Insulin-Mediated Glucose Disposal Is Decreased in Normal Subjects With Relatively Low Plasma Magnesium Concentrations

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The relationship between the plasma magnesium (Mg) concentration and steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations at the end of a 180-minute infusion of octreotide, insulin, and glucose was determined in 98 healthy nondiabetic subjects. For the purposes of data analysis, the population was divided into tertiles on the basis of the plasma Mg concentration: I, plasma Mg 0.83 mmol/L; II, plasma Mg 0.84 to 0.91 mmol/L; and III, plasma Mg 0.92 mmol/L. The three groups were identical in terms of age, gender distribution, and degree of obesity. However, both fasting plasma insulin ($P < .05$) and SSPG ($P < .05$) concentrations were significantly higher in the tertile (I) with the lowest plasma Mg concentration. Furthermore, there was a significant inverse correlation between plasma Mg and SSPG concentrations ($r = -.27$, $P < .01$) in the entire population. These results indicate that variations in the plasma Mg concentration have a relatively modest but significant effect on insulin-mediated glucose disposal in healthy subjects, with lower plasma Mg concentrations associated with increased insulin resistance.

BASED ON PUBLISHED EVIDENCE of an association between decreased plasma magnesium concentrations and insulin resistance in patients with type 2 diabetes,[1-3] we recently evaluated the possibility that a similar relationship might exist in nondiabetic individuals.[4] The results of our pilot study were positive in that insulin-mediated glucose disposal was decreased in nondiabetic subjects designated as having a low (mean ± SEM) plasma magnesium (Mg) concentration of 0.73 ± 0.01 mmol/L as compared with subjects with a high Mg concentration (0.90 ± 0.02 mmol/L). Although this was the first demonstration of a relationship between the plasma magnesium concentration and insulin resistance in nondiabetic subjects as distinguished from patients with type 2 diabetes, the relatively few subjects in each group (n = 9) detracted from the universality of our findings. In addition, all 18 subjects came to our attention on the basis of relatively minor medical complaints, and none were totally healthy and asymptomatic. Finally, the criteria we used to divide subjects into low Mg (<0.80 mmol/L) and high Mg (<0.83 mmol/L) groups were somewhat arbitrary.

The current study was thus initiated to respond to these concerns. The results presented involve a definition of the relationship between the plasma Mg concentration and insulin-mediated glucose disposal in 98 healthy nondiabetic subjects studied as part of a health survey.

SUBJECTS AND METHODS

The study population consisted of 48 male and 50 female subjects evaluated at the outpatient clinic of the Center of Preventive Medicine as part of a health survey conducted in Pilsen. They had a mean age of 52 ± 1 years, a body mass index (BMI) of 26.9 ± 0.4 kg/m^2, and a waist to hip ratio (WHR) of 0.89 ± .013 (mean ± SEM). All of the participants reported good health, were taking no medications, including magnesium-containing antacids, and were nondiabetic by the criteria of the National Diabetes Data Group.[5]

After informed consent was obtained, blood was drawn after an overnight fast for determination of fasting plasma glucose[6] and insulin[7] and the concentration of magnesium (Mg) in plasma and erythrocytes by an enzymatic method[8] using commercial kits (Alpha Dialab, Prague, Czech Republic). In addition, a 24-hour urine collection was used to determine magnesium and creatinine excretion, and the serum creatinine level was measured to calculate creatinine clearance.

Resistance to insulin-mediated glucose disposal was estimated by a modification[9] of the original insulin suppression test. After an overnight fast, catheters were placed in a superficial antecubital vein in each arm. One arm was used for a continuous 180-minute infusion of glucose (240 mg/m^2 · min), octreotide (a bolus of 25 μg followed by 0.5 μg/min), and insulin (25 mU/m^2 · min). Venous blood samples for glucose and insulin determinations were obtained from the contralateral arm every 30 minutes (to 150 minutes) and then every 10 minutes for the last 30 minutes of the infusion.

The mean of these last 4 values was used to calculate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations. Under these experimental conditions, endogenous insulin secretion is suppressed by octreotide, the SSPI concentration achieved is comparable in all individuals, and the SSPG concentration provides a measure of insulin-mediated glucose disposal—the higher the SSPG, the more insulin-resistant the individual.

Results are presented as the mean ± SEM. For purposes of assessing the effect of variations in the plasma Mg concentration on insulin-mediated glucose disposal, the 98 subjects were divided into tertiles: low Mg (<0.83 mmol/L, n = 30), middle Mg (0.84 to 0.91 mmol/L, n = 35), and high Mg (>0.92 mmol/L, n = 30) groups. Statistical comparisons between the three groups were performed with the Kruskal-Wallis test, and the relationship between groups was defined by multiple linear regression analysis.

RESULTS

The age, gender, BMI, WHR, and fasting plasma glucose and insulin concentrations of the tertiles formed on the basis of plasma Mg levels are listed in Table 1. The three groups did not vary in terms of these baseline descriptors. Furthermore, fasting plasma glucose concentrations were similar in the three groups, as were erythrocyte magnesium concentrations and creatinine clearance. However, fasting plasma insulin was significantly higher in subjects in the tertile with the lowest Mg concentration, whereas 24-hour urinary excretion of Mg was lower in this group.

SSPI and SSPG concentrations of the three tertiles are

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Table 1. Baseline Characteristics of the Three Experimental Groups

Variable	Mg Tertile Low (n = 33)	Middle (n = 35)	High (n = 30)	P
Plasma Mg (mmol/L)	0.79 ± 0.008	0.87 ± 0.004	1.00 ± 0.013	NS
Age (yr)	53 ± 2	51 ± 1	52 ± 2	NS
Gender (male/female)	16/17	18/17	14/16	NS
BMI (kg/m²)	27.9 ± 0.9	26.2 ± 0.6	26.7 ± 0.7	NS
WHR	0.91 ± 0.02	0.89 ± 0.02	0.87 ± 0.02	NS
Creatinine clearance (mL/min)	101 ± 18	91 ± 8	98 ± 11	NS
Plasma glucose (mmol/L)	4.6 ± 0.3	4.5 ± 0.1	4.6 ± 0.1	NS
Plasma insulin (μU/mL)	23 ± 2	11 ± 1	11 ± 1	<.05
Erythrocyte Mg (mmol/L)	2.02 ± 0.15	2.18 ± 0.27	2.01 ± 0.20	NS
Urinary Mg excretion (mmol/24 h)	1.21 ± 0.45	1.44 ± 0.36	1.58 ± 0.54	<.05

illustrated in Fig 1. Despite the similarity of SSPI concentrations in the three groups, SSPG concentrations were different ($P < .05$), with SSPG being highest in the tertile with the lowest plasma Mg concentration (I), and lowest in the highest Mg tertile (III).

Another way to evaluate the relationship between plasma Mg and insulin resistance is to consider the population as a whole, for which the correlation coefficient (r) between the two variables was $-.27$ ($P < .01$). This relationship was comparable in magnitude to that found between SSPG and BMI ($r = .32$, $P < .01$) and somewhat greater than that found between SSPG and WHR ($r = .18$, P = NS). Furthermore, the correlation between the Mg concentration and SSPG remained significant ($r = -.22$, $P < .05$) when corrected for the BMI and WHR.

DISCUSSION

The results of the current experiments extend our prior observations[4] that relatively low Mg concentrations in nondiabetic subjects are associated with a decrease in insulin-mediated glucose disposal. However, the two studies differ in that the experimental population in the current study was approximately 5-fold larger and consisted of healthy subjects without any disease, and separation into low and high Mg groups was avoided. Given the results of this and our previous study[4] in nondiabetic subjects, prior evidence of insulin resistance in patients with type 2 diabetes,[1-3] as well as supportive evidence in various animal models,[10-13] a substantial amount of evidence has now been assembled supporting the view that variations in the plasma Mg concentration affect the ability of insulin to stimulate glucose disposal.

If the proposition that decreases in plasma Mg contribute to insulin resistance in humans is accepted, it is necessary to ask two further questions. Firstly, what is the quantitative importance of the role of differences in plasma Mg concentrations in accounting for the relatively enormous variation in insulin-mediated glucose disposal found in healthy subjects?[14] Our results defining the relationship between plasma Mg concentrations and insulin-mediated glucose disposal in 98 healthy subjects provide the information to address this issue. Specifically, the simple correlation coefficient between plasma Mg and SSPG concentrations was $-.27$, which decreased further to $-.22$ when adjusted for differences in the BMI and WHR. Although this relationship remained statistically significant, it suggests that no more than 5% ($.22^2$) of the variability of insulin-mediated glucose disposal can be accounted for by differences in the plasma Mg concentration. To place this in context, it should be pointed out that variations in the degree of obesity and level of habitual physical activity each appear to account for 20% to 25% of the variability in insulin-mediated glucose disposal in healthy individuals.[15] On the other hand, the range of plasma Mg concentrations in the healthy subjects enrolled in this study was relatively normal, and more substantial decreases in plasma Mg may play a more significant role in reducing insulin sensitivity.

Although the answer is certainly less definitive, a second issue that can be addressed relates to the causal relationship between insulin resistance and lower plasma Mg concentrations. At the simplest level, since the 24-hour urinary excretion of Mg was significantly lower in those with the lowest plasma

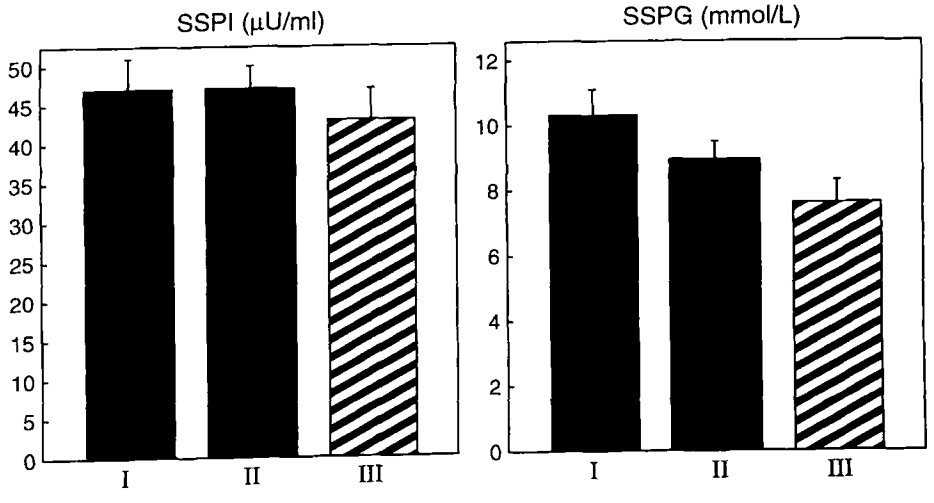

Fig 1. SSPI and SSPG concentrations during the insulin suppression test in the 3 tertiles of plasma Mg concentration: tertile I (lowest); tertile II (middle); and tertile III (highest). There were no differences in SSPI concentrations of the 3 groups. However, SSPG concentrations were significantly different ($P < .05$): highest in tertile I and lowest in tertile III.

Mg concentration, it suggests that the decrease in plasma Mg was secondary to a decrease in the dietary intake of Mg, not secondary to renal loss. A more difficult issue is the mechanism by which differences in the plasma Mg concentration affect insulin action. Given in vitro evidence that low Mg concentrations can reduce tissue glucose uptake,[12,13] it seems reasonable to speculate that decreases in plasma Mg interfere with the insulin signaling mechanism involved in glucose transport. In support of this possibility is evidence that muscle tyrosine kinase activity is decreased in rats fed a low-Mg diet.[13] However, it could be argued that a primary decrease in insulin action is the cause of the lower plasma Mg concentration, by either decreasing gastrointestinal absorption and/or increasing the renal excretion of Mg. Furthermore, it is possible that the association between a low plasma Mg concentration and insulin resistance is not primary, but is related to abnormalities of other cations, for example, a low plasma calcium concentration. Obviously, there is a great deal to be learned about the cellular/molecular mechanisms accounting for the inverse relationship between the plasma Mg concentration and insulin resistance.

In conclusion, the results of the present study in an unselected population of 98 healthy subjects, provide significant evidence that relatively low plasma Mg concentrations decrease the ability of insulin to stimulate glucose disposal. The decrease in plasma Mg is most likely secondary to lower dietary intake of Mg, and although the effect is modest in magnitude, it appears that variations in the plasma Mg concentration should be added to the list of nongenetic modulators of insulin action in nondiabetic healthy individuals.

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