Among participants with higher risk of diabetes, this figure was similar (*p* = 0.81).

No severe side effects (for example, death or onset of cardiovascular diseases) emerged in Mg or placebo groups, also considering the newly included RCTs. The most common side effects observed were of a gastrointestinal nature, particularly diarrhea.

4. Discussion

In this systematic review and meta-analysis, including 25 placebo-controlled RCTs on diabetes and conditions at high risk of diabetes, Mg supplementation significantly improved FPG levels in diabetic patients. However, the inclusion of new literature in the present updated review on patients at high risk of diabetes allowed for the observation that oral Mg supplementation not only significantly decreased plasma glucose after 2 h OGTT, but also FPG and HOMA-IR. Finally, the present review also suggests that in both people with and at high risk of diabetes, Mg supplementation is well tolerated and without significant adverse effects.

Mg may improve glucose metabolism and insulin sensitivity via several pathways. First, it is known from experimental models that chronic Mg deficiency is associated with impaired post-receptorial function, consequently reducing glucose utilization in cells [48]. Furthermore, Mg may have an action in improving insulin secretion from pancreatic beta-cells [49]. However, the present meta-analysis failed to show any significant effect of Mg compared to placebo in increasing serum insulin levels, whilst the main action of Mg seems to be attributable to a decrease in insulin resistance as shown by the improvements in HOMA-IR, particularly in those at high risk of diabetes [50], indicating that it is likely that Mg acts better when a deposit of insulin is present [9]. Moreover, findings regarding the improvement in insulin sensitivity are confirmed by other experimental results indicating that Mg is able to decrease oxidative stress [51] and inflammatory parameters [52], two main contributors of insulin resistance [53].

In this regard, it was observed in a review summarizing the role and the effect of Mg in women affected by polycystic ovary syndrome that an association between adequate Mg status and improved insulin resistance is likely, but that oral supplementation with Mg is unlikely to improve glucose and insulin resistance parameters in this specific population [54]. These findings were substantially confirmed by the RCTs included in our meta-analysis and investigating the effect of oral Mg supplementation on glucose metabolism in PCOS.

Furthermore, it is known that Mg may have important effects on other parameters closely related to glucose metabolism, such as body composition, general health, and sleep quality. In particular, serum Mg levels can be associated with inflammatory parameters, as cited before and as reported in a nice case control study involving women affected by fibromyalgia [55]. Moreover, Mg is important in muscle metabolism and it is known that muscle is involved in insulin resistance [56]. Therefore, this pleiotropic effect can help to better explain our findings. Finally, Mg could be important in ameliorating dyslipidemia

(particularly if given together with selenium) [57], body composition parameters related to adiposity [58] and sleep quality [59] and all these factors (dyslipidemia, obesity and poor sleep quality) can contribute to poor glycemic control.

As shown in a meta-regression analysis, another relevant finding from the present work is that the differences in serum Mg at follow-up between the treatment and placebo groups significantly correlated with improvements in glucose and insulin sensitivity markers people who are diabetic and in people at high risk of diabetes, confirming findings from the previous systematic review on this topic [9]. Unfortunately, due to the limited studies for other more sophisticated measurements of Mg (e.g., urinary excretion during 24 h), we were not able to assess whether these markers correlate with glucose or insulin sensitivity metabolism, indicating the necessity of future studies in this direction. An important point, however, is that a consistent proportion of the heterogeneity found in the present results is explained by the differences between the Mg serum-treated and placebo groups, indicating that RCTs characterized by a higher compliance and able to increase serum levels can improve glucose metabolism parameters.

The findings of the present meta-analysis should be interpreted within its limitations. First, RCTs consisted of small samples, with a short follow-up period, indicating the necessity of large RCTs with a long follow-up period. Second, dosage/types of Mg largely varied across RCTs: these factors may contribute to the high heterogeneity ($I^2 \geq 50\%$) observed in almost all outcomes included. Another limitation is that the evidence is mainly limited to type 2 diabetes. Future studies are needed to understand if Mg supplementation has a role in other types of diabetes, such as type 1 diabetes about which only one RCT is available.

5. Conclusions

The present systematic review with meta-analysis suggests a beneficial role of Mg supplementation compared to placebo in improving glucose parameters in diabetic patients, as well as glucose and insulin sensitivity markers in subjects at high risk of diabetes. Future larger studies, with a longer follow-up, are needed to further confirm these results.

References

1. Veronese, N.; Demurtas, J.; Pesolillo, G.; Celotto, S.; Barnini, T.; Calusi, G.; Caruso, M.G.; Notarnicola, M.; Reddavide, R.; Stubbs, B.; et al. Magnesium and health outcomes: An umbrella review of systematic reviews and meta-analyses of observational and intervention studies. *Eur. J. Nutr.* **2019**, *59*, 263–272. [CrossRef]
2. Swaminathan, R. Magnesium Metabolism and its Disorders. *Clin. Biochem. Rev.* **2003**, *24*, 47–66. [PubMed]
3. Fang, X.; Wang, K.; Han, D.; He, X.; Wei, J.; Zhao, L.; Imam, M.U.; Ping, Z.; Li, Y.; Xu, Y.; et al. Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality: A dose–response meta-analysis of prospective cohort studies. *BMC Med.* **2016**, *14*, 1–13. [CrossRef] [PubMed]
4. Dominguez, L.J.; Veronese, N.; Barbagallo, M. Magnesium and Hypertension in Old Age. *Nutrients* **2020**, *13*, 139. [CrossRef] [PubMed]
5. Kovacs, L.; Molnar, B.; Huhn, E.; Bodis, L. Magnesium substitution in pregnancy. A prospective, randomized double-blind study. *Geburtshilfe und Frauenheilkunde* **1988**, *48*, 595–600. [PubMed]
6. Gröber, U.; Schmidt, J.; Kisters, K. Magnesium in Prevention and Therapy. *Nutrients* **2015**, *7*, 8199–8226. [CrossRef] [PubMed]
7. Dominguez, L.J.; Veronese, N.; Guerrero-Romero, F.; Barbagallo, M. Magnesium in Infectious Diseases in Older People. *Nutrients* **2021**, *13*, 180. [CrossRef]
8. Barbagallo, M.; Veronese, N.; Dominguez, L. Magnesium in Aging, Health and Diseases. *Nutrients* **2021**, *13*, 463. [CrossRef] [PubMed]
9. Veronese, N.; Watutantrige-Fernando, S.; Luchini, C.; Solmi, M.; Sartore, G.; Sergi, G.; Manzato, E.; Barbagallo, M.; Maggi, S.; Stubbs, B. 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. *Eur. J. Clin. Nutr.* **2016**, *70*, 1354–1359. [CrossRef]
10. Dong, J.-Y.; Xun, P.; He, K.; Qin, L.-Q. Magnesium intake and risk of type 2 diabetes: Meta-analysis of prospective cohort studies. *Diabetes Care* **2011**, *34*, 2116–2122. [CrossRef] [PubMed]
11. Volpe, S.L. Magnesium in Disease Prevention and Overall Health. *Adv. Nutr.* **2013**, *4*, 378S–383S. [CrossRef]
12. Song, Y.; He, K.; Levitan, E.; Manson, J.E.; Liu, S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: A meta-analysis of randomized double-blind controlled trials. *Diabet. Med.* **2006**, *23*, 1050–1056. [CrossRef]
13. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J. Clin. Epidemiol.* **2009**, *62*, e1–e34. [CrossRef] [PubMed]
14. Jadad, A.R.; Moore, R.A.; Carroll, D.; Jenkinson, C.; Reynolds, D.J.M.; Gavaghan, D.J.; McQuay, H.J. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control. Clin. Trials* **1996**, *17*, 1–12. [CrossRef]
15. Association, A.D. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes—2019. *Diabetes Care* **2019**, *42*, S13–S28. [CrossRef] [PubMed]
16. Jadad, A.R. The merits of measuring the quality of clinical trials: Is it becoming a Byzantine discussion? *Transpl. Int.* **2009**, *22*, 1028. [CrossRef] [PubMed]
17. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
18. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **1997**, *315*, 629–634. [CrossRef] [PubMed]
19. Begg, C.B.; Mazumdar, M. Operating Characteristics of a Rank Correlation Test for Publication Bias. *Biometrics* **1994**, *50*, 1088–1099. [CrossRef] [PubMed]
20. Duval, S.; Tweedie, R. Trim and Fill: A Simple Funnel-Plot-Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis. *Biometrics* **2000**, *56*, 455–463. [CrossRef] [PubMed]
21. Talari, H.R.; Zakizade, M.; Soleimani, A.; Bahmani, F.; Ghaderi, A.; Mirhosseini, N.; Eslahi, M.; Babadi, M.; Mansournia, M.A.; Asemi, Z. Effects of magnesium supplementation on carotid intima–media thickness and metabolic profiles in diabetic haemodialysis patients: A randomised, double-blind, placebo-controlled trial. *Br. J. Nutr.* **2019**, *121*, 809–817. [CrossRef]
22. Asemi, Z.; Karamali, M.; Jamilian, M.; Foroozanfard, F.; Bahmani, F.; Heidarzadeh, Z.; Benisi-Kohansal, S.; Surkan, P.J.; Esmaillzadeh, A. Retracted: Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes: A randomized, double-blind, placebo-controlled trial. *Am. J. Clin. Nutr.* **2015**, *102*, 222–229. [CrossRef] [PubMed]
23. Jamilian, M.; Samimi, M.; Faraneh, A.E.; Aghadavod, E.; Shahrzad, H.D.; Chamani, M.; Mafi, A.; Asemi, Z. Magnesium supplementation affects gene expression related to insulin and lipid in patients with gestational diabetes. *Magnes. Res.* **2017**, *30*, 71–79. [CrossRef] [PubMed]
24. Joris, P.J.; Plat, J.; Bakker, S.J.L.; Mensink, R.P. Effects of long-term magnesium supplementation on endothelial function and cardiometabolic risk markers: A randomized controlled trial in overweight/obese adults. *Sci. Rep.* **2017**, *7*, 1–7. [CrossRef]
25. Solini, A.; Seghieri, M.; Giannini, L.; Biancalana, E.; Parolini, F.; Rossi, C.; Dardano, A.; Taddei, S.; Ghiadoni, L.; Bruno, R.M. The Effects of Dapagliflozin on Systemic and Renal Vascular Function Display an Epigenetic Signature. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 4253–4263. [CrossRef] [PubMed]
26. Sadeghian, M.; Azadbakht, L.; Khalili, N.; Mortazavi, M.; Esmaillzadeh, A. Oral Magnesium Supplementation Improved Lipid Profile but Increased Insulin Resistance in Patients with Diabetic Nephropathy: A Double-Blind Randomized Controlled Clinical Trial. *Biol. Trace Element Res.* **2019**, *193*, 23–35. [CrossRef] [PubMed]

27. Cunha, A.R.; D'El-Rei, J.; Medeiros, F.; Umbelino, B.; Oigman, W.; Touyz, R.M.; Neves, M.F. Oral magnesium supplementation improves endothelial function and attenuates subclinical atherosclerosis in thiazide-treated hypertensive women. *J. Hypertens.* **2017**, *35*, 89–97. [CrossRef]

28. Lee, S.; Park, H.; Son, S.; Lee, C.W.; Kim, I.; Kim, H. Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. *Nutr. Metab. Cardiovasc. Dis.* **2009**, *19*, 781–788. [CrossRef]

29. Chacko, S.A.; Sul, J.; Song, Y.; Li, X.; Leblanc, J.; You, Y.; Butch, A.; Liu, S. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: A randomized, double-blind, controlled, crossover trial in overweight individuals. *Am. J. Clin. Nutr.* **2010**, *93*, 463–473. [CrossRef] [PubMed]

30. Silva, M.D.L.L.D.S.E.; Cruz, T.; Rodrigues, L.E.; Ladeia, A.M.; Bomfim, O.; Olivieri, L.; Melo, J.; Correia, R.; Porto, M.; Cedro, A. Magnesium Replacement Does Not Improve Insulin Resistance in Patients With Metabolic Syndrome: A 12-Week Randomized Double-Blind Study. *J. Clin. Med. Res.* **2014**, *6*, 456–462. [CrossRef]

31. Navarrete-Cortes, A.; Ble-Castillo, J.L.; Guerrero-Romero, F.; Cordova-Uscanga, R.; Rojop, I.E.J.; Aguilar-Mariscal, H.; Tovilla-Zárate, C.A.; Lopez-Guevara, M.D.R. No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. *Magnes. Res.* **2014**, *27*, 48–56. [CrossRef] [PubMed]

32. Simental-Mendía, L.E.; Rodríguez-Morán, M.; Guerrero-Romero, F. Oral Magnesium Supplementation Decreases C-reactive Protein Levels in Subjects with Prediabetes and Hypomagnesemia: A Clinical Randomized Double-blind Placebo-controlled Trial. *Arch. Med. Res.* **2014**, *45*, 325–330. [CrossRef] [PubMed]

33. Guerrero-Romero, F.; Simental-Mendía, L.; Hernández-Ronquillo, G.; Rodriguez-Morán, M. Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: A double-blind placebo-controlled randomized trial. *Diabetes Metab.* **2015**, *41*, 202–207. [CrossRef] [PubMed]

34. Lima, M.D.L.; Cruz, T.; Pousada, J.C.; Rodrigues, L.E.; Barbosa, K.; Canguçu, V. The Effect of Magnesium Supplementation in Increasing Doses on the Control of Type 2 Diabetes. *Diabetes Care* **1998**, *21*, 682–686. [CrossRef]

35. De Valk, H.; Verkaaik, R.; Van Rijn, H.; Geerdink, R.; Struyvenberg, A. Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients. *Diabet. Med.* **1998**, *15*, 503–507. [CrossRef]

36. Paolisso, G.; Scheen, A.; Cozzolino, D.; Di Maro, G.; Varricchio, M.; D'Onofrio, F.; Lefèbvre, P.J. Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients. *J. Clin. Endocrinol. Metab.* **1994**, *78*, 1510–1514. [CrossRef] [PubMed]

37. Rodríguez-Morán, M.; Guerrero-Romero, F. Oral Magnesium Supplementation Improves Insulin Sensitivity and Metabolic Control in Type 2 Diabetic Subjects: A randomized double-blind controlled trial. *Diabetes Care* **2003**, *26*, 1147–1152. [CrossRef] [PubMed]

38. Solati, M.; Ouspid, E.; Hosseini, S.; Soltani, N.; Keshavarz, M.; Dehghani, M. Oral magnesium supplementation in type II diabetic patients. *Med. J. Islam. Repub. Iran* **2014**, *28*, 67. [PubMed]

39. Eibl, N.L.; Nowak, H.R.; Schnack, C.J.; Hopmeier, P.G.; Schernthaner, G.; Kopp, H.-P. Hypomagnesemia in Type II Diabetes: Effect of a 3-Month Replacement Therapy. *Diabetes Care* **1995**, *18*, 188–192. [CrossRef]

40. Corica, F.; Allegra, A.; Di Benedetto, A.; Giacobbe, M.S.; Romano, G.; Cucinotta, D.; Buemi, M.; Ceruso, D. Effects of oral magnesium supplementation on plasma lipid concentrations in patients with non-insulin-dependent diabetes mellitus. *Magnes. Res.* **1994**, *7*, 43–47.

41. Gullestad, L.; Jacobsen, T.; Dolva, L.O. Effect of Magnesium Treatment on Glycemic Control and Metabolic Parameters in NIDDM Patients. *Diabetes Care* **1994**, *17*, 460–461. [CrossRef] [PubMed]

42. Hägg, E.; Carlberg, B.C.; Hillörn, V.S.; Villumsen, J. Magnesium therapy in type 1 diabetes. A double blind study concerning the effects on kidney function and serum lipid levels. *Magnes. Res.* **1999**, *12*, 123–130. [PubMed]

43. Purvis, J.R.; Cummings, D.M.; Landsman, P.; Carroll, R.; Barakat, H.; Bray, J.; Whitley, C.; Horner, R.D. Effect of Oral Magnesium Supplementation on Selected Cardiovascular Risk Factors in Non–Insulin-Dependent Diabetics. *Arch. Fam. Med.* **1994**, *3*, 503. [CrossRef] [PubMed]

44. Mooren, F.; Krüger, K.; Völker, K.; Golf, S.; Wadepuhl, M.; Kraus, A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects–a double-blind, placebo-controlled, randomized trial. *Diabetes Obes. Metab.* **2011**, *13*, 281–284. [CrossRef] [PubMed]

45. Toprak, O.; Kurt, H.; Sarı, Y.; Şarkış, C.; Us, H.; Kırık, A. Magnesium Replacement Improves the Metabolic Profile in Obese and Pre-Diabetic Patients with Mild-to-Moderate Chronic Kidney Disease: A 3-Month, Randomised, Double-Blind, Placebo-Controlled Study. *Obes. Surg.* **2017**, *42*, 33–42. [CrossRef] [PubMed]

46. Alizadeh, M.; Karandish, M.; Jafarabadi, M.A.; Heidari, L.; Nikbakht, R.; Rezaei, H.B.; Mousavi, R. Metabolic and hormonal effects of melatonin and/or magnesium supplementation in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Nutr. Metab.* **2021**, *18*, 1–11. [CrossRef] [PubMed]

47. Farsinejad-Marj, M.; Azadbakht, L.; Mardanian, F.; Saneei, P.; Esmaillzadeh, A. Clinical and Metabolic Responses to Magnesium Supplementation in Women with Polycystic Ovary Syndrome. *Biol. Trace Element Res.* **2020**, *196*, 349–358. [CrossRef]

48. Barbagallo, M.; Dominguez, L.J.; Galioto, A.; Ferlisi, A.; Cani, C.; Malfa, L.; Pineo, A.; Paolisso, G. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol. Asp. Med.* **2003**, *24*, 39–52. [CrossRef]

49. Günther, T. The biochemical function of Mg2+ in insulin secretion, insulin signal transduction and insulin resistance. *Magnes. Res.* **2010**, *23*, 5–18. [CrossRef] [PubMed]

50. Hata, A.; Doi, Y.; Ninomiya, T.; Mukai, N.; Hirakawa, Y.; Hata, J.; Ozawa, M.; Uchida, K.; Shirota, T.; Kitazono, T.; et al. Magnesium intake decreases Type 2 diabetes risk through the improvement of insulin resistance and inflammation: The Hisayama Study. *Diabet. Med.* **2013**, *30*, 1487–1494. [CrossRef]

51. Morais, J.B.S.; Severo, J.S.; dos Santos, L.R.; Melo, S.R.D.S.; Santos, R.D.O.; de Oliveira, A.R.S.; Cruz, K.J.C.; Marreiro, D.D.N. Role of Magnesium in Oxidative Stress in Individuals with Obesity. *Biol. Trace Element Res.* **2017**, *176*, 20–26. [CrossRef]

52. Rayssiguier, Y.; Mazur, A. Magnesium and inflammation: Lessons from animal models. *Clin. Calcium* **2005**, *15*, 245–248. [PubMed]

53. Yaribeygi, H.; Farrokhi, F.R.; Butler, A.E.; Sahebkar, A. Insulin resistance: Review of the underlying molecular mechanisms. *J. Cell. Physiol.* **2019**, *234*, 8152–8161. [CrossRef]

54. Hamilton, K.P.; Zelig, R.; Parker, A.R.; Haggag, A. Insulin Resistance and Serum Magnesium Concentrations among Women with Polycystic Ovary Syndrome. *Curr. Dev. Nutr.* **2019**, *3*, nzz108. [CrossRef] [PubMed]

55. Andretta, A.; Schieferdecker, M.E.M.; Petterle, R.R.; Paiva, E.D.S.; Boguszewski, C. Relations between serum magnesium and calcium levels and body composition and metabolic parameters in women with fibromyalgia. *Adv. Rheumatol.* **2020**, *60*, 18. [CrossRef] [PubMed]

56. Capozzi, A.; Scambia, G.; Lello, S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas* **2020**, *140*, 55–63. [CrossRef] [PubMed]

57. Zhang, Q.; Qian, Z.-Y.; Zhou, P.-H.; Zhou, X.-L.; Zhang, D.-L.; He, N.; Zhang, J.; Liu, Y.-H.; Gu, Q. Effects of oral selenium and magnesium co-supplementation on lipid metabolism, antioxidative status, histopathological lesions, and related gene expression in rats fed a high-fat diet. *Lipids Health Dis.* **2018**, *17*, 1–12. [CrossRef] [PubMed]

58. Askari, M.; Mozaffari, H.; Jafari, A.; Ghanbari, M.; Mofrad, M.D. The effects of magnesium supplementation on obesity measures in adults: A systematic review and dose-response meta-analysis of randomized controlled trials. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 2921–2937. [CrossRef] [PubMed]

59. Nielsen, F.H.; Johnson, L.K. Magnesium (Mg) supplementation improves magnesium status and decreases elevated C-reactive protein in adults older than 51 years with poor quality sleep. *FASEB J.* **2010**, *24*, 325.8. [CrossRef]