Effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients

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No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia

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Abstract. There are limited and conflicting data from clinical trials concerning the beneficial effects of magnesium supplementation on diabetic patients. We investigated the effects of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. A total of 98 normomagnesemic subjects with type 2 diabetes were enrolled in a randomized, crossover, double-blind, placebo-controlled trial. Participants were randomly assigned to receive magnesium lactate (360 mg elemental magnesium) or placebo for three months, followed by a three-month washout period. Treatment assignments were then reversed over an additional three months of follow-up. The primary endpoint was a reduction in fasting glucose and HbA1c. A total of 56 subjects completed the follow-up in the magnesium and placebo supplementation groups. Urinary magnesium excretion was increased following magnesium supplementation in the intervention group compared with the placebo group ($p = 0.0002$). Fasting glucose, HbA1c, insulin and HOMA-IR, as well as lipid profile, did not change significantly during treatment. We concluded that magnesium supplementation does not improve metabolic control or insulin sensitivity in diabetic subjects with normomagnesemia.

Key words: magnesium, diabetes mellitus, metabolic control, insulin sensitivity

Diabetes is a serious, chronic disease affecting a large population worldwide, particularly in developing countries [1-3]. Mexico, having approximately 10.6 million people aged more than 20 years with diabetes, is one of the top 10 countries having the highest prevalence in the world [4].

The optimal goal in the management of diabetes is to achieve, and maintain, adequate serum glucose and lipids levels and normal blood pressure to prevent or delay chronic complications of the disease [5, 6].

Magnesium plays an important role in the regulation of cellular processes, and is a cofactor

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in a wide range of metabolic reactions including those of carbohydrate metabolism [7]. Some studies have demonstrated that magnesium intake exerts a protective effect as regards the incidence of diabetes in some populations [8-10]; however, this association appears to be weaker in other populations [11].

Magnesium can affect insulin secretion and insulin signal transduction. An increase in serum magnesium could reduce insulin secretion as a consequence of a reduction in the intracellular calcium concentration in beta cells. Moreover, the binding of insulin to its receptor results in receptor phosphorylation and internalization; internalized insulin receptors phosphorylate IRS and other kinases in the insulin cascade, which results in the expression of glucose transporters [12]. All these phosphorylating reactions are dependent on magnesium. Thus, increasing serum magnesium could improve insulin function, with a consequent reduction in glycemia. However, results from clinical trials involving the effects of magnesium supplementation on glycemic control and insulin sensitivity are controversial, with some studies showing beneficial effects on metabolic control and insulin sensitivity [13, 14], but others, not [15-17].

Given the limited and controversial data from randomized clinical trials, and because these inconsistent results might be attributable to environmental factors and/or basal magnesium status, we conducted a randomized, crossover study to investigate the effects of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia.

Materials and methods

After approval of protocol by the Mexican Social Security Institute (IMSS) Research Committee, and the signed, informed consent by participants, a randomized, crossover, double-blind, placebo controlled trial was conducted.

Study participants

A total of 98 type 2 diabetic subjects, aged 30-65 yrs, with less than 15 years of disease, attending the primary care offices of the IMSS in Villahermosa, Tab., Mexico, and able to follow instructions related to the study, were included. Smoking, alcoholism, pregnancy, lactation were regarded as exclusion criteria; patients participating in other studies or receiving treatment with insulin, diuretics, digoxin, vitamins, calcium-containing drugs, or any kind of supplements were not included (*figure 1*).

All participants were asked to maintain their usual diet and physical activity over the course of the study. Normomagnesemia was defined as serum magnesium concentrations equal to or greater than 0.74 mmol/L [18].

Study treatment

Subjects in the intervention group received oral magnesium lactate; subjects in the control group received inert placebo, both for three months. Randomization was carried out using computer-generated random numbers. Participants were instructed to take two tablets of magnesium lactate (750 mg each), twice daily after meals. Thus, patients received 1.5 g of magnesium lactate/d which is equivalent to 360 mg of elemental Mg/d. The control group received two tablets, twice daily of placebo, which had the same appearance, container, dose, and time period as the tablets used in the intervention group.

Magnesium lactate and placebo tablets were provided by Laboratorios Silanes, Mexico City, Mexico. The excipient used in the tablet manufacturing included microcrystalline cellulose, croscarmellose sodium, povidone and magnesium stearate. All these ingredients are considered inactive and were the base in the preparation of the placebo tablets. The magnesium stearate level was 13 mg/tablet in both the magnesium lactate and placebo tablets. After three months of treatment, a washout period of three months was carried out. Treatment assignments were then reversed for an additional three months of follow-up. Investigators, subjects participating in the study, and assistants were blinded; only the study coordinator was aware of the treatment assignment. Adherence was evaluated by checking the empty packages brought in by the participants. Patients with an intake lower than 80% of the magnesium or placebo treatments were excluded by reason of lack of adherence.

After randomization, participants attended four visits (baseline, post-treatment, post-washout and post-treatment) (*figure 1*). Before each visit, all participants were instructed to fast for 12 h and not to perform vigorous physical activity. At each

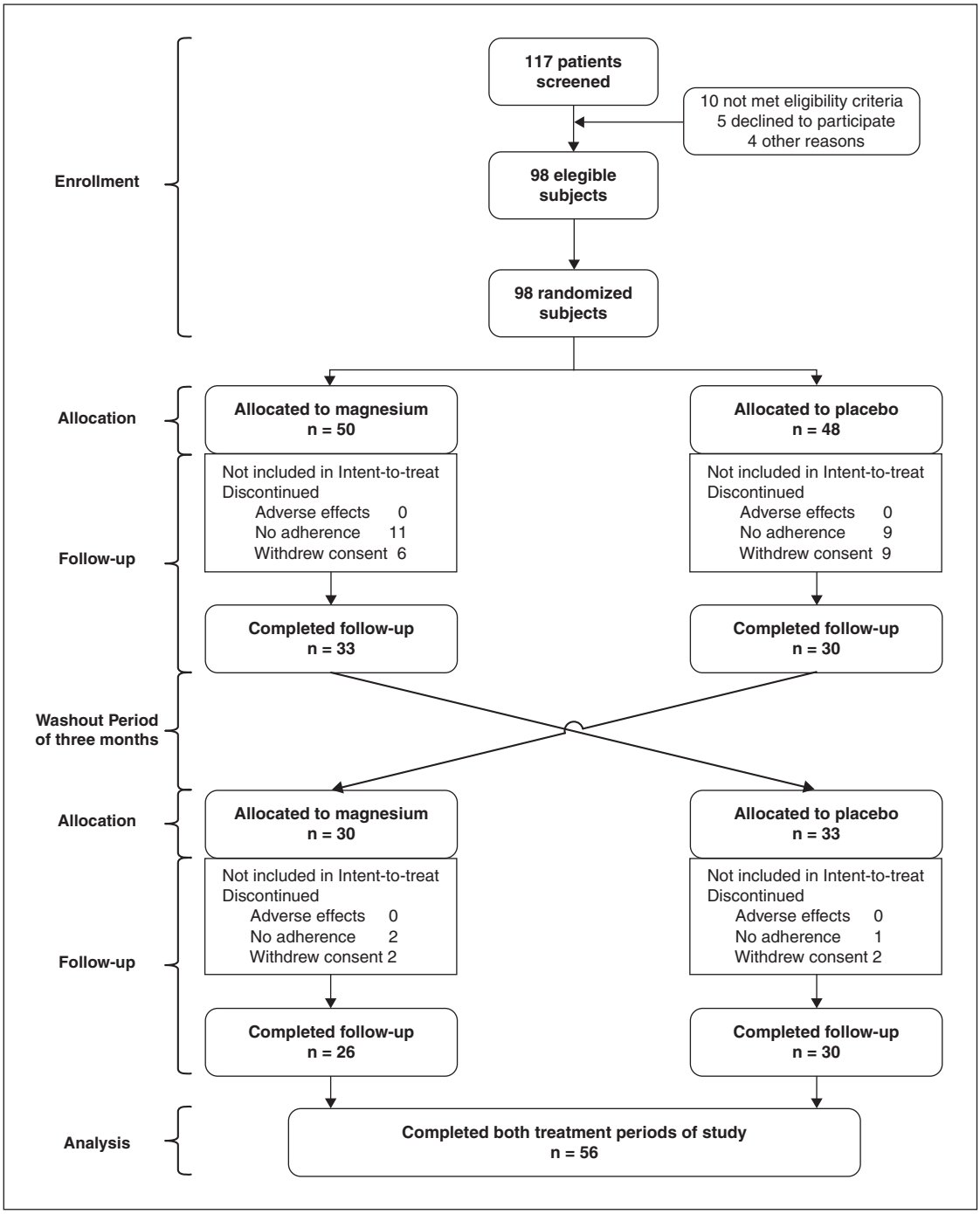

Figure 1. Flow diagram of participants.

visit, subjects underwent clinical examination, anthropometric measurements and, under fasting conditions, a venous blood sample was drawn into an untreated tube for serum, and into an EDTA-coated tube for plasma. In addition, a 24-h urine sample was collected.

Biochemical determinations

Laboratory determinations of glucose, cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), calcium, magnesium and insulin were performed using the Architect Clinical Chemistry Autoanalyzer System (Abbott Clinical Chemistry, Chicago, IL, USA). Glucose was determined by enzymatic assay with an imprecision of 5% total coefficient of variation (CV). The glycated hemoglobin assay consists of two separate concentration measurements, glycated hemoglobin (HbA1c) and total hemoglobin (THb). The HbA1c concentration was measured by immunoturbidimetric assay using a microparticle agglutination inhibition method. A six-level calibration curve was used. The calibration values are in line with those of the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry (IFCC). The HbA1c assay imprecision was <4% total CV. Insulin was measured using a chemiluminescent microparticle immunoassay (Abbott Laboratories, Chicago, IL, USA). The insulin assay imprecision was < 7% total CV. The method for measuring Mg was based on arsenazo dye, which binds preferentially to magnesium. Twenty four-hour urine specimens were collected in 30 ml of 6M HCl to prevent precipitation of magnesium complexes. After measuring the 24-h urine volume, two aliquots were obtained and stored at -70°C for future analysis. The imprecision of the serum and urine magnesium assay was <4% and <6% respectively.

Insulin resistance was estimated according to the Homeostasis Model Assessment (HOMA-IR), which was calculated by the product of fasting plasma glucose (mmol/L) and insulin (μU/mL) divided by 22.5 [19]. Corrected 24-h creatinine clearance (CrCl) expressed in mL/s/m^2 was calculated with the next formula:

$$\left[(\text{urinary creatinine, mmol/L})\,(\text{urinary 24 h volume, mL})\right] / \left[(\text{plasmatic creatinine, mmol/L})\,(86400)\,(1.73/\text{BSA, m}^2)\right]$$

Body surface area (BSA) was calculated according to Du Bois [20].

Magnesium clearance expressed in mL/s was calculated as:

$$\left[(\text{urinary magnesium, mmol/L})\,(\text{urinary 24 h volume, mL})\right] / \left[(\text{plasmatic magnesium, mmol/L})\,(86400)\right]$$

Statistical analysis

Sample size was estimated for detecting a difference of 10% or more between the two treatments with a power of 0.8 and alpha = 0.05; the sample size was 30 patients per group. However, to allow for non-compliance with treatment and assuming a dropout of 40% because of the characteristics of the population and study design, we included additional subjects per group, *figure 1*. The primary endpoint was a reduction in fasting glucose and HbA1c. Secondary endpoints included changes in insulin, HOMA-IR, magnesium, lipids and renal function markers. The D'Agostino-Pearson normality test was performed to assess consistency of data with Gaussian distribution. The relationship between serum magnesium and fasting glycemia was analyzed using the Pearson correlation test. Given the crossover design of the study, endpoints analyses were performed for completers only. We compared differences in the changes in the different variables between magnesium and placebo treatments using the two-tailed paired Student's *t* or Wilcoxon test. Differences were considered to be statistically significant for *p* values lower than 0.05. Data were processed and analyzed using GraphPad PRISMA software version 6.00 (GraphPad Software, Inc., San Diego, CA, USA).

Results

The flow chart for the magnesium-trial enrollment and design is shown in *figure 1*. Ninety eight subjects with a diagnosis of type 2 diabetes were enrolled and randomly assigned to receive magnesium supplementation or placebo.

During the first three-month treatment period, 17 patients dropped out from the intervention group; eleven because of lack of adherence and six withdrew informed consent. In the placebo group, 18 patients dropped-out; nine for lack of adherence

and nine withdrew informed consent. During the second three-month treatment period, four subjects from the intervention group and three from the placebo group dropped out because of lack of adherence or withdrew consent. So, a total of 56 (57.1%) individuals completed the follow-up (*figure 1*).

Baseline characteristics of the 56 participants who satisfactorily completed the follow-up period are shown in *table 1*. Thirty five subjects (62.5%) were uncontrolled with HbA1c values > 53.0 mmol/mol (7.0%). Twenty three patients (41%) were obese, defined as a body mass index (BMI) ≥30, and 23 subjects (41%) were overweight (BMI 25-29.9). Thirty five subjects (62.5 %) had dyslipidemia, defined as LDL ≥2.59 mmol/L (100 mg/dL). Forty six subjects (82%) had HOMA-IR values ≥2.5. Thirty one patients (55%) had abdominal obesity with waist circumference values ≥102 cm in men and ≥88 cm in women. An inverse relationship was observed between serum magnesium and fasting glycemia (r = -0.612, p <0.0001).

Table 1. Clinical characteristics at baseline of 56 subjects who completed both arms of the crossover intervention.

Clinical variable	
Age (y)	52.84 ± 8.42
Sex M/F (%)	36/64
Height (m)	1.57 ± 0.094
Body weight (Kg)	75.39 ± 15.60
BMI (Kg/m^2)	30.55 ± 5.72
Waist circumference (cm)	97.75 ± 12.76
Glycemia (mmol/L)	9.87 ± 3.86
HbA1c (mmol/mol)	61.20 (46.99, 90.49)
Insulin (pmol/L)	62.10 (45.90, 95.28)
HOMA-IR	4.16 (2.87, 6.50)
Serum magnesium (mmol/L)	0.92 ± 0.09
Urine magnesium (mmol/d)	34.95 (25.53, 48.37)
Magnesium clearance (mL/s)	0.0385 (0.0283, 0.0512)
Calcium (mmol/L)	2.325 ± 0.0825
Serum creatinine (μmol/L)	66.30 (61.0, 72.49)
Creatinine clearance (mL/s/m^2)	1.79 (1.53, 2.05)
Total cholesterol (mmol/L)	4.93 ± 0.82
HDL-Cholesterol (mmol/L)	1.16 ± 0.25
LDL-Cholesterol (mmol/L)	2.82 ± 0.72
Triglycerides (mmol/L)	1.78 (1.34, 2.36)
Uric acid (μmol/L)	261.71 (220.08, 330.11)

Values are expressed as mean ± SD or median (25^{th}, 75^{th} percentiles). All variables were measured in subjects in the fasted state.

Additional data for completers included: 91% of patients had had diabetes for less than 10 years, and 9% 11-15 years. The most important comorbidities in the target population were hypertension (26.7%) and dyslipidemia (14.3%); diabetic neuropathy was present in 3.6%; 51.8% of the enrolled patients had no associated comorbidities. The remaining 3.6% of patients exhibited hyperthyroidism and rheumatoid arthritis. Glibenclamide plus metformin was the hypoglycemic treatment in 55.3% patients, metformin in 23.2%, glibenclamide in 10.7%, and diet and exercise in 3.6% patients; the remaining 7.2% of patients received glibenclamide plus acarbose, or acarbose alone. The most important co-treatment was ECA inhibitor (17.8%). No changes in the treatment were made during follow-up

Magnesium supplementation was well tolerated and no side effects were reported. Most patients receiving magnesium lactate reported a subjective feeling of more physical energy or a better physical condition, 10% reported better sexual function, and 10% noticed a reduction of neuropathic pain.

The effects of magnesium supplementation, compared with placebo, on metabolic parameters are shown in *table 2*. There were no significant changes for glucose, HbA1c, insulin and HOMA-IR index after magnesium supplementation. Subjects in the intervention group exhibited higher urine magnesium clearance as compared to subjects in the placebo group (p = 0.0002). Other secondary outcomes, such as cholesterol, HDL-cholesterol, triglycerides, serum magnesium and markers of renal function (BUN, serum creatinine, and creatinine clearance) were not altered by supplementation or placebo.

Discussion

Our results show that magnesium supplementation does not improve metabolic control or insulin sensitivity in type 2 diabetic subjects with normomagnesemia. These findings are controversial, with early studies showing a beneficial effect of magnesium supplementation on metabolic control in normomagnesemic, elderly diabetic patients

Table 2. Effects of magnesium supplementation on clinical markers in a group of type 2 diabetic subjects who completed three months of 360 mg/d magnesium and placebo treatments in a randomized, crossover trial.

	Magnesium			Placebo			
	Baseline (n = 56)	**Post (n = 56)**	**Change**	**Baseline (n = 56)**	**Post (n = 56)**	**Change**	**P value**
BMI (kg/m^2)	30.56 ± 5.65	30.40 ± 5.61	-0.16	30.52 ± 5.80	30.52 ± 5.71	0	0.509
Waist circumference (cm)	97.05 ± 12.04	95.45 ± 12.16	-1.6	97.63 ± 13.08	95.01 ± 12.63	-2.62	0.226
Fasting glycemia (mmol/L)	8.55 (7.07, 13.45)	8.57 (6.62, 13.13)	0.02	8.88 (6.38, 12.52)	8.57 (6.38, 11.79)	-0.31	0.946
HbA1c (mmol/mol)	62.84 (46.78, 90.38)	69.40 (50.05, 96.61)	6.56	63.93 (47.98, 88.96)	71.58 (52.46, 101.97)	7.65	0.431
Insulin (pmol/L)	62.40 (43.50, 101.40)	67.20 (39.78, 97.50)	4.8	57.0 (35.88, 94.80)	60.0 (42.3, 106.98)	3.0	0.459
HOMA-IR	4.45 (2.89, 6.89)	4.51 (2.71, 9.09)	0.06	4.13 (2.56, 6.41)	4.51 (2.39, 7.60)	0.38	0.353
Serum magnesium (mmol/L)	0.90 (0.82, 0.98)	0.95 (0.86, 0.99)	0.05	0.86 (0.82, 0.95)	0.90 (0.83, 0.99)	0.04	0.390
Magnesium clearance (ml/s)	0.035 (0.028, 0.048)	0.052 (0.039, 0.071)	0.017	0.039 (0.029, 0.047)	0.036 (0.026, 0.048)	-0.003	0.0002
Calcium (mmol/L)	2.33 (2.30, 2.40)	2.33 (2.27, 2.37)	0	2.33 (2.27, 2.40)	2.33 (2.20, 2.35)	0	0.443
Serum creatinine (μmol/L)	68.07 (61.88, 75.14)	66.30 (60.11, 72.49)	-1.77	67.18 (61.88, 76.02)	66.30 (60.11, 74.26)	-0.88	0.435
CrCl * (ml/s/m^2)	1.64 (1.36, 1.94)	1.77 (1.34, 2.14)	0.13	1.65 (1.41, 1.91)	1.70 (1.36, 2.16)	0.05	0.293
Total cholesterol (mmol/L)	4.80 (4.08, 5.54)	4.87 (4.21, 5.66)	0.07	5.13 (4.43, 5.62)	4.95 (4.31, 5.62)	-0.18	0.219
HDL-Cholesterol (mmol/L)	1.09 (0.96, 1.37)	1.09 (0.93, 1.24)	0	1.11 (0.96, 1.32)	1.05 (0.88, 1.24)	-0.06	0.103
LDL-Cholesterol (mmol/L)	2.70 (2.24, 3.32)	2.54 (2.24, 3.33)	-0.16	2.87 (2.33, 3.48)	2.83 (2.27, 3.31)	-0.04	0.723
Triglycerides (mmol/L)	1.69 (1.29, 2.36)	1.94 (1.28, 2.78)	0.25	1.65 (1.24, 2.99)	1.78 (1.24, 3.03)	0.13	0.732
Uric acid (μmol/L)	276.58 (221.86, 308.11)	276.58 (243.87, 309.30)	0	264.69 (223.05, 325.95)	279.56 (243.87, 344.98)	14.87	0.277

Values are expressed as mean ± SD or median (25^{th}, 75^{th} percentiles). *P* values for differences in changes between magnesium and placebo treatments were calculated using the Wilcoxon matched-pairs signed rank test or the paired Student *t* test. * Creatinine clearance.

[14, 21]. These discrepancies could be related to differences in the methodology and target populations. In this regard, these studies were focused on elderly, type 2 diabetic subjects, and although they used a euglycemic hyperinsulinemic glucose clamp, both the sample size and follow-up period were small. However, we are in agreement with other studies that show no beneficial effects of magnesium supplementation on glycemic control [15, 16, 22].

Given that normomagnesemia does not exclude, with certainty, the presence of a magnesium deficit, it is a matter of controversy and current discussion in the field as to whether serum magnesium is a reliable enough marker to indicate magnesium supplementation. Our results, showing no effect of magnesium supplementation in type 2 diabetic subjects with normomagnesemia, strongly suggest that magnesium supplementation is not indicated in normomagnesemic individuals [23]. However, it is necessary to bear in mind that serum magnesium levels are usually decreased in patients with diabetes as a consequence of an increase in the urinary loss of magnesium. Indeed, results from previous studies conducted in hypomagnesemic individuals with type 2 diabetes consistently show the beneficial effect of magnesium on glucose and lipid profiles. Therefore, it is sensible to assess routinely serum magnesium levels in diabetic patients in order to proceed to oral supplementation when necessary.

In the present study, an inverse relationship between low serum magnesium levels and poor glycemic control was observed, as has been previously reported [24, 25]. However, we did not observe an increase in serum magnesium following magnesium supplementation, a finding that could be attributable to renal magnesium regulation mechanisms [26, 27].

Interestingly in this study, a small increase in HbA1c was observed at end of follow-up in both the magnesium and placebo groups, suggesting the worsening of glycemic control. This finding cannot be explained satisfactorily since the hypoglycemic drug dosages were not modified during the experimental period. Other unknown variables could have exerted an influence over these results. In a recent meta-analysis, Song *et al*. analyzed nine randomized, double-blind, controlled trials and suggested that magnesium supplementation may be effective in reducing fasting plasma glycemia in type 2 diabetics [17]. However, in this analysis, half of the trials reported a null effect of magnesium in the improvement of HbA1c.

As magnesium is strictly regulated, it is probable that the lack of any beneficial effect on the metabolic parameters in normomagnesemic diabetic patients is related to an appropriate magnesium status; as far as this is concerned, the increase in urinary magnesium excretion supports the statement above. It is necessary to emphasize that Tabasco, south east of Mexico, is characterized by tropical weather with rich soils that are good for green vegetables, black beans, avocado, and cacao seeds, which are included in the customary diet of the local population and may contribute to improving the body's magnesium store, thus minimizing the effect of the urinary excretion of magnesium that usually is found in diabetic patients.

Some limitations deserve mention: 1) we did not measure intracellular magnesium, so we have not certainty about the magnesium status; however, taking into account that all patients had normomagnesemia, the possibility of magnesium deficiency in the target population was minimal; 2) the supplementation period was three months; nonetheless, other studies conducted on hypomagnesemic individuals show beneficial effects within three months of magnesium supplementation; 3) we did not use the gold standard method for measurement of insulin sensitivity, that said, it is necessary to emphasize that HOMA-IR has been validated to assess insulin sensitivity in population studies; 4) we did not measure the usual diet or the physical activity of the target population; however, because all of them were diabetic patients, they had received counseling concerning diet and exercise from the physician in charge of their treatment, indications that did not change during follow-up.

The crossover design that reduced between-subject variability, the sufficiently long periods of both treatment and washout, and the use of magnesium lactate, an organic salt with high bioavailability [28], were the main strengths of our study.

Conclusions

Oral magnesium supplementation does not improve metabolic control or insulin sensitivity in type 2 diabetic patients with normomagnesemia.

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Disclosure

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Contributions

ANC conducted the clinical study, supervised data collection and helped in drafting the manuscript. JLBC conceived the idea, organized the contents and prepared the manuscript. FGR participated in the interpretation of data, analysis and the preparation of the final manuscript. RCU performed biochemical studies and helped in supervising the experiment and data collection. IEJR and HAM carried out some experiments and participated helping to draft the manuscript. CATZ and MRLG participated in the data analysis and the preparation of the manuscript. All authors read and approved the final manuscript.

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