Hypomagnesemia in Type II Diabetes: Effect of a 3-Month Replacement Therapy

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OBJECTIVE — To investigate the effects of long-term high-dose oral magnesium (Mg) therapy (30 mmol/day) in patients with type II diabetes. Low plasma magnesium levels have been reported in type II diabetes and are associated with insulin resistance and diabetic late complications.

RESEARCH DESIGN AND METHODS — Forty patients with type II diabetes and hypomagnesemia were observed in a randomized double-blind placebo-controlled trial for 3 months (body mass index: 28 ± 4 kg/m^2; HbA_{1c}: 7.4 ± 0.8%). Plasma and urine magnesium and metabolic control parameters were determined, and side effects were considered, especially with regard to patients' compliance.

RESULTS — A significant increase in plasma magnesium levels was observed after 3 months of treatment (Mg: 0.73 ± 0.8 vs. 0.81 ± 0.1 mmol/l), reaching magnesium levels of the control group (0.88 ± 0.8 mmol/l; NS); metabolic control, however, was not altered (HbA_{1c}: 7.2 ± 0.7 vs. 7.4 ± 0.9%). Six months after the end of the trial, plasma magnesium declined to pretreatment levels (Mg: 0.73 ± 0.07 mmol/l). The prevalence of side effects was high at the beginning and was reduced significantly during treatment.

CONCLUSIONS — We conclude that oral magnesium replacement therapy corrects hypomagnesemia after a minimum treatment period of 3 months. These observations might be important for the prevention of diabetic late complications.

Reduced plasma magnesium levels were reported in both type I and type II diabetic patients (1–3) and are associated with diabetic late complications (2–5). In type I diabetic patients, hypomagnesemia is related to poor metabolic control and attributed to increased urinary magnesium losses. In type II diabetes, hypomagnesemia is associated with insulin resistance. Whether hypomagnesemia precedes or follows insulin resistance is not clear yet, but it may be associated with the insulin-resistant state per se (6–8). There is evidence that hypomagnesemia favors the risk of cardiovascular abnormalities, ranging from cardiac arrhythmias and ischemic heart disease to myocardial infarction (9,10). Although magnesium is used for treatment of some cardiovascular disorders (11–13), the beneficial effect of magnesium replacement in preventing cardiovascular complications has not yet been proven in long-term studies. Hypomagnesemia per se may indicate the development of diabetes in groups known to be at high risk, although correction of low magnesium levels has not been shown to reduce this risk. The consensus statement of the American Diabetes Association discusses whether magnesium replacement will decrease the incidence of diabetes and its complications. This statement suggests studies to investigate magnesium replacement to demonstrate the safety and beneficial results of such treatment (14).

The aim of our study was to show the effect of long-term oral magnesium replacement therapy not only on plasma magnesium levels but also on metabolic control parameters. Further possible side effects of long-term magnesium therapy are still not known and may be of interest for patients' safety and compliance.

RESEARCH DESIGN AND METHODS

— Forty type II diabetic patients participated in a placebo-controlled randomized double-blind trial. The clinical and metabolic characteristics of the patients are shown in Table 1. All patients were treated with diet and oral hypoglycemic agents. They did not suffer from any clinical conditions associated with hypomagnesemia besides diabetes, nor were they taking any drug known to interfere with magnesium metabolism. Patients with abnormal liver and kidney parameters were excluded; there were no

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Table 1—*Clinical and metabolic characteristics of type II diabetic patients in the verum and placebo groups*

	Verum group	Placebo group
n	18	20
Age (years)	63 ± 8	54 ± 1.5
Duration of diabetes (years)	7.6 ± 6.9	6.1 ± 5.2
Body mass index (kg/m^2)	27.5 ± 3.2	29.3 ± 5
Sex (M/F) (%)	47/40	53/60
Plasma magnesium (mmol/l)	0.73 ± 0.1	0.72 ± 0.08
Systolic blood pressure (mmHg)	140 ± 18	145 ± 14
Diastolic blood pressure (mmHg)	83 ± 8	84 ± 7
Cholesterol (mmol/l)	5.9 ± 0.9	5.7 ± 1.8
Triglycerides (mmol/l)	2 ± 1.04	1.9 ± 1
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.3 ± 0.4
LDL cholesterol (mmol/l)	3.5 ± 0.9	3.2 ± 0.9
Sodium (mmol/l)	142 ± 2	142 ± 2
Potassium (mmol/l)	4.3 ± 0.2	4.2 ± 0.4
Creatinine (μmol/l)	88.4 ± 0.8	88.4 ± 1.6

Data are means ± SD.

patients with a history of increased alcohol consumption. All patients were in good metabolic control (HbA_{1c} <8%) to exclude an additional magnesium loss through urinary excretion. All patients gave their informed consent, and the study was approved by the ethical committee of our hospital.

After a 4-week prestudy period, the patients were randomly assigned to two groups receiving either magnesium citrate (30 mmol/day; Magnosolv granulate, Asta Medica) or placebo for 3 months. To reduce side effects and optimize the resorption of the magnesium citrate, the patients were asked to take the magnesium twice a day between meals and were told to keep their regular diets to avoid an influence of a special diet on metabolic control. The patients were seen monthly before commencement of the replacement therapy and were then seen once a month for 3 months (−1, 0, 1, 2, and 3) and finally 6 months after the conclusion of the study.

At the beginning and at the end of the study, an oral glucose tolerance test with a 75-g oral glucose load was performed. In a special questionnaire, patients were asked at each visit to report any side effects including diarrhea, gastrointestinal pain, meteorism, hypotension, or neuromuscular symptoms. The control group consisted of 30 healthy subjects matched for age and sex. The patients were asked to keep their regular diabetic diet. In a dietary questionnaire, we evaluated the diets of all patients and the control subjects. The intake and the amount of dairy products, fish, meat, bread, vegetables, and fruit were evaluated and kept constant throughout the study. From these data, we calculated the average daily magnesium intake. The patients were also asked to report their exact food intake on the day before blood testing.

Analytical procedures

Blood samples were taken in the morning after overnight fasting for at least 12 h each month. Plasma magnesium was measured by a calorimetric method (Xylidyl blue reaction) using an automatic analysis system (13 M Hitachi 737). Blood glucose, lipids, and routine clinical parameters were determined by a parallel analyzer, and HbA_{1c} was measured by high-pressure liquid chromatography (Diamat, Bio-Rad). Urine magnesium was determined from a 24-h urine sample and was measured by atomic absorption spectrophotometry using a Perkin-Elmer apparatus. Plasma insulin was determined by an enzyme-linked immunosorbent assay (Enzymuntest insulin, ES 600, Boehringer Mannheim). Statistical analyses were performed using Student's *t* test, and the data are expressed as means ± SD unless otherwise stated.

RESULTS — Of 40 patients, 38 completed the 3-month trial. Two patients of the verum group dropped out: one developed an exanthema that was related to the magnesium medication, and the other reported gastrointestinal pain and wished to stop the medication. At the beginning of the study, plasma magnesium levels in the verum and the placebo groups were significantly reduced compared with the control subjects (0.73 mmol/l ± 0.09 vs. 0.88 ± 0.08; $P < 0.0001$). After a 2-month treatment period, the magnesium levels remained almost unchanged in the two groups (NS) (Table 3), whereas after 3 months, the magnesium levels

Table 2—*Metabolic parameters at the beginning and at the end of magnesium replacement*

	Verum group		Placebo group	
	0 months	3 months	0 months	3 months
Cholesterol (mmol/l)	5.9 ± 0.9	5.8 ± 1	5.7 ± 1.8	5.8 ± 0.9
Triglycerides (mmol/l)	2 ± 1	1.8 ± 0.8	1.9 ± 1	1.9 ± 1
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.3	1.3 ± 0.3	1.3 ± 0.4
LDL cholesterol (mmol/l)	3.5 ± 0.9	3.5 ± 0.9	3.2 ± 0.9	3.7 ± 0.9
HbA_{1c} (%)	7.2 ± 0.7	7.4 ± 0.9	7.5 ± 0.9	7.6 ± 1.4

Data are means ± SD.

Table 3—*Changes in plasma and urinary magnesium levels during substitution therapy*

	Serum magnesium (mmol/l)				Urinary magnesium (mmol · l^{-1} · 24 h^{-1})	
	0 month	2 months	3 months	6 months	0 month	3 months
Verum	0.73 ± 0.8	0.76 ± 0.09	0.81 ± 0.1	0.73 ± 0.07	2 ± 1.8	2.8 ± 1.2
Placebo	0.72 ± 0.8	0.74 ± 0.1	0.69 ± 0.8	0.71 ± 0.9	2.26 ± 1	1.8 ± 1

Data are means ± SD. After 2 months, plasma magnesium levels were still low in both groups, whereas after 3 months, magnesium levels increased significantly ($P < 0.007$) in the verum group similar to those of the control subjects (0.88 ± 0.8, NS) despite increased urinary magnesium losses ($P < 0.01$). Six months after the end of the therapy, plasma magnesium declined to pretreatment levels ($P < 0.02$).

were significantly higher in the verum group, similar to those of the control subjects (NS) (Table 3). Six months after the end of the replacement therapy, the plasma magnesium of the verum group declined to pretreatment levels ($P < 0.02$). Urinary magnesium losses were similar in both groups at the beginning and increased significantly after 3 months in the verum group (Table 3). There was no correlation between urine magnesium and urine glucose or urine phosphate (NS). Serum levels of calcium and phosphate were in the normal range, remained unchanged during therapy, and were not correlated with serum magnesium (NS). Changes in metabolic control and lipid parameters were not significant (Table 2).

No influence on serum creatinine or on systolic or diastolic blood pressure levels was seen. Figure 1 shows the glucose and insulin concentrations after an oral glucose load before and after 3 months of magnesium replacement. Basal insulin levels were not changed significantly, nor was fasting blood glucose. The oral glucose tolerance test showed no significant differences in insulin or blood glucose concentrations in both groups at the beginning and at the end of the study.

The dietary questionnaire showed no detectable difference of magnesium intake from magnesium-rich foods between the two groups nor between diabetic patients and control subjects. After 1 month of treatment, side effects were significantly higher in the verum group (66 vs. 25%; $P < 0.01$), evaluated with a χ^2 test. After 3 months of treatment, a decline of side effects was reported in both groups (33 vs. 16%; NS).

CONCLUSIONS — Previous studies have reported that hypomagnesemia plays a key role in cardiovascular disease (9,10) and may be associated with diabetic late complications (2,3). The beneficial effect of intravenous magnesium therapy for cardiac arrhythmias is known (12) and has also been described in patients with ischemic heart disease and congestive heart failure (11). Hypomagnesemia is a common finding in diabetic patients (1–3). A relationship between hypomagnesemia and diabetic late complications has been shown in several studies, although the mechanism is still unknown (2–5). Grafton et al. (15) suggest that hypomagnesemia leads to a reduction of inositol transport and subsequent inositol depletion that might increase the development of diabetic complications.

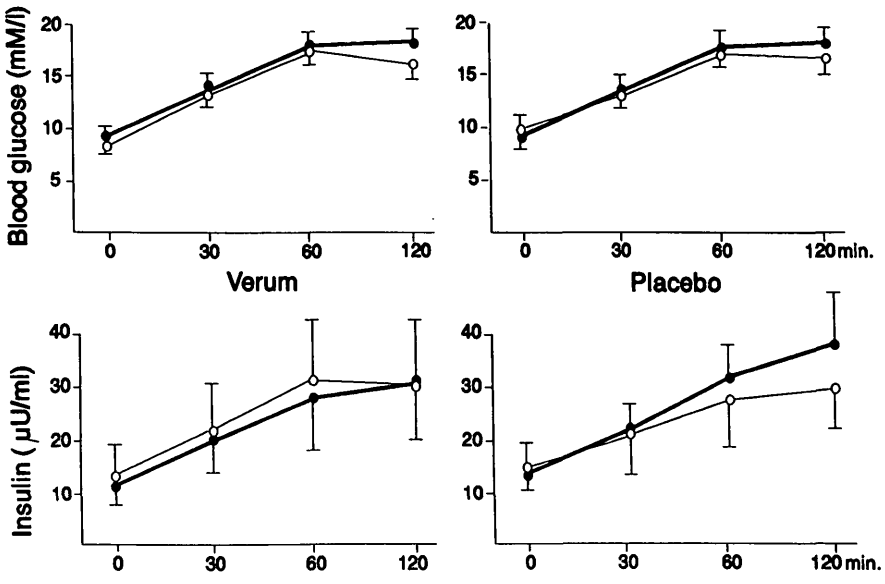

Figure 1—*Insulin (μU/ml) and blood glucose (mmol/l) levels after an oral glucose load (75 g) at baseline (●) and after 3 months (○) showed no differences between the verum and the placebo groups.*

Table 4—*Number of patients affected by various side effects during replacement therapy in the verum and placebo groups by months*

	Verum group (n = 18)			Placebo group (n = 20)		
	1 month	2 months	3 months	1 month	2 months	3 months
Nausea	—	1	—	1	1	—
Diarrhea	10	7	4	4	2	2
Tiredness	—	—	—	—	1	—
Meteorism	3	2	2	1	—	1
Gastric pain	4	2	2	2	1	1
Improvement of cardiac pain	—	—	2	—	—	—

Whether the correction of hypomagnesemia reduces the risk of cardiovascular disease and other diabetic late complications is not known yet.

Our data show that magnesium treatment with a high dosage (30 mmol/day) for at least 3 months can increase plasma magnesium to nearly normal levels, whereas after 2 months of replacement, magnesium levels are still low. This long period may be due to increased urinary magnesium losses, but also to intracellular magnesium depletion. Six months after the end of magnesium intake, plasma magnesium declines to pretreatment levels. This observation may be of great clinical relevance, because it demonstrates that magnesium replacement has to be long lasting to correct hypomagnesemia permanently. We were unable to observe an effect of high-dose magnesium intake on metabolic control. However, all the patients were already in a good metabolic state at the beginning of the study to avoid additional urinary magnesium losses due to glucosuria. Fasting insulin levels were not increased, and there was no decline in fasting blood glucose. We did not observe any significant changes in the oral glucose tolerance test with regard to blood glucose and insulin levels. This observation suggests that there is no clinical improvement of insulin resistance and confirms the hypothesis that hypomagnesemia is associated with the insulin-resistant state per se. Our previous observation (7) that improvement in metabolic control does not alter plasma magnesium levels in diabetic patients is also in accordance with this hypothesis.

By contrast, Paolisso et al. (16) described in type II diabetic patients an improved insulin response and a fall of fasting blood glucose level after magnesium administration. A number of differences in the design of the study of Paolisso et al. could be responsible. The patients studied by Paolisso et al. did not receive any other medication, whereas our patients also received sulfonylurea and metformin. Further, a very high dosage of magnesium was used in the study by Paolisso et al., and metabolic control was only tested by fasting blood glucose levels, whereas HbA_{1c} levels were not analyzed. The study of Paolisso et al. was only 4 weeks long in comparison to this study, which was 12 weeks long. Taking into account the results of both studies, we conclude that magnesium therapy does not further improve the metabolic state in type II diabetic patients treated with oral hypoglycemic agents, whereas a beneficial effect of magnesium therapy in dietary-treated obese type II diabetics was found (16). More studies are needed to observe possible metabolic effects of magnesium therapy in patients with poor metabolic control.

Very few studies specify side effects during magnesium therapy. In two patients, the dosage of magnesium was reduced because of severe gastrointestinal pain; the lower magnesium dose was well tolerated. In long-term treatment, however, side effects are of great clinical relevance with regard to patient compliance (Table 4). It should be further investigated if a lower dose will be sufficient once plasma magnesium is normal.

In summary, plasma magnesium levels can be elevated by oral magnesium therapy; however, this effect is not permanent because magnesium levels decline after the end of the therapy. Once normal plasma magnesium levels are achieved, a lower dosage for substitution may be sufficient.

More investigations are needed to evaluate the beneficial effect of oral magnesium replacement on cardiovascular and other diabetic late complications. Which patients might benefit from magnesium substitution in terms of metabolic control warrants further investigation.

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