The Effect of Magnesium Supplementation in Increasing Doses on the Control of Type 2 Diabetes

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OBJECTIVE — Hypomagnesemia occurs in 25–38% of patients with type 2 diabetes. Several studies have suggested an association between magnesium (Mg) depletion and insulin resistance and/or reduction of insulin secretion in these cases. Our purpose was to evaluate if Mg supplementation (as magnesium oxide [MgO]) would improve metabolic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied 128 patients with type 2 diabetes (32 men, 96 women, aged 30–69 years), treated by diet or diet plus oral antidiabetic drugs, in the Bahia Federal University Hospital, Brazil. Patients at risk for hypomagnesemia or with reduced renal function were excluded. This study was a clinical randomized double-blind placebo-controlled trial. Patients received either placebo, 20.7 mmol MgO, or 41.4 mmol MgO daily (elementary Mg) for 30 days. Mg concentrations were measured in plasma, in mononuclear cells, and in 24-h urine samples. Fasting blood glucose, HbA_1, and fructosamine were used as parameters of metabolic control.

RESULTS — Of the patients, 47.7% had low plasma Mg, and 31.1% had low intramononuclear Mg levels. Intracellular Mg in patients with diabetes was significantly lower than in the normal population (62 blood donors; 1.4 ± 0.6 vs. 1.7 ± 0.6 μg/mg of total proteins). No correlation was found between plasma and intracellular Mg concentrations ($r = -0.179$; $P = 0.15$) or between Mg concentrations and glycemic control ($r = -0.165$; $P = 0.12$). Intracellular Mg levels were lower in patients with peripheral neuropathy than in those without (1.2 ± 0.5 vs. 1.5 ± 0.6 μg/mg). Similar findings were observed in patients with coronary disease (1.0 ± 0.5 vs. 1.5 ± 0.6 μg/mg). In the placebo and in the 20.7 mmol Mg groups, neither a change in plasma and intracellular levels nor an improvement in glycemic control were observed. Replacement with 41.4 mmol Mg tended to increase plasma, cellular, and urine Mg and caused a significant fall (4.1 ± 0.8 to 3.8 ± 0.7 mmol/l) in fructosamine (normal, 1.87–2.87 mmol/l).

CONCLUSIONS — Mg depletion is common in poorly controlled patients with type 2 diabetes, especially in those with neuropathy or coronary disease. More prolonged use of Mg in doses that are higher than usual is needed to establish its routine or selective administration in patients with type 2 diabetes to improve control or prevent chronic complications.

Magnesium, the fourth most abundant cation in the organism and the second in intracellular environment, takes part in more than 300 enzymatic reactions (1). Because magnesium is a predominantly intracellular ion, serum and plasma measurements may not be representative of the total body content, and a significant ion depletion with normal serum levels may occur (2). Erythrocyte, mononuclear cell, and muscle have been used for determination of intracellular magnesium concentrations (3). Mononuclear cells are probably the compartment that best correlates with muscular magnesium (4).

Hypomagnesemia has been shown to occur in 25–38% of patients with diabetes, especially in those without good metabolic control (5–10). Magnesium modulates glucose transport through the membranes and is a cofactor in several enzymatic systems involving glucose oxidation (11). Its deficiency may increase insulin resistance or may be its result (12). It is an ATPase allosteric effector involved in inositol transport and possibly contributes to the prevention or delay of the development of chronic complications (13).

Some observations have suggested that chronic magnesium supplementation may be useful in the treatment of patients with diabetes, improving the glycemic control and preventing the development of chronic complications (14,15). However, studies diverge as to the amount of the daily dose, the period of replacement, and the degree of glycemic control of the patients under treatment (16–19).

The aim of this study was to evaluate the effect of magnesium in increasing doses on the control of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

This study was performed on 128 patients with type 2 diabetes without good metabolic control ($HbA_{1c} > 8.0$ %), treated by diet or diet plus oral hypoglycemic drugs, seen in the Diabetic Clinic of Bahia Federal University Hospital (Hospital Universitário Professor Edgard Santos), Salvador-Bahia-Brazil. The oral agents used were sulfonylureas (glybenclamide) in 106 patients and biguanides (metformin) in 3 patients. Two patients used a combination of glybenclamide and metformin. Seventeen were treated by diet only. Exclusion criteria were reduction of renal function, expressed by creatinine clearance <70 ml · min^{-1} · 1.73 m^{-2}; age >70 years; use of diuretics; persistent diarrhea; and alcoholism. A control group of 57 blood donors was used in the study as reference values for magnesium concentrations.

Study design

The study design was a clinical random-

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Received for publication 13 August 1997 and accepted in revised form 8 January 1998.

Abbreviations: RV, reference value.

Table 1—*Descriptive analysis of sample characteristics*

	Group1 Placebo	Group 2 MgO (20.7 mmol)	Group 3 MgO (41.4 mmol)
n (%)	54 (42.2)	35 (27.3)	39 (30.5)
Age (years)	55.5 ± 8.3	55.4 ± 10.2	51.2 ± 11.0
Sex			
Men	13 (24.1)	11 (31.4)	8 (30.5)
Women	41 (75.9)	24 (69.0)	31 (79.5)
Duration of diabetes (years)	7.3 ± 5.4	7.2 ± 4.9	7.1 ± 5.5
BMI (kg/m²)	25.5 ± 6.5	25.3 ± 8.0	25.5 ± 6.5

Data are means ± SD or *n* (%).

ized double-blind placebo-controlled trial. The patients were initially subjected to a clinical and laboratory evaluation and then randomized to receive placebo (group 1) or magnesium oxide (20.7 or 41.4 mmol/day MgO, in three doses) (groups 2 and 3) for 30 days. After this period, patients were subjected to a subsequent evaluation when compliance to treatment was assessed. All subjects gave their informed consent, and the study was approved by the ethics committee of our institution.

Analytical procedures

Laboratory tests performed were determinations of fasting blood glucose (glucose oxidase; reference value [RV], 3.9–6.3 mmol/l), HbA_1 (ionic exchange resin; RV, 6.0–8.0%), and fructosamine (nitrotetrazolium blue reduction; RV, 1.87–2.87 mmol/l) and determinations of magnesium in plasma (RV, 0.70–0.88 mmol/l), 24-h urine (RV, 50–150 mg/24 h), and mononuclear cells (RV, 1.07–1.31 μg/mg of protein) by atomic absorption spectrophotometry.

Mononuclear cells separation was performed as follows. All reagents used for white cell isolation were washed with HCl and deionized water. Whole blood was collected in heparinized vacutainer tubes. Ten ml of whole blood was layered on 3 ml of Histopaque (Sigma; n 1077) and centrifuged at 400*g* for 30 min at room temperature (20). The plasma was separated, and the mononuclear cells were aspirated by Pasteur's pipettes, layered into another tube, washed three times with 0.9% NaCl, and frozen at −35°C until ready for assay. The magnesium content of cells was measured after lysis by defrosting and measured by atomic absorption spectrophotometry. Magnesium concentration in mononuclear cells was expressed as micrograms per milligram total protein. Cell protein was measured using the method described by Lowry and modified by Rodrigues (21). The final suspension consisted of a mean of 97.5% lymphocytes, 2.3% monocytes, and 0.15% neutrophils.

All the assays were completed in the Endocrine Division Laboratory of Bahia Federal University Hospital. The protein determination in mononuclear cells was performed in the Department of Biochemistry of Bahia Federal University.

Statistical analysis

Continuous quantitative data are expressed as means ± SD. Two-tailed parametric tests were used for comparison of normally distributed variables. Nonparametric tests were used to compare variables when the assumption of normal distribution was not met. After preliminary analysis of variance for the comparison of mean values between the three groups, Student's paired *t* test or Wilcoxon test was performed before and after treatment comparisons. For nonpaired comparison, independent *t* test or Mann-Whitney test was used. For the categorical variables comparisons, χ^2 or Fisher's exact test was used. To assess possible relationships between continuous variables, Pearson's correlation coefficient was used. A two-tailed *P* value ≤ 0.05 was considered statistically significant.

Data analysis was performed by means of the Statistical Package for the Social Sciences (SPSS), version 6.0.1.

RESULTS — Basal characteristics of the studied groups are shown in Table 1. As a reference population for establishing normal magnesium levels in our area, 57 healthy blood donors were studied (36 men and 21 women) with ages varying between 18 and 54 years (32 ± 8.6 years).

Of the 128 patients who started the study, 29 did not follow instructions correctly. The data were analyzed according to their original groups, based on the intention to treat. Reasons for interruption of treatment were irregular use of oral hypoglycemic drugs in 4 patients, other medical problems in 9 patients, and irregular use of Mg or placebo in 16 patients. Of these, 6 forgot to use the drug and the remaining 10 discontinued treatment due to side effects. Of the group treated with 41.4 mmol MgO, only one patient interrupted treatment due to undesirable event. The most frequent side effect was diarrhea, in 12% of the group that used 41.4 mmol MgO, but only the above-mentioned patient interrupted the treatment for this reason. Abdominal pain and nausea were not reasons for discontinuation of Mg administration in this group.

Before magnesium replacement, 47.7% of patients had low plasma Mg levels, and 31.1% had low intramononuclear levels. Intracellular Mg in patients with diabetes was significantly lower than in normal individuals, but no statistically significant differences were found among plasma magnesium concentrations (Table 2). No correlation was seen either between plasma and intracellular Mg concentrations ($r = 0.179$; $P = 0.15$) or between Mg levels and glycemic control, as expressed by HbA_1 concentration ($r = 0.165$; $P = 0.12$).

In the 29 patients with peripheral neuropathy, intracellular Mg levels were lower than in those without it (1.2 ± 0.15 vs. 1.5 ± 0.6 μg/mg total protein; $P < 0.05$). Similar observations was made in eight patients with coronary disease (1.03 ± 0.48 vs. 1.47 ± 0.34 μg/mg total protein). No differences were observed in intracellular magnesium of patients with retinopathy (1.45 ± 0.46 vs. 1.45 ± 0.57 μg/mg; Fig. 1).

Table 2—*Comparison of Mg levels between diabetic patients and reference population*

	Diabetic patients	Reference population
Plasma Mg^{2+} (mmol/l)	0.74 ± 0.17	0.79 ± 0.09
Intramononuclear Mg^{2+} (μg/mg of total protein)	1.44 ± 0.57*	1.69 ± 0.62

Data are means ± SD. *$P < 0.05$.

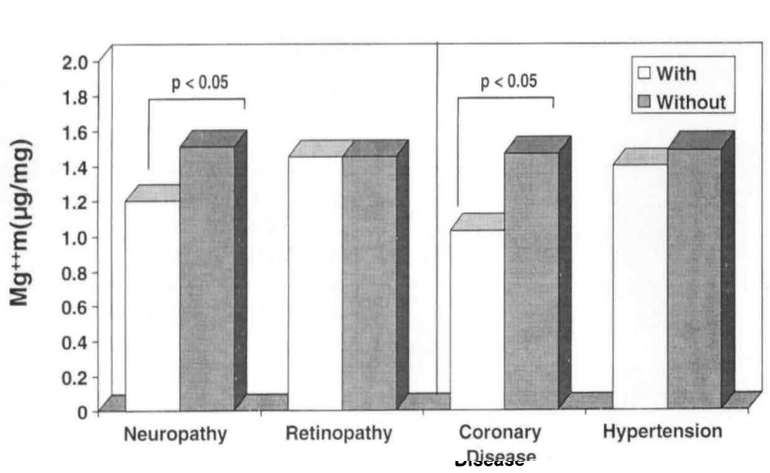

Figure 1—*Intracellular levels of magnesium in chronic complications related to diabetes and diseases associated with diabetes.*

Table 3 shows magnesium concentrations and glycemic control parameters before and after treatment. In the placebo and the 20.7 mmol MgO groups, neither a change in plasma and intracellular levels nor improvement in glycemic control was observed. An increase in ion urinary excretion in the patients who received MgO was observed ($P < 0.005$). Replacement with 41.4 mmol MgO tended to increase plasma, cellular, and urine MgO and caused a significant fall in fructosamine levels (4.1 ± 0.8 to 3.8 ± 0.7 mmol/l; $P < 0.05$). No changes in fasting blood glucose or HbA_1 concentrations were observed.

The percentage of patients with improvement of metabolic control during treatment is shown in Fig. 2. Of patients who used the higher dose of magnesium, 73% showed a decrease in fructosamine. This finding was significant when compared with data from the placebo group.

Weight, as expressed by BMI, did not change significantly in our patients during the study (BMI: group 1, 25.5 ± 6.5 → 25.4 ± 6.0; group 2, 25.3 ± 8.0 → 25.2 ± 7.8; group 3, 25.5 ± 6.1 → 25.4 ± 6.2 kg/m²).

CONCLUSIONS — In this study, magnesium deficiency in plasma and mononuclear cells occurred with a frequency higher than that found by other researchers (5,7–10). This is probably due to the fact that the patients under study were not in good metabolic control.

Levels of intracellular magnesium were lower than those in the reference population. Blood donors, although younger than the population studied, were used as a reference group. This is justified by the fact that Reinhart et al. (2), after measuring concentrations of plasma and mononuclear magnesium in 88 volunteers, observed no differences between sex and age.

There was no correlation between intracellular and serum magnesium levels. This finding confirms what has been encountered by other authors (2,22,23). Quamme and Dirks (24) analyzed 13 studies where magnesium determination in mononuclear cells was used, and 10 of these considered the method useful, correlating well with muscular cells (where 27% of the total body magnesium was found) .

Some authors point to a negative correlation between magnesium levels and glycemic control (5,10,25), but other researchers do not confirm this (26). Neither does our current study observe a correlation between levels of magnesium in plasma or in mononuclear cells with glycemic control parameters.

The link between magnesium deficiency and chronic diabetes complications is reported by several researchers, probably as a result of its positive action in inositol transport (through ATPase activation) (13) or of its action reducing blood platelet aggregation (27). In this study, we observed that intramononuclear magnesium levels were low in patients with peripheral neuropathy. To our knowledge, these data have not yet been reported.

Despite the small number of patients with coronary disease, the intramononuclear magnesium was significantly lower in this group of individuals. Some researchers suggest an association between hypomagnesemia and coronary disease (28,29). Nadler et al. (27) point out that hypomagnesemia may double the risk of developing coronary disease in a diabetic patient because of the increase in platelet reactivity usual in this situation.

The dose of elementary magnesium used in various studies varies greatly (15–125 mmol/day) (16–19). However, doses greater than 41.4 mmol are not usu-

Table 3—*Laboratory evaluation before and after treatment*

	Group 1 Placebo	Group 2 MgO (20.7 mmol/l)	Group 3 MgO (41.4 mmol/l)
n	54	35	39
Plasma Mg^{2+} (mmol/l)			
Before	0.72 ± 0.14	0.70 ± 0.18	0.73 ± 0.19
After	0.74 ± 0.17	0.76 ± 0.19	0.80 ± 0.24
Mononuclear Mg^{2+} (µg/mg total protein)			
Before	1.41 ± 0.53	1.56 ± 0.63	1.39 ± 0.58
After	1.48 ± 0.59	1.59 ± 0.60	1.62 ± 0.75
Urinary Mg^{2+} (mg/24 h)			
Before	96 ± 53	87 ± 39	106 ± 59
After	79 ± 26	121 ± 59*	113 ± 29*
Glycemia (mmol/l)			
Before	12.9 ± 4.3	10.3 ± 3.3	12.6 ± 4.2
After	12.2 ± 73	11.5 ± 4.4	12.7 ± 4.2
HbA_{1c} (%)			
Before	9.3 ± 2.6	10.2 ± 2.8	9.0 ± 2.4
After	9.5 ± 2.2	9.7 ± 2.3	9.2 ± 3.0
Fructosamine (mmol/l)			
Before	3.68 ± 0.70	3.40 ± 0.68	4.13 ± 0.80
After	3.65 ± 0.75	3.43 ± 0.73	3.75 ± 0.72*

Data are means ± SD. *$P < 0.05$.

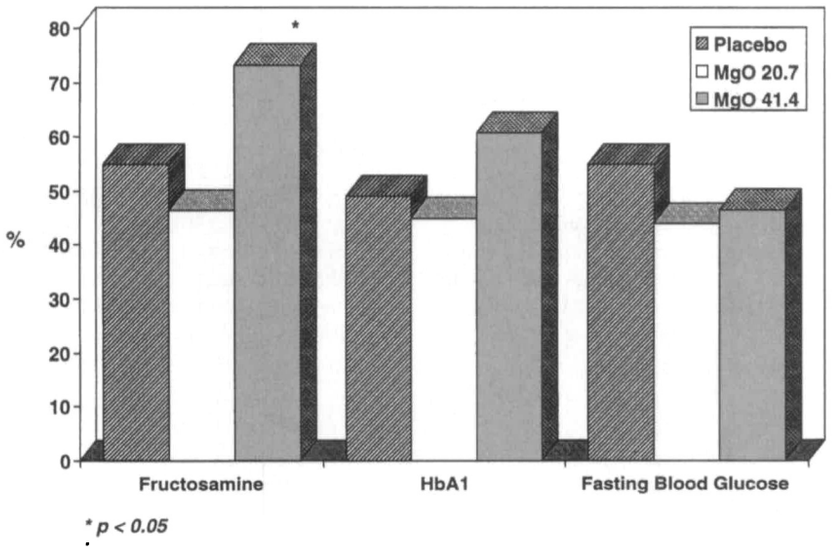

Figure 2—*Percentage of patients with improvement of metabolic control during treatment.*

ally tolerated. The formulation selected was MgO because it is recommended as the one less associated with diarrhea, the most feared side effect (30). Tolerance to the drug was excellent, even in patients who used a higher dose.

Taking into account the necessary period for replenishment of intracellular magnesium stores, the fructosamine assay was considered the appropriate parameter for evaluating the effect of replacement of the ion in patients' metabolic control.

In the present study, neither placebo nor 20.7 mmol/day of Mg improved metabolic control compared with 41.4 mmol/day. This dose tended to increase intracellular magnesium levels as well as improving recent metabolic control as expressed by fructosamine decrease. BMI did not change during the study. Thus, the fall observed in fructosamine levels in these patients was not a consequence of weight loss due to diet or to diarrhea.

Group 3 patients had the highest pretreatment fructosamine. This suggest that magnesium supplementation has a better effect in poorly controlled patients with type 2 diabetes.

Because type 2 diabetes is a state of insulin resistance and insulin mediates magnesium transport to cells (31), doses of magnesium required to perform this action may be higher, both to increase its intracellular levels and to improve metabolic control.

In conclusion, a decrease in serum and mononuclear magnesium concentration is common in patients with poorly controlled type 2 diabetes, especially in those with coronary disease and peripheral neuropathy. Patients with poor control receiving 41.4 mmol/day MgO improved glycemic control in the last 2 weeks as evidenced by the fall in fructosamine. More prolonged use of magnesium in doses higher than usual is needed to definitely establish its routine or selective administration in type 2 diabetes, either for improving control or preventing chronic complications.

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