Oral Magnesium Supplementation Improves Insulin Sensitivity and Metabolic Control in Type 2 Diabetic Subjects

A randomized double-blind controlled trial

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OBJECTIVE — To determine whether oral magnesium supplementation (as magnesium chloride [$MgCl_2$] solution) improves both insulin sensitivity and metabolic control in type 2 diabetic subjects with decreased serum magnesium levels.

RESEARCH DESIGN AND METHODS — This study was a clinical randomized double-blind placebo-controlled trial. A total of 63 subjects with type 2 diabetes and decreased serum magnesium (serum magnesium levels ≤0.74 mmol/l) treated by glibenclamide received either 50 ml $MgCl_2$ solution (containing 50 g $MgCl_2$ per 1,000 ml solution) or placebo daily for 16 weeks. Chronic diarrhea, alcoholism, use of diuretic and/or calcium antagonist drugs, and reduced renal function were exclusion criteria. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the parameter of insulin sensitivity and glucose and HbA_{1c} as parameters of metabolic control.

RESULTS — At the end of the study, subjects who received magnesium supplementation showed significant higher serum magnesium concentration (0.74 ± 0.10 vs. 0.65 ± 0.07 mmol/l, $P = 0.02$) and lower HOMA-IR index (3.8 ± 1.1 vs. 5.0 ± 1.3, $P = 0.005$), fasting glucose levels (8.0 ± 2.4 vs. 10.3 ± 2.1 mmol/l, $P = 0.01$), and HbA_{1c} (8.0 ± 2.4 vs. 10.1 ± 3.3%, $P = 0.04$) than control subjects.

CONCLUSIONS — Oral supplementation with $MgCl_2$ solution restores serum magnesium levels, improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum magnesium levels.

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Hypomagnesemia, a frequent condition in patients with diabetes (1,2), could be involved in the development of poor metabolic control and chronic complications (3,4). A large body of evidence that shows a link between hypomagnesemia and reduction of tyrosine-kinase activity at the insulin receptor level, which may result in the impairment of insulin action and development of insulin resistance, has been progressively accumulated in previous years (5–10). Although evidence suggests that magnesium supplementation could be useful in the treatment of diabetes and to prevent the development of its chronic complications (11–13), the possible benefits of magnesium administration as an adjuvant factor for the treatment of type 2 diabetes, based in a randomized controlled trial, are scarce (14–19) and controversial (19).

So, the aim of this study was to determine whether oral magnesium supplementation, as magnesium chloride ($MgCl_2$) solution, 2.5 g daily, improves insulin sensitivity and metabolic control in type 2 diabetic subjects with decreased serum magnesium levels.

RESEARCH DESIGN AND METHODS

— With approval of the protocol by the Mexican Social Security Institute (MSSI) Research Committee and after obtaining informed consent from subjects, a randomized double-blind placebo-controlled trial was carried out.

Type 2 diabetic subjects recruited from an outpatient Primary Level Medical Care Office in Durango, a city in Northern Mexico, were eligible to participate in the study if they had decreased serum magnesium levels. Based on previous results of healthy subjects from our population, in whom normal values ranged from 0.75 to 0.99 mmol/l, decreased serum magnesium levels were defined by magnesium concentration ≤0.74 mmol/l (20).

Before their inclusion at the study, all of the subjects were clinically evaluated and laboratory tested in order to determine the presence of chronic diarrhea, alcohol intake (≥30 g per day), use of diuretic and/or calcium antagonist drugs, and reduced renal function (exclusion criteria). In addition, subjects receiving magnesium supplementation were not included.

The primary trial end point was the change in insulin sensitivity and metabolic control. Sample size was estimated based on a statistical power of 80%, α value 0.05, and allowing for nonimprovement in the serum insulin level of 35 and 75% for the subjects receiving magne-

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Abbreviations: HOMA-IR, homeostasis model assessment for insulin resistance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

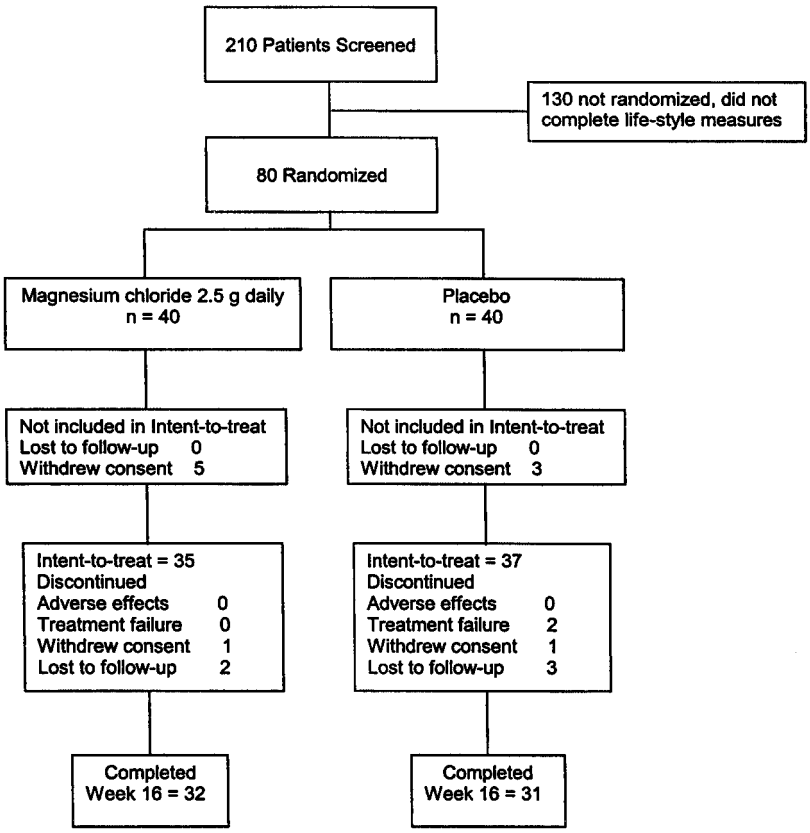

Figure 1—*Study participant flow diagram.*

sium supplementation and placebo, respectively. The required sample size to detect a treatment effect was 24 subjects per group (21).

A total of 65 eligible subjects were enrolled and randomly allocated to receive either magnesium supplementation or placebo daily for 16 weeks. We used the $MgCl_2$ solution (50 g $MgCl_2$ per 1,000 ml solution [5% solution]) because $MgCl_2$ solution shows a higher bioavailability than other commercial magnesium preparations (22). In fasting conditions, subjects in the $MgCl_2$ group drank 50 ml of the 5% solution (2.5 g $MgCl_2$ daily).

Computer-generated random numbers were used to assign participants to oral magnesium supplementation or placebo groups. The final distribution was as follows: 32 subjects in the $MgCl_2$ group (group A) and 31 subjects in the placebo group (group B) (Fig. 1).

All of the subjects withdrew pharmacological treatment and were advised to consume a diet with >50% of daily calories from carbohydrates, <10% from saturated fat, 20% from mono- and polyunsaturated fat, and ~1 g protein per kg ideal body wt per day for the 3 months before the beginning of the trial (23). In addition, and according to age and physical condition of each participant, all of the subjects were advised to perform physical activity. The goal was achieved when the subjects performed 30 min of physical activity at least three times per week. After 3 months of lifestyle intervention, glibenclamide was started and individually adjusted to achieve glucose control. Subjects who reached serum glucose levels ≥16.7 mmol/l during the lifestyle intervention period began pharmacological treatment and were not included in the study (Fig. 1).

At baseline and after 16 weeks of treatment, anthropometric measurements, HbA_{1c}, lipid profile, serum glucose, and serum insulin and magnesium levels were measured. Furthermore, serum glucose and magnesium levels were measured every 4 weeks. The type 2 diabetic patients and the personnel assessing outcomes were blinded to group assignment. Subjects in the group A received 2.5 g $MgCl_2$ daily, and those in group B received placebo.

Adherence to pharmacological treatment and lifestyle intervention was assessed every month by personal interview, tablet count and remnant solution measurement, and independent interview with the individual in charge of preparing meals for the family.

Measurements. Height and weight were taken using standard protocols with the subjects in light clothing and without shoes. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Waist circumference was taken as the minimum circumference at umbilicus level.

Serum glucose was measured by the glucose-oxidase method with the intra- and interassay variations of 2.5 and 4.0%, respectively. Insulin levels were measured by radioimmunoassay with intra- and interassay variation coefficients of 4.5 and 6.9%, respectively. Serum magnesium concentrations were measured by colorimetric method, with intra- and interassay variations of 1.0 and 2.5%, respectively.

The homeostasis model assessment for insulin resistance (HOMA-IR) (fasting glucose [mmol/l] × fasting insulin [μUI/ml]/22.5) was used for estimating insulin sensitivity (24).

Statistical analysis. The preplanned intent-to-treat analysis of the primary study end point was done for all the randomly allocated participants who satisfactorily completed the follow-up (Fig. 1).

To establish the differences between the groups, we used two-tailed unpaired Student's *t* test for comparison of normally distributed variables (Mann Whitney *U* test for skewed data) or the χ^2 test for categoric variables. Two-tailed paired *t* test (or Wilcoxon's test) was performed before and after treatment comparisons. A 95% CI was considered, and a *P* value <0.05 defined the level of statistical significance. Data analysis was performed using the SPSS version 10.0 statistical package.

RESULTS — A total of 210 patients were screened (Fig. 1). Of these, 130 subjects did not satisfactorily complete the phase of lifestyle intervention and 80 that fulfilled the inclusion criteria were randomized to receive either $MgCl_2$ solution or placebo. Eight subjects withdrew consent and were not included in the intent-to-treat period; finally, 35 subjects were included in the $MgCl_2$ group and 37 in

Table 1—*Baseline characteristics of subjects randomly allocated to receive either magnesium chloride 2.5 g daily ($MgCl_2$ group) or placebo (control group) for 16 weeks*

	$MgCl_2$ group (n = 32)		Control group (n = 31)	
	Baseline*	End	Baseline*	End
Age (years)	59.7 ± 8.3	—	54.1 ± 9.6	—
Time since diagnosis of diabetes (years)	8.8 ± 4.9	—	9.4 ± 5.5	—
BMI (kg/m^2)	27.6 ± 9.1	27.7 ± 9.6	28.6 ± 4.2	28.9 ± 4.7
Weight (kg)	72.9 ± 10.7	73.1 ± 10.4	69.3 ± 10.1	69.6 ± 9.9
Waist-to-hip ratio	0.98 ± 0.06	0.98 ± 0.07	0.96 ± 0.04	0.96 ± 0.06
Systolic blood pressure (mmHg)	148.3 ± 32.3	140.2 ± 28.1	138.1 ± 25.6	135 ± 19.6
Diastolic blood pressure (mmHg)	86.3 ± 17.0	82.7 ± 16.4	80.5 ± 14.6	79.1 ± 13.5
Fasting glucose (mmol/l)	12.8 ± 5.6	8.0 ± 2.4†	14.2 ± 3.9	10.3 ± 2.1‡§
HbA_{1c} (%)	11.5 ± 4.1	8.0 ± 2.4†	11.8 ± 4.4	10.1 ± 3.3‡§
Fasting insulin (mmol/l)	47.4 ± 30.0	67.8 ± 39†	48.6 ± 34.8	75.6 ± 33.0‡§
HOMA-IR index	4.3 ± 1.2	3.8 ± 1.1†	4.7 ± 1.5	5.0 ± 1.3
Total cholesterol (mmol/l)	6.8 ± 1.7	6.4 ± 1.9	7.1 ± 1.4	7.0 ± 1.7
HDL cholesterol (mmol/l)	0.9 ± 0.2	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
LDL cholesterol (mmol/l)	4.8 ± 1.6	4.7 ± 1.8	4.9 ± 2.0	4.8 ± 2.2
Triglycerides (mmol/l)	2.4 ± 1.4	2.3 ± 1.5	2.5 ± 1.1	2.5 ± 1.6
Magnesium (mmol/l)	0.64 ± 0.12	0.74 ± 0.10†	0.65 ± 0.09	0.65 ± 0.07§
Calcium (mmol/l)	2.5 ± 0.4	2.5 ± 0.5	2.4 ± 0.4	2.4 ± 0.4
Calcium-to-magnesium ratio	3.9 ± 3.3	3.4 ± 3.2†	3.7 ± 3.4	3.7 ± 3.5

Data are means ± SD. *At baseline, there were no significant differences for any parameters between both groups; †$P < 0.05$ from beginning to end for magnesium-supplemented subjects; ‡$P < 0.05$ from beginning to end for control subjects; §$P < 0.05$ at end of the study between magnesium-supplemented and control subjects.

the placebo group. Nine subjects dropped-out (three in $MgCl_2$ group and six in placebo group) (Fig. 1). Magnesium supplement was well tolerated, and there were no serious adverse events or side effects due to $MgCl_2$ or placebo. Slight abdominal and unspecific bone pain in the first month, which did not require treatment or discontinuation of magnesium administration, was the most frequent side effect in the magnesium-supplemented subjects (37.5%). In addition, slight diarrhea with duration <2 days that did not require interruption of the treatment was present in two magnesium-supplemented (6.25%) and one control (3.2%) patient.

Altogether, 63 subjects who satisfactorily completed the follow-up were included in the analysis of data. Adherence to treatment was achieved for 32 (91.4%) subjects in the $MgCl_2$ group and 31 (88.6%) subjects in the placebo group.

From the beginning of the study, the oral hypoglycemic drug used was glibenclamide (5 mg t.i.d.), in doses that remained without change for all participants during the study. In addition, there were no significant differences for treatment with other drugs, such as ACE inhibitors, statins, etc., between both groups. In the same way, other complications, such as cardiovascular disease, were also similarly distributed (68 vs. 71% for the magnesium-supplemented and control patients, respectively).

Table 1 shows the characteristics of the evaluated participants, which at the beginning of the study did not differ between the groups. On the other hand, at the end of the study the serum magnesium levels showed a significant increase in the subjects who received $MgCl_2$ and remained without significant change in the control subjects. In addition, subjects in both groups had reduced fasting glucose and HbA_{1c}, which were significantly lower in the magnesium-supplemented than in the control subjects. Finally, fasting insulin levels increased in the subjects of both groups, but only subjects who received $MgCl_2$ significantly reduced their HOMA-IR index.

Magnesium levels in the $MgCl_2$ group decreased by the first 4 weeks of treatment, showing a gradual and sustained increase in the following weeks, whereas serum magnesium in the control subjects did not show significant variations (Fig. 2).

CONCLUSIONS — This study shows the benefits of oral magnesium supplementation as an adjuvant therapy for reducing fasting glucose, HbA_{1c}, and HOMA-IR index in subjects with type 2 diabetes and decreased serum magnesium levels treated with glibenclamide.

In the early 1980s, the importance of magnesium on insulin sensitivity was suggested (25,26) and in following years was supported by clinical evidence showing the essential role of magnesium on insulin-mediated glucose uptake (17,27,28). However, the benefits of chronic administration of magnesium salts given to subjects with type 2 diabetes is controversial (4,29,30) and remains to be adequately evaluated.

In this study, subjects who received magnesium supplementation showed an important increase in serum magnesium concentration (15.5%) and reductions of fasting glucose (−37.5%), HbA_{1c} (−30.4%), and HOMA-IR index (−9.5%) that were more significant than those observed in control subjects, despite the fact that time since diagnosis of diabetes, doses and type of hypoglycemic drugs used, and lifestyle intervention were similar. In this regard, although serum glucose (−27.5%) and HbA_{1c} (−14.4%) levels were reduced in control subjects, HOMA-IR index

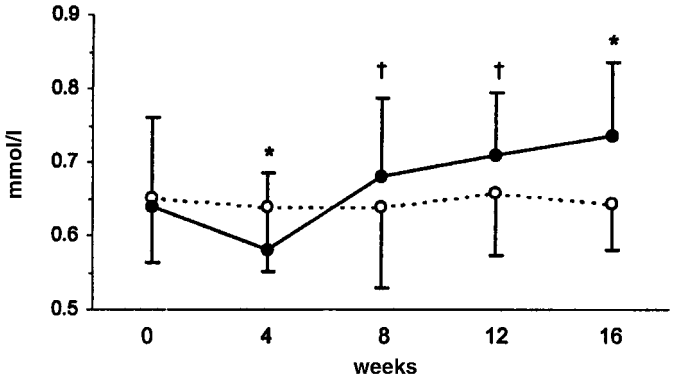

Figure 2—*Mean and SD of serum magnesium in all participants evaluated (●, 32 $MgCl_2$ recipients; ○, 31 placebo recipients). Magnesium levels in the subjects who received $MgCl_2$ showed a significant reduction for the first month, followed by a sustained and significant increase. Until the end of the study, subjects who received $MgCl_2$ achieved a significant increase of serum magnesium levels.* $^*P < 0.001$; $^†P < 0.05$.

(6.4%) increased and there were no significant variations in serum magnesium levels (−1.3%). This could be explained by taking into account the fact that control subjects remained with impaired metabolic control (average serum glucose and HbA_{1c} 10.3 mmol/l and 10.1%, respectively), one of the most important sources for magnesium reduction. These findings support the necessity of oral magnesium supplementation to achieve an increase in serum magnesium concentration and to improve insulin sensitivity in type 2 diabetic subjects with decreased serum magnesium levels.

On the other hand, although time since diagnosis of diabetes and doses of glibenclamide in the subjects of both groups were similar, at the end of the study insulin levels in the magnesium-supplemented group were lower than those in the control group. This is a controversial finding because there are previous reports showing a high insulin response in subjects with low serum magnesium levels (26,30), and yet other reports (2,7) show an impairment of insulin secretion in magnesium deficiency subjects. In this regard, it is necessary to take into account the fact that the participants in our study were treated with sulfonylureas, which exert secretory stimuli on pancreatic β-cells (31). However, whether the lower insulin levels that we documented in the magnesium-supplemented subjects were a direct effect of magnesium on β-cell or a consequence of improvement in the insulin-mediated glucose disposal cannot be adequately elucidated in this study; as such, further research is needed to address this issue.

In addition, magnesium-supplemented subjects showed a significant reduction in HOMA-IR index values. The decrease of magnesium concentration results in both defective tyrosine-kinase activity and reduction of autophosphorylation on the β-subunit at the insulin-receptor level (5,32), exerting deleterious effects on glucose metabolism due to insulin sensitivity reduction (2,7–9,31–34), which contributes to poor metabolic control in diabetic subjects (1,3,35,36). Thus, the main question is not related to the benefits of magnesium supplementation in the treatment of diabetic subjects, but rather to the type, dose, and time of administration of magnesium salts. Based on improvement of metabolic control and minimal side effects, it seems to be recommendable to add $MgCl_2$ solution as an adjuvant therapy for patients with type 2 diabetes and decreased serum magnesium levels, at least by 4 months. In addition, for adequate surveillance of magnesium levels in patients with type 2 diabetes, determination of serum magnesium must be done twice a year because magnesium levels have a propensity to decline (4).

Interestingly, in the magnesium-supplemented subjects, serum magnesium concentration showed a significant decrease by the first month, followed by a gradual and sustained increase in the following months. This early change in serum magnesium could be related to a shift of magnesium into intracellular stores, thus causing magnesium compartment redistribution; however, because we did not measure intracellular magnesium, we cannot be sure that this is actually the case. This finding is in contrast with that reported by Lima et al. (16), showing that diabetic subjects who received magnesium oxide (41.4 mmol/l) for 1 month achieved serum magnesium levels similar to those of healthy control subjects. Differences in magnesium salt and doses used could explain the divergence between both studies. In addition, and most importantly, neither Lima et al. (16) nor us measured the duration of hypomagnesemic status or magnesium pool distribution, which are powerful confounding variables that must be controlled for in order to demonstrate the nature of early serum magnesium variations in magnesium-supplemented subjects.

Several limitations of this study deserve mentioning. First, we did not measure erythrocyte or lymphocyte magnesium content. As magnesium is a predominantly intracellular ion, its serum measurements are not representative of magnesium status or intracellular pool. In this regard, significant intracellular magnesium depletion could be seen with normal serum concentrations (37); however, because we only included diabetic subjects with decreased serum magnesium levels, this potential limitation did not influence (or minimally influenced) our objective and conclusions. Second, we did not measure pancreatic store or β-cell function, which influence pancreatic insulin secretion; in this regard, because diabetic subjects in both groups had similar time since diagnosis of diabetes and received the same type and doses of sulfonylureas, this potential limitation is also slight. In addition, because diabetic patients usually require pharmacological treatment to achieve metabolic control, all of the subjects received glibenclamide, which does not influence insulin sensitivity, in order to minimize the influence of antidiabetic agents on our results. Finally, it was not possible to calculate baseline or daily food and water intake in terms of magnesium. However, because there are not variations in the source of water in Durango, the subjects received similar foods and were randomly allocated, again only minimally influencing the results.

In conclusion, oral magnesium supplementation with 2.5 g $MgCl_2$ restores serum magnesium and improves insulin

sensitivity in subjects with type 2 diabetes and decreased serum magnesium levels, thus contributing to metabolic control.

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