Serum Magnesium Status During Lipid-Lowering Drug Treatment in Non–Insulin-Dependent Diabetic Patients

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Serum magnesium concentration (S-Mg) has been reported to be inversely associated with atherogenic lipid fractions and with blood glucose concentrations. In some studies on humans, oral magnesium supplementation has been found to improve the lipoprotein balance. Against this background the present study was undertaken to determine whether reductions in atherogenic lipid fractions are associated with S-Mg alterations. Total S-Mg was measured in 23 patients with non–insulin-dependent diabetes mellitus (NIDDM) treated with the lipid-lowering drugs gemfibrozil and simvastatin in a double-blind cross-over study. The mean S-Mg at the end of the initial placebo period, ie, before active treatment, was 0.80 (SD 0.06) mmol/L. Treatment with gemfibrozil 600 mg twice daily for 4 months decreased S-Mg by 0.02 mmol/L ($P = .02$), and treatment with simvastatin 10 mg daily for 4 months again decreased S-Mg by 0.02 mmol/L ($P = .10$; not significant [NS]) The changes in S-Mg during the 2 different treatment periods were closely correlated ($r = 0.66$, $P < .001$). Fasting plasma glucose concentrations increased significantly by 17% during both drug regimens. The changes in fasting plasma glucose and S-Mg were significantly correlated both during gemfibrozil treatment ($r = -0.56$, $P < .01$) and during treatment with simvastatin ($r = -0.44$, $P < .05$). Changes in glucose tolerance or insulin sensitivity did not correlate to changes in S-Mg. The associations between changes in serum very-low-density lipoprotein (VLDL) fractions and S-Mg did not reach statistical significance ($r = -0.37$, $P < .10$). Changes in low-density lipoprotein (LDL) cholesterol and S-Mg did not correlate. In conclusion, total S-Mg concentration decreased during treatment with gemfibrozil and simvastatin in patients with NIDDM. During both drug regimens changes in S-Mg status were inversely correlated to changes in plasma glucose concentrations, while changes in lipid status were not significantly correlated with changes in S-Mg.

IT HAS BEEN CONCLUDED on the basis of geographic surveys that low magnesium intake is associated with increased mortality from ischemic heart disease (IHD).[1] Epidemiologic studies have shown lower serum magnesium (S-Mg) concentrations in partcipants with IHD, hypertension, and diabetes than in those free of these diseases.[2] Magnesium deficiency in experimental animals has been found to cause adverse alterations in the blood lipid composition[3-6] and to affect lipid infiltration into the endothelium.[7] In humans, the S-Mg concentration has been reported to be inversely associated with atherogenic lipid fractions and with blood glucose concentrations.[8] In rabbits, dietary supplementation with magnesium increased the S-Mg level and reduced the cholesterol content, as well as the area of the atherosclerotic lesions in aortas, in a dose-dependent manner.[9] In some studies on humans, oral magnesium supplementation has been found to improve the lipoprotein balance.[10-13] An inverse correlation between alterations in serum triglyceride and magnesium concentrations was previously observed during treatment with angiotensin-converting enzyme (ACE) inhibitors in essential hypertension.[14] Against the background of observed decreases in circulating lipid concentrations after magnesium supplementation, the present study was undertaken to determine whether reductions in atherogenic lipid fractions are associated with increased S-Mg concentrations accordingly. Changes in S-Mg were analyzed after serum lipid and lipoprotein concentrations were significantly reduced by treatment with the hepatic hydroxymethyl glutaryl coenyzme A (HMG CoA) reductase inhibitor simvastatin or the fibrate gemfibrozil in subjects with non–insulin-dependent diabetes mellitus (NIDDM).[15]

More recently introduced drugs such as HMG CoA reductase inhibitors and fibrates are widely used for reducing the circulating atherogenic lipid fractions and decreasing cardiovascular morbidity and mortality.[16-21] The effects of simvastatin and gemfibrozil treatment on lipid and glucose metabolism in subjects with NIDDM have previously been described.[15] Regarding gemfibrozil- and simvastatin-mediated effects on the circulating magnesium status, there are no previous reports, although several data bases were surveyed.

SUBJECTS AND METHODS

Informed consent was obtained from all patients. The study protocol was approved by the Human Ethics Committee of the Medical Faculty of Uppsala University. The subjects and methods have been described previously.[15] Twenty-nine patients with NIDDM and hyperlipoproteinemia or dyslipoproteinemia (LDL $>$ 5 mmol/L and/or high-density lipoprotein [HDL] $<$ 1 mmol/L and/or triglycerides $>$ 2.3 mmol/L) being treated with dietary therapy alone or combined with oral hypoglycemic agents, participated in this double-blind, randomized cross-over study. Patients with other major diseases or with a history of hepatic, renal, coronary, or central nervous system disease during the preceding 6 months were not included in the study. Patients with elevated levels of plasma alanine aminotransferase (> 0.8 μkat/L) were excluded.

Twenty-five patients completed the gemfibrozil treatment period, and 24 completed the period of simvastatin treatment. Three patients were excluded during the course of the study: 1 because of surgical treatment for a fracture of the femoral neck, 1 due to muscular pains, and 1 who lost his tablets. One patient was unable to not participate in

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the final test because of depression, and 2 patients were excluded from 1 period of active treatment because of low compliance. Thus, 23 participants, 17 males and 6 postmenopausal females, with a mean age of 63 years (range, 46 to 78), completed both periods of active treatment in the cross-over study, and constitute the basis of the present analysis. Seven patients were being treated with sulfonylurea, 3 with metformin, and 8 with a combination of these drugs. Four of the 23 participants were receiving beta-blockers for hypertension and/or stable ischemic heart disease. Another 7 patients were hypertensive and being treated with calcium blockers, ACE inhibitors, or combinations of these drugs. The medication regimens were not changed during the study. The partcipants were informed not to change their diet or activity level in connection with the study.

Protocol

A placebo run-in period of 4 to 6 weeks was followed by randomization to treatment with either gemfibrozil 600 mg twice daily or simvastatin 10 mg once daily in the evening, given together with a placebo tablet that had the appearance of the alternative drug. The doses used in the present study are in accordance with the directions from the medical product agency and the pharmaceutical companies, respectively. The half-life values of gemfibrozil is about 1.5 hours and that for simvastatin, about 2 hours.[22] The first phase of active treatment lasted 4 months and was followed by cross-over to the alternative medication and placebo formulation for another 4 months. At the end of the run-in phase and at the end of each of the active treatment periods, a laboratory investigation was performed. All patients were studied after an overnight fast and without taking their morning medication.

Laboratory Tests

Body weight was recorded to the nearest hectogram with subjects in normal clothing but without shoes and with jacket or outer coat removed. Height was measured, by use of a ruler fixed to the wall, to the nearest centimeter with the patients without shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of length (in meters).

Lipoprotein and lipid concentrations in serum were assessed. VLDL, LDL, and HDL were isolated by a combination of preparative ultracentrifugation and precipitation with a sodium phosphotungstate and magnesium chloride solution. Triglyceride and cholesterol concentrations were measured in serum and in isolated lipoprotein fractions by enzymatic methods using the IL Test Cholesterol Trinder′s Method 181618-80 and IL Test Enzymatic-Colorimetric Method 181709-00 for use in a Monarch apparatus (Instrumentation Laboratories, Lexington, MA). Serum free fatty acids (FFA) were determined by an enzymatic method, using a commercial kit (Wako Chemicals GmbH, Neuss, Germany) applied for a Monarch 2000 multicentrifugal analyzer (Instrumentation Labortory).

An intravenous glucose tolerance test (IVGTT) was performed as previously described,[23] with injection of 300 mg/kg body weight of glucose (Opotimate; Ames-Gilford, Elkhart, IN). The plasma glucose level was measured by the glucose oxidase method. Immunoreactive insulin was assayed in plasma using a commercial radioimmunoassay kit (Phadeseph Insulin RIA, Pharmacia, Uppsala, Sweden). Glucose tolerance was expressed as the k value as described by Ikkos and Luft.[24] The peak insulin response was defined as the mean of values obtained at 4, 6, and 8 minutes after the start of the glucose injection, and the insulin increment was defined as the difference between the peak insulin response and basal plasma insulin value (mean of values at -10, -5, and 0 minutes).

The euglycemic hyperinsulinemic clamp tests was performed according to the method described by DeFronzo et al.[25] The insulin (Actrapid Human, Novo, Copenhagen, Denmark) infusion rate during the clamp study was 56 mU/m^2 body surface area/min, resulting in a mean plasma insulin concentration of approximately 120 mU/L. The target plasma glucose concentration during the clamp test was 5.1 mmol/L, which was maintained by measuring the plasma glucose concentration every 5 minutes and adjusting the rate of glucose infusion (Glucose 20%, Pharmacia) accordingly. The glucose uptake (M) per minute was calculated on the basis of the amount of glucose infused per minute and expressed per kilogram body weight. The insulin sensitivity index (M/I index) was calculated by dividing the mean glucose uptake, M, by the mean insulin concentration, I, during the steady-state phase, ie, during the last 60 minutes of the 120-minute clamp study.

Total S-Mg concentrations were measured by atomic absorption photometry (Instrumentation Laboratories) at the Department of Clinical Chemistry at the University Hospital, Uppsala. The blood samples for magnesium analysis were collected in vacuum tubes for serum analysis (Vacutainer 367788BN326SST4, Becton Dickinson Vacutainer Systems, Rutherford, NJ). The measurement capacity per se of the magnesium concentration in serum samples with different glucose concentrations was tested by measuring S-Mg concentration in serum samples in which the glucose concentration was changed to different levels, from 6.0 to 14.2 mmol/L, by addition of glucose solution or saline, respectively, with an equal volume change in all samples. No trend for lower or higher S-Mg concentrations in samples with higher glucose concentrations was observed.

Statistics

Descriptive measurements used were mean and standard deviation (SD). Continuous variables were tested for normality (Shapiro-Wilk′s test). Mean changes in variables during the periods of active treatment were tested by the paired Student′s *t* test or Wilcoxon signed-rank test in case the data were not normally distributed, and the results are presented as mean change and *P* value for the change. Carry-over effects were analyzed by comparing the group-by-period mean values for different variables using *t* tests.[26] Bivariate associations are expressed as Pearson′s correlation coefficients. Nonparametric measures of associations (Spearman′s rank-order correlations) were used in case of not normally distributed variables. Mahalanobis distance method was used to evaluate multivariate outliers.[27] Statistical analyses were performed with the statistical software package JMP 3.2 (SAS Institute, Cary, NC).

RESULTS

The mean S-Mg concentration at the end of the initial placebo period was 0.80 (SD 0.06) mmol/L. At baseline, S-Mg was inversely correlated to the plasma insulin concentration (r = -0.50, $P < .01$), but not significantly (NS) to the fasting plasma glucose level (r= -0.20).

The effects on the lipid and glucose status, and differences between the effects of the drug regimens, observed during lipid-lowering treatment with gemfibrozil and simvastatin have been reported previously.[15] In summary, gemfibrozil treatment significantly reduced the VLDL cholesterol and triglyceride fractions, and serum total triglycerides (Table 1). Simvastatin treatment reduced the VLDL and LDL cholesterol fractions. The HDL cholesterol fraction was increased by both drug regimens. The fasting blood glucose level was significantly increased by the 2 treatment regimens. Fasting plasma insulin increased significantly in both treatment groups. Insulin sensitivity was decreased by both drug regimens, and significantly so during gemfibrozil treatment (Table 1). No carry-over ef-

Table 1. Mean Values (SD) for BMI, Concentrations of Circulating Lipid Fractions, Free Fatty Acids, Magnesium, and Variables Reflecting Glucose Disposal and Insulin Sensitivity, and Changes in These Variables During Treatment With Simvastatin and Gemfibrozil

Variable	Baseline	Δ Simvastatin	Δ Gemfibrozil
BMI (kg/m^2)	29.1 (4.7)	+0.2 (0.7), NS	−0.3 (0.7), NS
S-total Tg (mmol/L)	2.89 (1.38)	−0.41 (1.22), NS	−0.93 (0.95)‡
S-VLDL Tg (mmol/L)	2.29 (1.29)	−0.31 (1.11), NS	−0.89 (0.85)‡
S-total Chol (mmol/L)	6.06 (1.03)	−1.12 (0.74)‡	−0.21 (1.16), NS
S-VLDL Chol (mmol/L)	1.10 (0.61)	−0.32 (0.59)*	−0.47 (0.47)‡
S-LDL Chol (mmol/L)	4.06 (1.14)	−0.96 (0.77)‡	−0.08 (1.01) NS
S-HDL Chol (mmol/L)	0.95 (0.17)	+0.08 (0.13)*	+0.10 (0.12)†
S-FFA (mmol/L)	0.67 (0.28)	+0.02 (0.20), NS	+0.14 (0.28)*
fP-glucose (mmol/L)	8.9 (2.3)	+1.5 (2.0)‡	+1.5 (2.7)†
fP-insulin (mU/L)	13.3 (6.6)	+2.3 (4.8)*	+2.9 (6.1)*
k value	0.53 (0.14)	+0.03 (0.26), NS	−0.05 (0.18), NS
Insulin peak (mU/L)	16.3 (7.2)	+2.6 (7.4), NS	+4.5 (11.1), NS
Insulin increment (mU/L)	3.3 (5.2)	+0.4 (7.2), NS	+1.7 (10.0), NS
M (mg/kg BW/min)	2.94 (1.18)	−0.28 (1.02), NS	−0.28 (0.80), NS
M/I (mg/kg BW/min/mU/L × 100)	2.76 (1.47)	−0.40 (1.09), NS	−0.58 (0.82)‡
S-Mg	0.80 (0.06)	−0.02 (0.06), NS	−0.02 (0.06)*

Abbreviations: BMI, body mass index; S, serum; Tg, triglyceride; Chol, cholesterol; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FFA, free fatty acid; fP, fasting plasma; k value, glucose disappearance rate at the intravenous glucose tolerance test; M, glucose infusion rate at the hyperinsulinemic euglycemic clamp test; M/I, insulin sensitivity index at the hyperinsulinemic euglycemic clamp test.

Probability indicated by: NS, not significant, *$P < .05$, †$P < .01$, ‡$P < .001$.

fects between the 2 periods of active treatment were observed in the variables shown in Table 1.

Addition of gemfibrozil treatment decreased S-Mg by 0.023 (SD 0.06) mmol/L ($P < .03$). During the simvastatin treatment period S-Mg again decreased by 0.020 (SD 0.06) mmol/L, ($P = .10$, NS), without a significant difference between the 2 treatment regimens. The reductions in S-Mg during the 2 treatment periods were not predicted by the baseline S-Mg, ie, the S-Mg concentration before treatment did not significantly correlate to the changes in S-Mg during the active treatment periods. Thus, the S-Mg changes during the active treatment periods are probably not explained by a regression towards the mean phenomenon. The changes in S-Mg during the 2 different treatment periods were closely correlated ($r = 0.66$, $P = .001$). This was also the case for the changes in circulating glucose concentrations during the 2 drug treatment regimens ($r = 0.57$, $P < .01$).

The changes in fasting plasma glucose and S-Mg concentrations were significantly correlated both during gemfibrozil treatment ($r = -0.56$, $P < .01$; Table 2 and Fig 1A) and during treatment with simvastatin ($r = -0.44$, $P < .05$; Table 2 and Fig 1B). Changes in BMI, glucose tolerance, and insulin sensitivity did not correlate with changes in S-Mg. Changes in serum VLDL fractions and S-Mg during the 2 drug regimens tended to correlate ($r = -0.37$, $P < .10$), however, without reaching statistical significance. Changes in LDL cholesterol and S-Mg did not correlate (Table 2).

DISCUSSION

The main finding in the present study on patients on NIDDM was that the circulating total magnesium concentration decreased during gemfibrozil and simvastatin treatment although atherogenic lipoprotein concentrations were significantly reduced. The reductions in S-Mg levels were similar in the two treatment groups. Regarding gemfibrozil-mediated effects on the magnesium status, there are no previous reports to be referred to, although several data bases were surveyed (Medline, Embase, Biosis, SciSearch, Derwent Drug File, Parke-Davis internal). In one study, hypercholesterolemic patients treated with statins, 20 mg daily, showed a reversible increase in the erythrocyte magnesium level and reduced tubular magnesium reabsorption after intravenous magnesium loading, but changes in the serum magnesium concentration were not reported.[28] In the present study, magnesium concentration was measured only in serum, which makes it difficult to speculate

Table 2. Bivariate Correlations Between the Changes in Serum Magnesium Concentrations and Changes in Variables Reflecting Lipid and Glucose Metabolism During Treatment With Simvastatin or Gemfibrozil in Patients With Non–Insulin-Dependent Diabetes Mellitus (N = 23)

	Simvastatin		Gemfibrozil	
Variable (Δ S-Mg)	*r*	*P*	*r*	*P*
Δ BMI (kg/m^2)	0.32	.14	−0.16	.48
Δ S-Tg (mmol/L)	−0.39	.06	−0.37	.08
Δ S-VLDL Tg (mmol/L)	−0.40	.06	−0.37	.08
Δ S-Chol (mmol/L)	−0.22	.31	−0.24	.26
Δ S-VLDL Chol (mmol/L)	−0.31	.16	−0.39	.07
Δ S-LDL Chol (mmol/L)	−0.11	.63	0.06	.78
Δ S-HDL Chol (mmol/L)	−0.04	.84	−0.44	.04
Δ S-FFA (mmol/L)	−0.24	.29	−0.57	<.01
Δ fP-Glucose (mmol/L)	−0.44	<.05	−0.56	<.01
Δ fP-Insulin (mU/L)	−0.01	.98	−0.14	.53
Δ k value	−0.06	.80	0.25	.26
Δ insulin peak (mU/L)	0.11	.60	0.35	.10
Δ insulin increment (mU/L)	0.16	.48	0.28	.19
Δ M (mg/kg BW/min)	−0.22	.32	0.04	.87
Δ M/I (mg/kg BW/min/mU/L × 100)	−0.09	.67	−0.06	.78

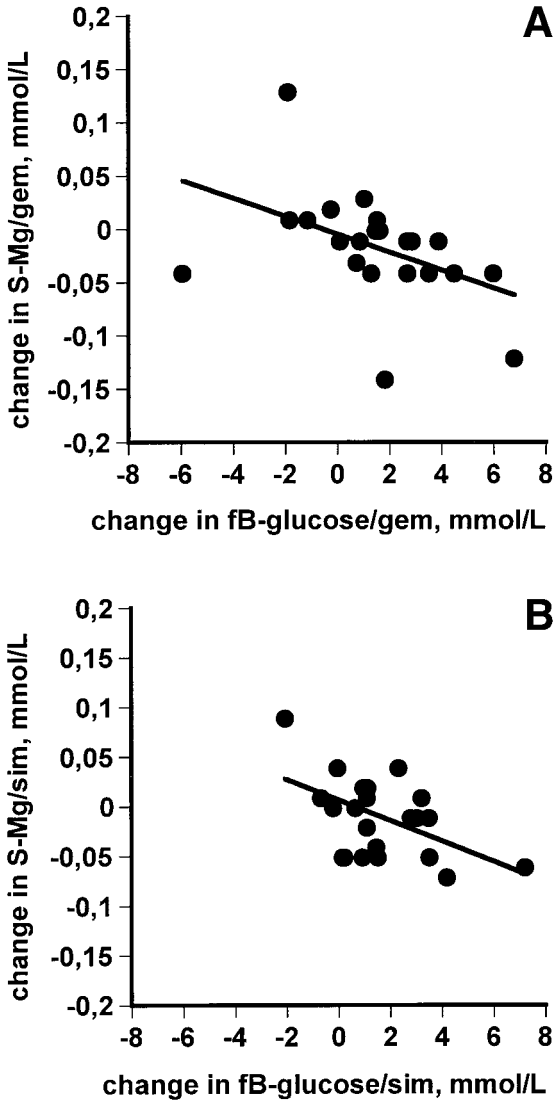

Fig 1. Changes in fasting plasma glucose (fP-glucose) and S-Mg concentrations were correlated during treatment with (A) gemfibrozil ($r = -0.56$, $P < .01$) and (B) simvastatin ($r = -0.44$, $P < .05$).

whether the changes in S-Mg are due to shifts between pools or explained by changes in renal magnesium excretion.

In a previous intervention study on the effects of a low-fat diet for a 12-week period Puska et al observed reduced levels of total serum cholesterol, whereas the effects on magnesium excretion were small or nonexistent.[29] These results and the observations in the present study indicate that there are probably no direct relationship between serum total magnesium concentration and lipoprotein fractions. However, relations between changes in magnesium status and changes in atherogenic lipid fractions cannot be excluded, since only changes in the total S-Mg concentration were analyzed. It has previously been reported that atherogenic lipid fractions are more closely related to plasma ionized magnesium than to the total magnesium concentration.[8] The present study did not assess the ionized magnesium status.

During both the gemfibrozil and the simvastatin treatment period the reduction in S-Mg correlated to the increase in plasma glucose. In previous studies on diabetic patients, S-Mg concentrations have been found to be inversely correlated to blood glucose concentrations or glycosylated hemoglobin levels.[30,31] Recently, Corsonello et al reported that serum ionized magnesium concentration correlated inversely to plasma hemoglobin A_{1c} in NIDDM patients with microalbuminuria or proteinuria.[32] The inverse relationship between the changes in serum magnesium and glucose concentrations might be explained by an increase in renal magnesium excretion related to glycosuria, however, Djurhuus et al recently observed an increase in renal magnesium excretion during hyperglycemia also in conditions without glycosuria.[33] It has also been reported that administration of insulin with or without glucose increases the renal magnesium excretion.[34,35] However, in the present study the changes in S-Mg were not explained by alterations in fasting plasma insulin concentrations. Conditions of insulin resistance have been associated with impaired cellular magnesium uptake and decreased intracellular magnesium concentrations.[36,37] Since the insulin sensitivity was not improved during treatment with the 2 drugs in the present study, it may be speculated that the reduced S-Mg concentrations were probably not explained by an increased cellular uptake. However, this possibility might be contradicted by previous findings that hypercholesterolemic patients treated with statins showed a reversible increase in erythrocyte magnesium levels.[28]

Some limitations of the present study should be kept in mind. First, most of the participating patients were being treated with antidiabetic and/or antihypertensive drugs, which might have influenced the results. Second, only total S-Mg was measured, which does not exclude alterations in circulating ionized magnesium concentrations.

The drug effects on lipid and glucose metabolism have been discussed in a previous report.[15]

In summary, gemfibrozil treatment significantly reduced the VLDL cholesterol and triglyceride fractions. Simvastatin treatment reduced the VLDL and LDL cholesterol fractions. The HDL cholesterol fraction was increased by both drug regimens. The fasting blood glucose level was significantly increased by the 2 treatment regimens. Fasting plasma insulin increased significantly in both treatment groups. Insulin sensitivity was decreased by both drug regimens, and significantly so during gemfibrozil treatment. The total S-Mg concentration decreased with both drug regimens. The changes in S-Mg were inversely correlated with the changes in the circulating glucose concentration, whereas the correlations between changes in S-Mg concentration and the lipid status failed to reach statistical significance.

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