ONLINE FIRST | May 5, 2017 | https://doi.org/10.15605/jafes.032.01.07

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Efficacy of Magnesium Supplementation on Glycemic Control in Type 2 Diabetes Patients: A Meta-analysis

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Abstract

Objective. To evaluate if magnesium supplementation, in addition to standard therapy, improves fasting blood sugar (FBS) and/or glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus (T2DM) compared to placebo or other comparator.

Methodology. We searched MEDLINE/PubMed, Cochrane Library, Acta Medica Philippina, Health Research and Development Information Network (HERDIN) and references of reviewed journals from 1966 to July 2015 using the following search terms: "magnesium" OR "magnesium supplementation" OR "magnesium replacement", AND randomized controlled trial AND diabetes OR diabetes mellitus OR non-insulin dependent diabetes mellitus OR diabetic OR diab* (with MeSH, where available). Studies were retrieved and rated independently using the standards provided by The Cochrane Collaboration. High quality trials were included in a systematic review and meta-analysis.

Results. Of the 689 records screened, 10 studies were included in the qualitative synthesis and 7 studies in the meta-analysis. Pooled data showed a non-significant trend towards improvement in glycemic control in the magnesium-treated group (mean difference -0.19, CI -0.58 to 0.21). There was a stronger but still non-significant trend in T2DM patients with hypomagnesemia (mean difference -1.16, CI -2.92 to 0.6).

Conclusion. Routine magnesium supplementation for improvement in glycemic control in T2DM patients cannot be recommended based on data from included studies in this meta-analysis.

Key words: diabetes, magnesium, supplementation, glycemic control, meta-analysis

INTRODUCTION

Diabetes is one of the leading causes of morbidity and mortality around the world. Its prevalence is rapidly increasing every year: by 2035, the International Diabetes Federation estimates that the number of diabetics will increase to 592 million from 382 million in 2013.[1] While diabetes is caused by a variety of hereditary and acquired factors, the diabetes pandemic has been attributed to an increasingly poor diet and sedentary lifestyle.[1] Magnesium deficiency, one of the nutritional factors associated with diabetes, has been attributed to urinary magnesium loss, inadequate intake or a combination of both.[2-5]

Magnesium is a major intracellular cation that acts as a co-factor in more than 300 enzymatic reactions, including those in the glycolytic pathway.[2] Several studies have shown that magnesium deficiency is associated with decreased insulin sensitivity and increased insulin resistance. Fasting plasma magnesium levels have been positively correlated with glucose disposal rate.[3,5,6] Oral supplementation or intravenous infusion of magnesium in diabetic patients increases acute insulin response and glucose disposal rate, and decreases insulin resistance.[7-10]

Because of these findings, magnesium has been suggested as a possible treatment for diabetes. Several randomized controlled trials on the effect of magnesium supplementation on glycemic control in diabetes have conflicting results. A meta-analysis done by Song et al., in 2006 found that magnesium supplementation for 4 to 16 weeks may be effective in reducing fasting blood sugar (FBS) levels in patients with type 2 diabetes mellitus.[11] However, glycemic control is better evaluated by HbA1c, which is less affected by acute or transient changes. We also wanted to see if any improvement in glycemic control was related to plasma magnesium levels, which was not studied in the previous meta-analysis. This study reviews available data on magnesium supplementation and its effect on glycemic control in patients with type 2 diabetes.

eISSN 2308-118x
Printed in the Philippines

Received: May 4, 2016. Accepted: July 13, 2016.
https://doi.org/10.15605/jafes.032.01.07

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ONLINE FIRST | May 5, 2017 | https://doi.org/10.15605/jafes.032.01.07

Serum Magnesium Levels in Patients with Diabetes and Insulin Resistance

Several studies have demonstrated that magnesium levels are significantly lower in patients with diabetes and in obese people with insulin resistance, compared to normal controls.[12-14] While frank hypomagnesemia (serum level less than 0.61 mmol/L) usually occurs only in patients with uncontrolled diabetes, patients with magnesium concentrations less than 0.75 mmol/L may have preclinical disease.[15]

Recommended Daily Intake and Dietary Adequacy

The recommended daily intake (RDI) in the United States for magnesium is 420 mg for males and 320 mg for females, based on magnesium balance studies.[2,4] The National Health and Nutrition Examination Survey (NHANES) of 2005-2006 showed that 45 to 80% of Americans failed to meet these daily requirements.[5] In contrast, findings from a meta-analysis showed that higher dietary magnesium intake was associated with a lower risk for incident type 2 diabetes mellitus.[16] Note that the studies on daily magnesium intake were estimated from food questionnaires and not from supplementation using magnesium salts. The major sources of dietary magnesium from these questionnaires were green leafy vegetables and nuts, which are components of a healthy diet recommended by various endocrine and diabetes societies.

Urinary Magnesium Loss in Patients with Diabetes

Patients with poorly controlled diabetes have increased urinary magnesium excretion.[13,16-18] A study by Khan et al., compared the serum and urinary magnesium and blood glucose levels of 40 diabetic patients with 26 healthy and malnourished controls. They found significantly higher urinary magnesium (30 mmol/L versus 6.3 mmol/L, $p<0.05$) and low serum magnesium (0.66 mmol/L versus 0.73 mmol/L, $p<0.05$) in patients with diabetes mellitus from pancreatic disease compared to normal individuals.[19] A recent study by Xu et al., evaluated urinary magnesium levels in patients with prediabetes, type 1 and type 2 diabetes mellitus, with different end-organ complications of diabetes. Patients with type 1 or type 2 diabetes had significantly lower serum magnesium and higher urinary magnesium excretion compared to healthy controls.[20]

Magnesium Levels, Glycemic Control and Insulin Levels

Plasma glucose levels were found to be inversely correlated to plasma magnesium levels in patients with diabetes ($rs=-0.33$, $p<0.01$). In this group, patients who were on insulin had lower mean plasma magnesium (0.84 mmol/L) compared to those on oral hypoglycemic agents (0.89 mmol/L) and non-diabetic patients (0.95 mmol/L).[3] This finding is consistent with a cross-sectional study by Kumari, which showed that 74% of the study patients with diabetes were hypomagnesemic. Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) was inversely correlated with serum magnesium levels (Spearman $r=-0.44$, $p<0.05$).[21]

Magnesium Intake, Risk of Diabetes and Insulin Resistance

Several studies demonstrated that diets with higher amounts of magnesium were associated with a significantly lower risk of diabetes, and a 100 mg/day increase in magnesium intake was associated with a 15% lower risk of diabetes.[16,21] Conversely, higher intake of magnesium-rich food was inversely correlated with serum insulin levels and HOMA-IR. Patients with high magnesium intake (mean 597 ± 224.1 mg/day or 7.99 ± 3.6 mg/kg/day) had significantly lower HOMA-IR and insulin levels compared to medium and low magnesium intake.[22]

Chronic magnesium supplementation was found to improve insulin response to glucose load and glucose disposal rate in hyperinsulinemic euglycemic clamp studies.[7,9] In a study by Wang et al., patients with T2DM who were in the upper quartile of magnesium intake (quantified through food questionnaires) had a mean HOMA-IR of 3 (a value of >3.6 interpreted as insulin resistant).[23]

Multiple prospective cohort studies have tested the efficacy of magnesium supplementation on glycemic control, with conflicting results.[10, 24-29]

METHODOLOGY

We followed the recommendations of the Cochrane Collaboration on the flow and content of conducting a systematic review/meta-analysis.

We searched the literature for relevant randomized clinical trials on oral magnesium supplementation and glycemic parameters in patients with type 2 diabetes mellitus. The authors searched MEDLINE/PubMed, Cochrane Library, Acta Medica Philippina, HERDIN and references of reviewed journals from 1966 to July 2015 using the following search terms: "magnesium" OR "magnesium supplementation" OR "magnesium replacement" AND randomized controlled trial AND diabetes OR diabetes mellitus OR non-insulin dependent diabetes mellitus OR diabetic OR diab* (with MeSH, where available)

We included only published randomized controlled studies in the English language or with English translation. The studies met the following criteria for inclusion: random assignment of treatment and control, use of placebo or alternative treatment, human subjects with non-insulin dependent diabetes mellitus/T2DM, indication of magnesium status pre- and post-treatment, and measurement of glycemic status (FBS, HbA1c) pre- and post-treatment. Each journal was evaluated for eligibility by two of the authors independently.

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Discrepancies were resolved by group discussion, with the third author assigned to adjudicate.

Data Extraction

The authors independently performed the literature search, study selection, quality assessment and data extraction. A standardized reporting form was used to independently extract data from each included study. The data collected included first author's name, year of publication, country where study was conducted, title, number of subjects, sample size, type and duration of diabetes, mean age, sex ratio, number of study groups, study design, type of magnesium supplement, equivalent dose of elemental magnesium, treatment duration, pre- and post-treatment glycemic and magnesium status (or placebo/alternative treatment phase versus magnesium phase in crossover studies). The primary outcome measures were mean reductions in FBS and HbA1c.

Data Analysis

The collected data was coded and analyzed using RevMan 5.3 software provided by the Cochrane Collaboration. The principal summary of measures used was the difference in means for the outcome measures between the magnesium-treated group versus placebo. Pre- and post-treatment (magnesium versus comparator) mean FBS and HbA1c values and standard deviations were extracted and coded into the software for incorporation into the Forrest plot. The Chi-square test was used to test for heterogeneity across studies. Subgroup analysis was done on studies with normomagnesemic and hypomagnesemic patients.

Bias Assessment

Each study was assessed for bias using the Cochrane Collaboration tool for bias risk assessment which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

For crossover studies, the domains for assessment were: appropriate crossover design, randomized treatment order, carry over effect, unbiased data, allocation concealment, blinding, incomplete outcome data and selective outcome reporting.

RESULTS

Following electronic and manual searches, a total of 12 full text articles were identified to have met the inclusion criteria. However, 2 of these did not include the outcome of interest. Three more studies were excluded from the quantitative analysis because of the use of different measures of glycemic control/utilization, but were included in the qualitative analysis. Subjects included in the studies were of similar age and sex ratio, and were treated with diet and/or oral hypoglycemic agents. The work flow for screening and assessment of journals are outlined in Figure 1.

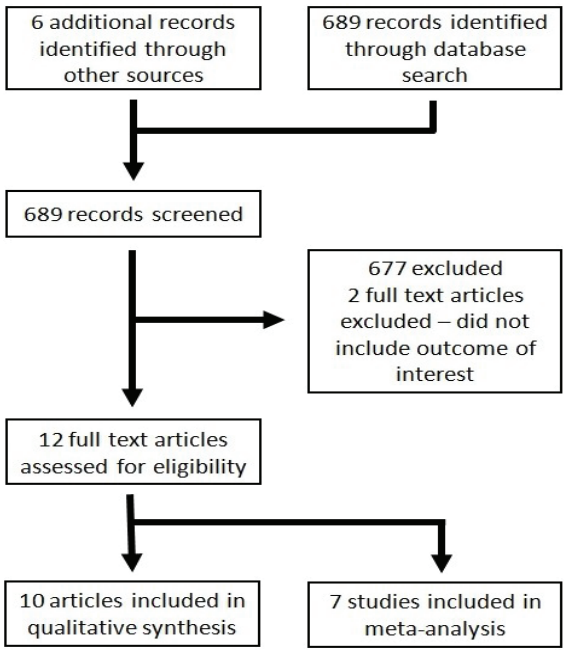

Figure 1. Flowchart for article selection for meta-analysis.

Of the 7 studies included in the meta-analysis, 2 had a crossover study design and 5 had a parallel study design. Majority of the studies included patients with normal plasma magnesium levels (>0.75 mmol/L), while 2 studies had subjects with hypomagnesemia. The studies utilized various magnesium salts with different amounts of elemental magnesium. While there is no consensus on the bioavailability of these magnesium salts, all of the studies reported an increase in plasma magnesium in the treatment arm at the end of the supplementation/ replacement period, suggesting that magnesium from the varied supplements were systemically absorbed.

The study by Eriksson et al., included patients with NIDDM and insulin-dependent diabetes mellitus (IDDM), but did not indicate if the IDDM patients had type 1 or type 2 DM.[28] Because of this, we opted to compare the data from the NIDDM group with the placebo group.

The study by de Lordes Lima compared placebo, low dose magnesium and high dose magnesium.[24] We compared the data from the high dose group with the placebo group. The studies and their respective results are described in Tables 1 and 2.

Majority of the included studies reported that they were randomized, double-blind, placebo-controlled trials. Only 2 reported the method of randomization (Rodriguez-Morán 2003[30] and Navarrete-Cortes 2014[31]), and none of them reported the method of allocation concealment and method of blinding. We were in agreement, though, that blinding was unlikely to have affected the outcomes of

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Table 1. Characteristics of populations and interventions of included studies

Author, place and year of publication	Population	Intervention, equivalent elemental magnesium	Comparator	Number of patients (Comparator/ Treatment)	Type and duration of study	Glycemic outcomes measured
Gullestad et al, Norway, 1989[35]	Elderly NIDDM[a]	Magnesium lactate, 184.5mg, No diet specified	Placebo	29/25	Parallel, 2 weeks pre-study (placebo tablets) followed by 4 months treatment	FBS[c], HbA1c[d]
Eibl et al, Austria, 1995[34]	T2DM[b] with hypomagnesemia	Magnesium citrate, 730mg, No specified diet but stated equal dietary magnesium	Placebo	20/18	Parallel, 3 months treatment	HbA1c[d]
Eriksson et al, Finland, 1995[29]	NIDDM[a]	Unspecified magnesium supplement (600mg?), No diet specified	Ascorbic Acid	27 NIDDM	Crossover, 3 months run-in period, 3 months treatment, 1 month washout, then crossover	FBS[c], HbA1c[d]
de Valk et al, Netherlands, 1998[27]	T2DM[b]	Magnesium L-aspartate HCl, 184.5mg, No diet specified	Placebo	56/56	Parallel, 1 month treatment	FBS[c], HbA1c[d]
de Lourdes Lima et al, Brazil, 1998[26]	NIDDM[a] with HbA1c >8% and hypomagnesemia	Magnesium oxide, 254mg and 508mg, No specified diet	Placebo	54/35/39	Parallel, 4 months treatment	FBS[c], HbA1c[d]
Rodriguez-Morán et al, Mexico, 2003[30]	T2DM[b] with hypomagnesemia	Magnesium chloride 50 mL 5% solution, 638g, No diet specified	Placebo	25/25	Parallel, 3 months treatment	FBS[c], HbA1c[d]
Navarrete-Cortes et al, Mexico, 2014[31]	T2DM[b]	Magnesium lactate, 360mg, No diet specified	Placebo	56	Crossover, 3 months treatment with 3 months washout, then crossover	FBS[c], HbA1c[d]

[a]NIDDM, non-insulin dependent diabetes mellitus
[b]T2DM, type 2 diabetes mellitus
[c]FBS, fasting blood sugar
[d]HbA1c, glycosylated hemoglobin

Table 2. Pre- and post-treatment glycemic control and magnesium levels in parallel studies

Author, Place and Year of Publication	Magnesium, mmol/L		HbA1c[a], %		FBS[b], mg/dL	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Gullestad et al, Norway, 1989[35]	Normal and not significantly different between groups and between pre- and post-treatment		M: 7.3 ± 1.5 P: 7.4 ± 1.6	M: 7.8 ± 1.5 P: 7.4 ± 1.6	M: 158.4 ± 41.4 P: 153 ± 48.6	M: 172.8 ± 57.6 P: 160.2 ± 54
Eibl et al, Austria, 1995[34]	M: 0.73 ± 0.8 P: 0.72 ± 0.8	M: 0.81 ± 0.1 P: 0.69 ± 0.8	M: 7.2 ± 0.7 P: 7.5 ± 0.9	M: 7.4 ± 0.9 P: 7.6 ± 1.4	No FBS[b]	
Rodriguez-Morán et al, Mexico, 2003[30]	M: 0.64 ± 0.12 P: 0.65 ± 0.09	M: 0.74 ± 0.1 P: 0.65 ± 0.07	M: 11.5 ± 4.1 P: 11.8 ± 4.4	M: 8 ± 2.4 P: 10.1 ± 3.3	M: 230.4 ± 100.8 P: 255.6 ± 70.2	M: 144 ± 43.2 P:185.4 ± 37.8
de Valk et al, Netherlands, 1998[27]	M: 0.79 ± 0.04 P: 0.77 ± 0.08	M: 0.81 ± 0.07 P: 0.77 ± 0.05	M: 8.65 ± 1.45 P: 8.72 ± 1.27	M: 9.1 ± 1.5 P: 9.1 ± 1.1	M: 212.4 ± 64.8 P: 214.2 ± 102.6	M: 196.2 ± 68.4 P: 223.2 ± 117
de Lourdes Lima et al, Brazil, 1998[26]	M: 0.73 ± 0.19 P: 0.72 ± 0.17	M: 0.80 ± 0.24 P: 0.72 ± 0.17	M: 9 ± 2.4 P: 9.3 ± 2.6	M: 9.2 ± 3 P: 9.5 ± 2.2	M: 226.8 ±75.6 P: 232.2 ± 77.4	M: 228.6 ± 75.6 P: 219.6 ± 131.4

[a]HbA1c, glycosylated hemoglobin
[b]FBS, fasting blood sugar
M, magnesium-treated group
P, placebo-treated or comparator group

Table 3. Pre- and post-treatment glycemic control and magnesium levels in crossover studies

Author, Place and Year of Publication	Magnesium, mmol/L		HbA1c[a], %		FBS[b], mg/dL	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Eriksson et al, Finland, 1995[28]	0.76 ± 0.02	M: 0.8 ± 0.01 P: 0.78 0.01	9.1 ± 0.3	M: 8.9 ± 0.3 P: 8.9 ± 0.3	169.2	M: 157.86 ± 16.2 P: 198 ± 18
Navarrete-Cortes, Mexico, 2014[31]	M: 0.9 ± 0.12 P: 0.86 ± 0.13	M: 0.95 ± 0.06 P: 0.9 ± 0.13	M: 7.9 ± 3.7 P:8 ± 3.4	M: 8.5 ± 3.7 P: 8.69 ± 4.15	M: 153.9 ± 130.8 P: 159.84 ± 97	M: 154.3 ± 140.8 P: 154.3 ± 117.1

[a]HbA1c, glycosylated hemoglobin
[b]FBS, fasting blood sugar
M, magnesium-treated group
P, placebo-treated or comparator group

FBS and HbA1c levels. All included studies provided information on missing data from attrition, including reason of attrition and group assignment (placebo or magnesium). All studies fully reported the expected glycemic outcomes. For the 2 crossover studies, there were appropriate settings and washout periods, and randomization of treatment order. Data from the different periods of the study were all reported.

The Philippine Food and Nutrition Research Institute (FNRI) recommended nutrient intake (RNI) for magnesium is 240 mg/day for males and 210 mg/day for females, or 3.5 to 5 mg/kg/day with average male weight of 60 kg and female weight of 55 kg, adapted from the World Health Organization (WHO)/Food and Agriculture Organization (FAO).[32-33] The recommendation from the WHO/FAO 2004 was based on a combination of magnesium balance studies and the absence of any evidence of magnesium deficiency at these intake levels. The report only included decreased bone density, hypocalcemia and hypokalemia as the possible consequences of magnesium deficiency.[33] We were not able to find any studies on magnesium sufficiency in the Philippines or the Southeast Asian region.

There was no significant difference in the mean post-treatment FBS and HbA1c between the magnesium supplementation groups and placebo (or other comparator) groups (Figures 2 and 3). There were wide variations in FBS and HbA1c levels of subjects since none

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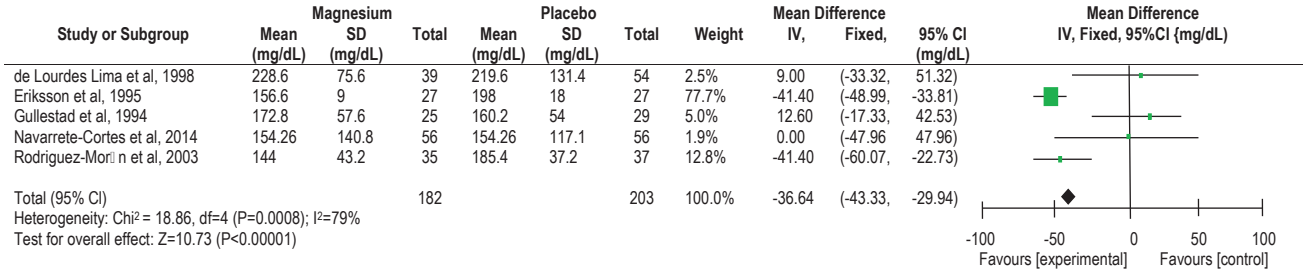

Figure 2. Weighted mean difference and forrest plot of FBS levels in magnesium-treated and placebo groups.

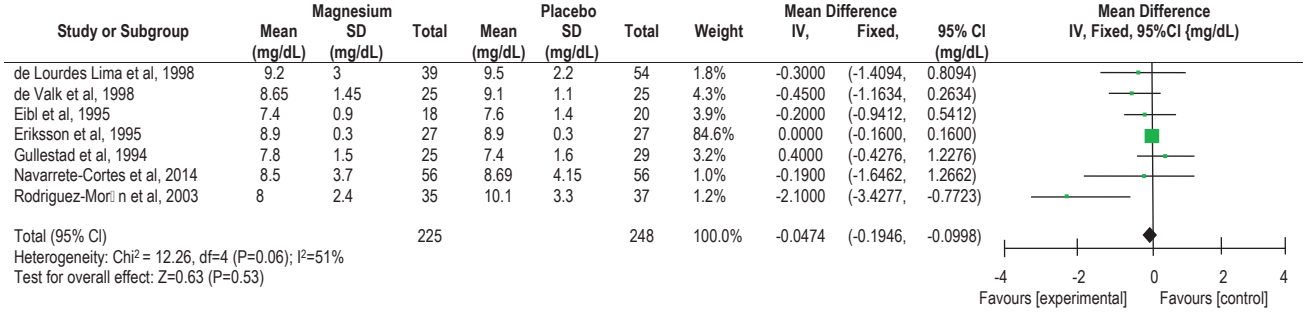

Figure 3. Weighted mean difference and forrest plot of HbA1c in magnesium-treated and placebo groups.

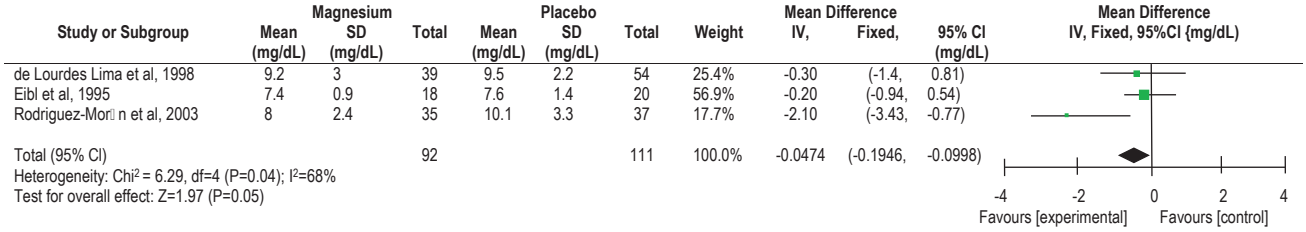

Figure 4. Weighted mean difference in HbA1c of magnesium-treated and placebo groups among subjects with hypomagnesemia (serum Mg <0.75 mmol/L).

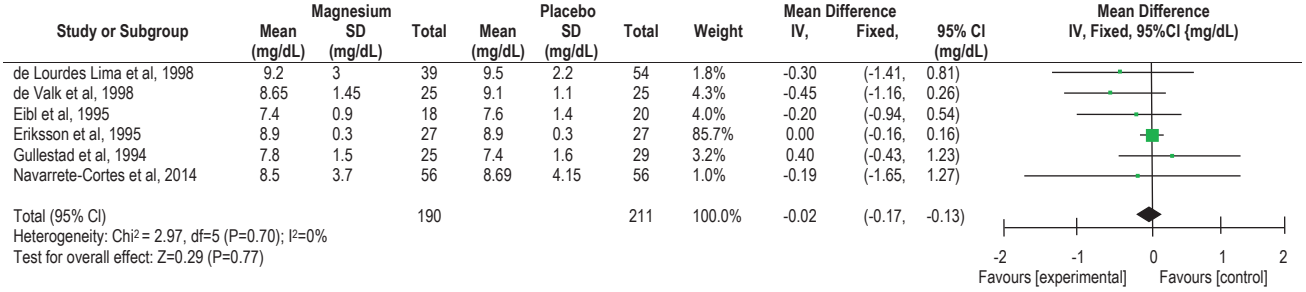

Figure 5. Weighted mean difference in HbA1c of magnesium-treated and placebo groups, analyzed without the study with severe hypomagnesemia (Rodriguez-Morán, 2003[30]).

of the studies used a glycemic range as inclusion criteria. These wide variations in FBS and HbA1c resulted to a short and broad normal distribution of values, making it difficult to conclude that there was no difference between the two groups. The differences between two groups with short and broad normal distributions may not be detected unless the magnitude of effect was very large, because of the significant overlap that will occur.

Subgroup analysis of the trials on hypomagnesemic patients showed a larger but non-significant trend toward benefit for the magnesium-treated group (Figure 4). There was moderate to substantial heterogeneity between studies, with I² of 71%, 59% and 68%, for studies with FBS as outcome, HbA1c as outcome and among hypomagnesemic patients with HbA1c as outcome, respectively (Figures 2 to 4).

DISCUSSION

In this meta-analysis of randomized controlled trials, we found no significant difference in short-term and long-term glycemic control between the two groups. There seemed to be a trend favoring magnesium supplementation,

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Table 4. Bias risk assessment for included parallel studies

Author, place and year of publication	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Gullestad et al, Norway, 1989[35]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 2: intercurrent illness	Low risk: outcomes fully reported	None identified
Eibl et al, Austria, 1995[34]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 1: rash, 1: GI effects	Low risk: outcomes fully reported	None identified
Rodriguez-Morán et al, Mexico, 2003[30]	Low risk: computer random number generator	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 2: treatment failure, 2: withdrawal of consent, 5: loss to follow up	Low risk: outcomes fully reported	None identified
de Valk et al, Netherlands, 1998[27]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data due to dropout from: 4: personal circumstances, 1: difficulty swallowing, 3: non-compliance, 7: HbA1c outside 7–11%, 1: physician-instigated change in insulin regimen	Low risk: outcomes fully reported	None identified
de Lourdes Lima et al, Brazil, 1998[26]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data due to dropout from: 20: did not follow instructions correctly, 9: other medical problems, 16: irregular use of Mg or placebo, 6: forgot to take the drug, 10: stopped due to side effects	Low risk: outcomes fully reported	None identified

Table 5. Bias risk assessment for included crossover studies

First author, place and date of publication	Appropriate crossover design	Randomized treatment order	Carry over effect	Unbiased data	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting
Eriksson et al, Finland, 1995[28]	Low risk: condition is chronic, intervention provides only temporary effect with appropriate washout	Low risk: method is appropriate and clearly described	Low risk: carry over effect was assessed and no persistent effect after washout period	Low risk: data for each period was reported	Uncertain: method of randomization not specified	Uncertain	Low risk: no missing data	Low risk: outcomes fully reported
Navarrete-Cortes et al, Mexico, 2014[31]	Low risk: condition is chronic, intervention provides only temporary effect with appropriate washout	Low risk: method is appropriate and clearly described	Low risk: carry over effect was assessed and no persistent effect after washout period	Low risk: data for each period was reported	Low risk: computer random number generator	Uncertain	Low risk: missing data explained by attrition from poor compliance, withdrawal of consent and ADR	Low risk: outcomes fully reported

particularly in the 3 studies which included diabetic subjects with hypomagnesemia (de Lourdes Lima, Eibl,[34] and Rodriguez Morán[30]). It must be noted that while baseline characteristics of patients in the magnesium and comparator arms were not significantly different, the magnesium supplementation groups had a lower mean HbA1c values at the start of the trial. Measurement of mean HbA1c change from baseline would have been more meaningful.

Only one study (Rodriguez-Morán[30]) showed a significantly lower mean HbA1c value (with a reduction in mean HbA1c from baseline) in the magnesium treated group. While this may be due to the fact that the patients in that group had much more severe hypomagnesemia (Rodriguez-Morán et al.,[30] 0.64 mmol/L ± 0.12 mmol/L versus Eibl et al.,[34] 0.73 mmol/L ± 0.08 mmol/L; and de Lourdes Lima et al.,[26] 0.73 mmol/L ± 19 mmol/L), the true effect could not be ascertained. Excluding this study from other studies with HbA1c as an outcome yields a mean difference of -0.02 (-0.17, 0.13 at 95% CI) (Figure 5).

The trend for improved glycemic control in the magnesium-treated arm may not have been statistically significant for at least 2 reasons. The treatment effect of magnesium is likely related to blood levels of magnesium, with diminishing returns with higher magnesium values. Additionally, patients included in the studies had a large variance in FBS and HbA1c values, which may lead to a failure in detecting a significant change in glycemic parameters.

CONCLUSIONS

Available data from present studies do not support a recommendation for routine magnesium supplementation in patients with T2DM with normal serum magnesium, defined in most included studies as a plasma magnesium concentration above 0.75 mmol/L. This is consistent with the ADA recommendation that micronutrient supplementation should not be given in patients without micronutrient deficiency. Only one study (Rodriguez-Morán[30]) showed a significant benefit for magnesium

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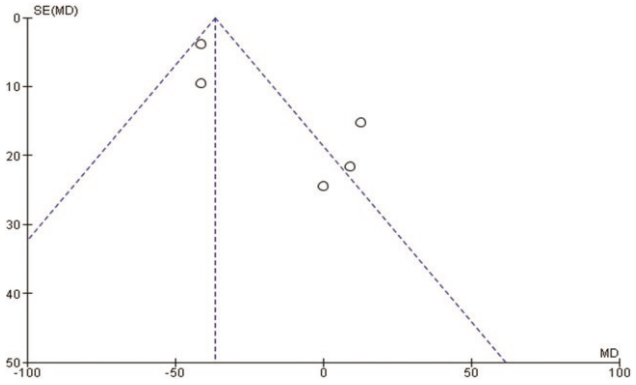

Figure 6. Funnel plot of included studies with FBS as an outcome measure.

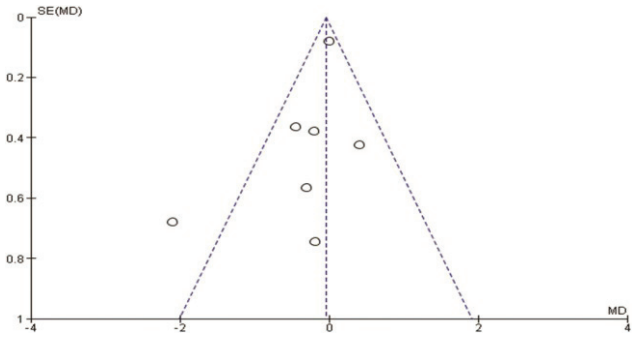

Figure 7. Funnel plot of included studies with HbA1c as an outcome measure.

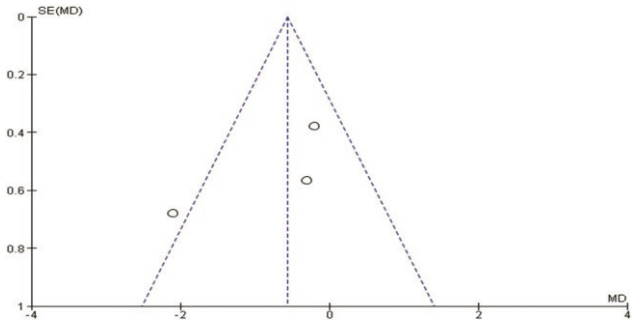

Figure 8. Funnel plot of included studies on subjects with hypomagnesemia at baseline, with HbA1c as an outcome measure.

supplementation in patients with hypomagnesemia. More studies are needed to make appropriate recommendations on magnesium supplementation for patients with type 2 diabetes.

RECOMMENDATIONS

We recommend a larger randomized controlled study of magnesium supplementation on patients with diabetes mellitus with a small HbA1c range, similar to more recent clinical trials. Investigation of other parameters, such as estimated dietary magnesium intake and use of newer anti-diabetic agents are also timely. A separate study on sufficiency of magnesium intake and serum magnesium levels will also provide better insight. A positive finding of a treatment effect in patients with suboptimal magnesium levels in future studies will be helpful in fulfilling our goal of individualized medical care by targeting specific defects in insulin secretion or action.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors have declared no conflict of interest.

Funding Source

None.

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