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Effects of Insulin on Plasma Magnesium in Noninsulin-Dependent Diabetes Mellitus: Evidence for Insulin Resistance*

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ABSTRACT

Insulin influences both glucose metabolism and magnesium homeostasis in humans. The present studies sought to determine whether insulin-induced stimulation of magnesium uptake is impaired in noninsulin-dependent diabetes mellitus (NIDDM) and enhanced by acute hyperglycemia. To do so, we measured plasma magnesium concentrations in diabetic and nondiabetic subjects on two occasions: once when glucose concentrations were maintained constant and once when glucose concentrations were varied to mimic a postprandial pattern. The same amount of insulin was infused on both occasions in a manner that reproduced the systemic insulin concentrations normally observed after glucose ingestion. During the prandial insulin infusion, the decrement in the plasma magnesium concentration was lower ($P < 0.05$) in the diabetic patients than that in the nondiabetic subjects during both the euglycemic (4.1 ± 0.9 *vs.* 7.8 ± 1.3 mmol/L·4 h) and hyperglycemic (1.7 ± 1.1 *vs.* 6.6 ± 1.4 mmol/L·4 h) studies. Glucose disappearance also was lower ($P < 0.05$) in the diabetic patients than that in the nondiabetic subjects, and the insulin-induced decrement in plasma magnesium was correlated ($P < 0.01$) with glucose disappearance. On the other hand, despite higher ($P < 0.05$) rates of disappearance in the hyperglycemic than euglycemic experiments, the decrement in plasma magnesium did not differ in either group on either occasion. We conclude that insulin resistance in subjects with NIDDM impairs the ability of insulin to stimulate magnesium as well as glucose uptake. (*J Clin Endocrinol Metab* **80:** 1376–1381, 1995)

MAGNESIUM, the second most abundant intracellular cation, is indispensable to cellular metabolism (1). Insulin stimulates magnesium uptake in insulin-sensitive tissues (2). Recent evidence suggests that magnesium deficiency may, in an as yet undefined way, predispose to cardiovascular disease (3–5). For this reason, the recent observations that intracellular magnesium concentrations are decreased in insulin-resistant states such as hypertension, obesity, and noninsulin-dependent diabetes mellitus (NIDDM) (6); that magnesium deficiency can cause insulin resistance (4); and that insulin resistance in itself is associated with an increased risk of atherosclerosis (7) are provocative.

Previous studies in subjects with NIDDM have shown that plasma magnesium is inversely correlated with the degree of glycemic control (8, 9). This inverse relationship is believed to be due at least in part to the increased urinary loss of magnesium (10). Such losses could readily lead to decreased intracellular magnesium concentrations. Alternatively, if tissue magnesium uptake is normally regulated by insulin (11–13), then impairment of this process by insulin resistance could either cause or exacerbate intracellular magnesium deficiency. The latter hypothesis is supported by the report by Paolisso *et al.* (14) that insulin-induced erythrocyte magnesium accumulation is decreased in subjects with NIDDM, and that the severity of the defect correlates with the glucose disposal present during a hyperinsulinemic glucose clamp. The physiological significance of these observations remain uncertain, however, because erythrocytes are not considered to be a classic insulin-sensitive tissue, and insulin is rarely if ever maintained at a constant elevated concentration for several hours under conditions of daily living.

The present experiments were, therefore, undertaken to determine whether insulin-stimulated magnesium uptake is impaired in subjects with NIDDM. We also sought to determine whether hyperglycemia *per se*, by enhancing glucose disposal, has an additional effect on magnesium transport over that observed with insulin alone. To address these questions, we measured plasma magnesium concentrations in diabetic and nondiabetic subjects during their participation in a separate series of experiments in which we independently assessed insulin action and glucose effectiveness (15). We examined these parameters in the presence of insulin concentrations that mimicked those observed in nondiabetic subjects after glucose ingestion. We used this approach because recent studies have shown that insulin exerts a greater biological effect when its concentration is changing than when an identical amount of insulin is given as a constant infusion (16, 17). In the present experiments we report that the insulin-induced fall in plasma magnesium is impaired in NIDDM and is not enhanced by hyperglycemia.

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Subjects and Methods

Subjects

After approval by the Mayo Institutional Review Board, 11 subjects with NIDDM and 10 nondiabetic subjects gave written informed consent to participate in the study. Diabetic and nondiabetic subjects were matched for gender, age, body mass index, waist/hip ratio, and percent body fat (Table 1). Diabetes duration averaged 5.1 ± 1.1 yr (mean ± SEM). Fasting plasma glucose and glycosylated hemoglobin levels were measured during the initial visit. At that time, 7 patients were being treated with sulfonylureas, and 4 with diet alone. In the former, sulfonylurea treatment was discontinued 3 weeks before the study. All subjects were in good health, had normal blood pressure, and were at stable weight. None regularly engaged in vigorous aerobic exercise or was taking any medications other than sulfonylureas. The nondiabetic subjects did not have a family history of diabetes.

Experimental design

Subjects were admitted to the Mayo Clinical Research Center on the evening before the study. A standard meal was given between 1700–1800 h. All subjects were fasted thereafter until the end of the study. After placement of an 18-gauge catheter in a forearm vein, an insulin infusion was started at the time of the evening meal in the diabetic subjects and adjusted throughout the night using the algorithm of White to maintain euglycemia (18). The nondiabetic subjects were infused with 0.9% saline. On the following morning, two additional iv catheters were placed: one in a forearm vein to permit hormone, glucose, and tracer infusion and one retrograde in a contralateral hand vein. That hand was then placed in a Plexiglass box that was heated to 55–60 C to permit sampling of arterialized venous blood. An infusion of somatostatin (60 ng/kg·min), glucagon (0.65 ng/kg·min), and GH (3 ng/kg·min) was initiated at 0700 h (−240 min) to insure that endogenous hormone secretion was constant and equal in both groups throughout the study. Insulin was also infused in all subjects in an amount sufficient to maintain euglycemia. The last adjustment in the rate of this basal insulin infusion was made 30 min before the start of the prandial insulin infusion. A primed (3-μCi) continuous (0.03 μCi/min) infusion of [6-^{14}C]glucose was started at −120 min to enable measurement of glucose turnover. At time zero, the prandial insulin infusion was initiated using a computer-driven infusion pump, as previously described (19). Glucose containing [6-^{14}C]glucose was infused in amounts sufficient to maintain euglycemia on one occasion; on a second occasion, a prandial glucose profile was mimicked, as previously described (19). The order of the studies was random. Euglycemic studies were performed in all subjects; nine nondiabetic and eight diabetic subjects also participated in the hyperglycemic studies.

Blood was collected for glucose, insulin, C-peptide, glucagon, GH, glucose specific activity, and magnesium determinations before and at regular intervals during the prandial insulin infusion. Samples for magnesium were placed in tubes containing ethylenediamine tetraacetate.

Analytical techniques

Analysis of plasma magnesium was performed by atomic absorption spectroscopy, as described by Wills (20). All analysis was completed within 8 h of sample collection. Plasma insulin, C-peptide, glucagon, GH, and glucose specific activity were measured as previously described (21, 22). Body fat composition was determined by dual energy x-ray absorptiometry (DPX scanner, Lunar Corp., Madison, WI). The glycosylated hemoglobin concentration was measured by affinity chromatography (Gly-Affin, Isolab, Akron, OH; normal range, 4–7%).

TABLE 1. Clinical characteristics of subjects

	Nondiabetic subjects	NIDDM subjects
No.	10	11
Sex (M/F)	5/5	8/3
Age (yr)	55 ± 2	54 ± 2.3
Body mass index (kg/m^2)	28.4 ± 1	29.0 ± 1.0
Waist/hip ratio	0.90 ± 0.02	0.94 ± 0.02
Body fat (%)	34 ± 3.0	32 ± 3
Fasting plasma glucose (mmol/L)	5.3 ± 0.05	12.4 ± 1.2
Glycosylated hemoglobin-A_1 (%)		10.2 ± 0.7

Calculations and statistical analysis

Glucose disappearance was calculated using the two-compartment model proposed by Radziuk (23). Data in the text and figures are expressed as the mean ± SEM. Integrated responses were calculated using the trapezoidal rule. The area below the baseline was used to calculate the decrement in plasma magnesium during the insulin infusion. Results between groups (diabetic *vs.* nondiabetic), nonpaired and within-group (hyperglycemia *vs.* euglycemia), were compared using paired Student's *t* test. Linear regression analysis and, where appropriate, Spearman rank analysis were used to test for correlations. $P < 0.05$ was considered statistically significant.

Results

Glucose and insulin concentrations

Glucose concentrations did not differ in the diabetic and nondiabetic subjects before or during the prandial insulin infusion on either the euglycemic or hyperglycemic study days (Fig. 1). Basal insulin concentrations were slightly, but not significantly, higher in the diabetic compared to the nondiabetic subjects during both the euglycemic (126 ± 18 *vs.* 87 ± 8 pmol/L) and hyperglycemic (124 ± 28 *vs.* 88 ± 12 pmol/L) studies. The increment in plasma insulin concentrations was equal in the diabetic and nondiabetic subjects during both studies. Plasma C-peptide, glucagon, and GH concentrations were similar before and remained constant and comparable during the prandial insulin infusion in both groups on both study days (data not shown).

Glucose disappearance

Glucose disappearance during the prandial insulin infusion was lower ($P < 0.05$) in the diabetic patients than in the nondiabetic subjects in the presence of both euglycemia (2.19 ± 0.14 *vs.* 3.08 ± 0.23 mmol/kg·4 h) and hyperglycemia (2.73

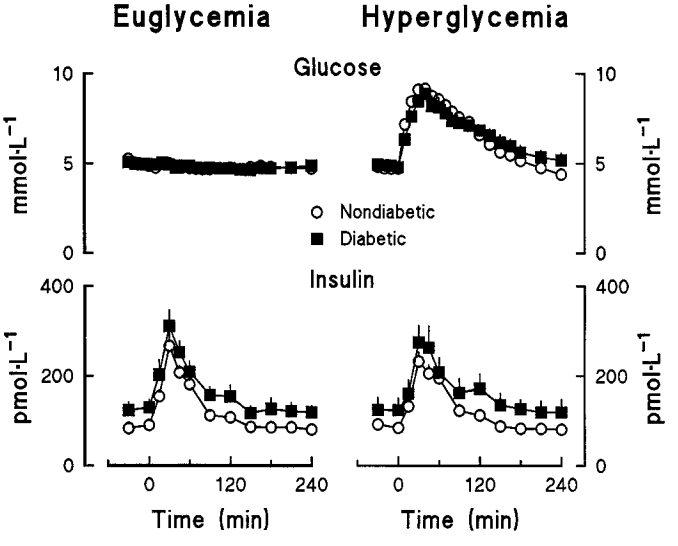

FIG. 1. Plasma glucose and insulin concentrations during the physiological insulin infusion (0–240 min) in diabetic and nondiabetic subjects during euglycemic and hyperglycemic studies.

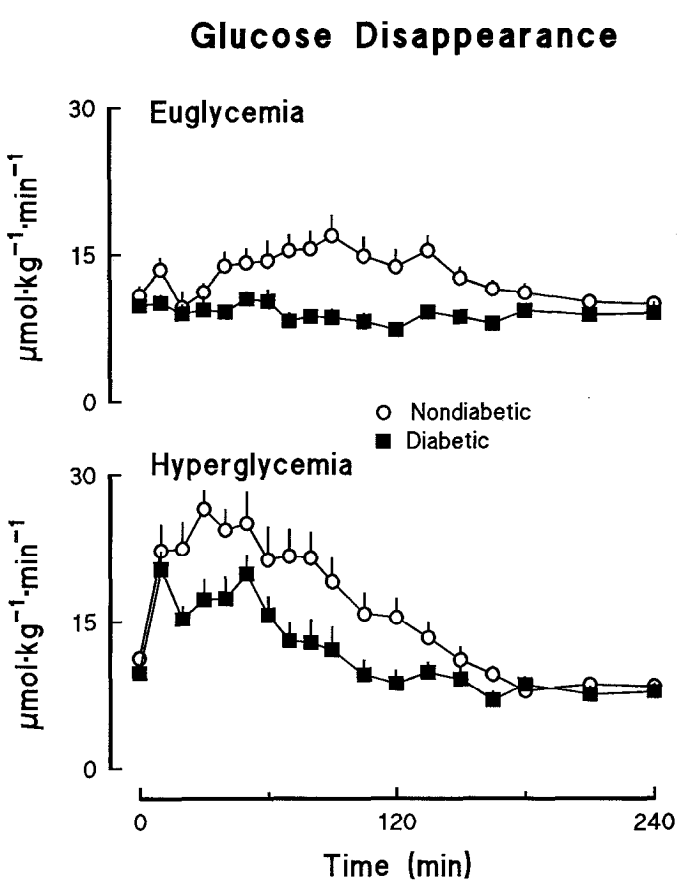

FIG. 2. Rates of glucose disappearance observed in the diabetic and nondiabetic subjects during the euglycemic and hyperglycemic studies.

± 0.21 *vs.* 3.69 ± 0.32 nmol/kg·4 h; Fig. 2). Glucose disappearance in the presence of hyperglycemia was higher ($P <$ 0.02) than that observed during euglycemia in both groups.

Effects of insulin on plasma magnesium concentration

Despite comparable glucose concentrations, the plasma magnesium concentration was lower ($P < 0.05$) in the diabetic patients than that in nondiabetic subjects on both the euglycemic (0.81 ± 0.03 *vs.* 0.89 ± 0.02 mmol/L; $P < 0.05$) and hyperglycemic (0.79 ± 0.03 *vs.* 0.86 ± 0.02 mmol/L) study days. The prandial insulin infusion resulted in a decrease in magnesium in both groups on both study days (Fig. 3). The decrement in plasma magnesium below baseline during the prandial insulin infusion was smaller ($P < 0.05$) in the diabetic patients than in the nondiabetic subjects during both euglycemic (4.1 ± 0.9 *vs.* 7.8 ± 1.3 mmol/L·4 h) and hyperglycemic (1.7 ± 1.1 *vs.* 6.6 ± 1.4 mmol/L·4 h) studies (Fig. 3). Of note, despite substantially higher rates of glucose disappearance, the decrement in plasma magnesium during the hyperglycemic study did not differ from that observed during the euglycemic study in either the nondiabetic (−16.1 ± 3.4 *vs.* −17.9 ± 3.3 mmol/L·4 h; $P = 0.58$) or diabetic (−4.1 ± 2.6 *vs.* −11.1 ± 2.6 mmol/L·4 h; $P = 0.068$) subjects (Fig. 4).

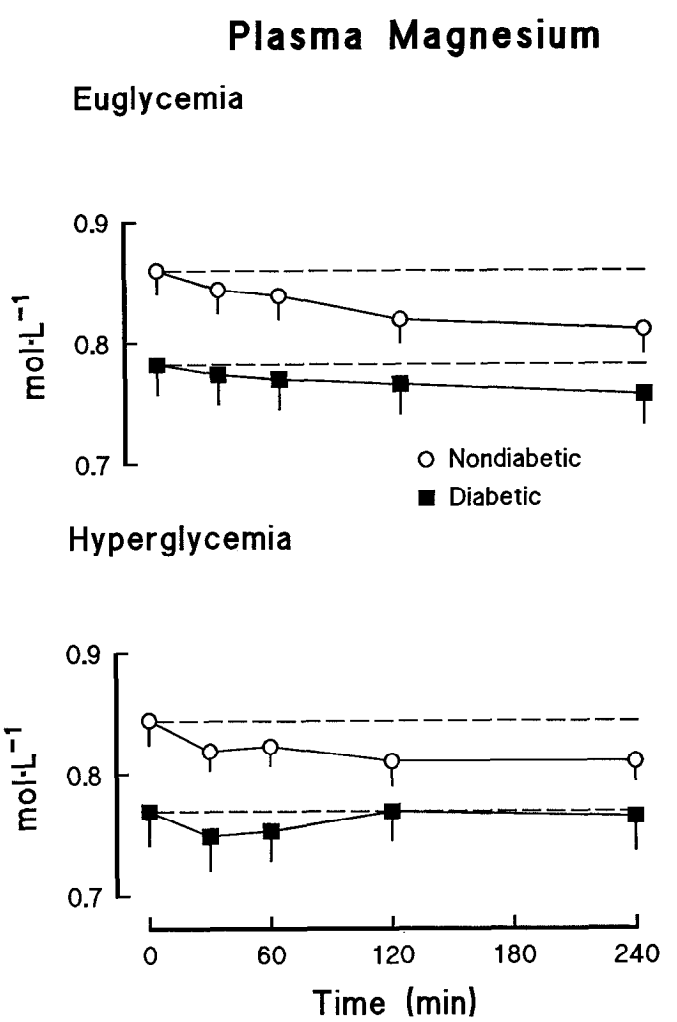

FIG. 3. Response of plasma Mg to a physiological insulin infusion in the diabetic and nondiabetic subjects during euglycemic (*upper panel*) and hyperglycemic (*lower panel*) studies. The *broken lines* represent extensions of the respective baseline values.

Correlations

Plasma magnesium was inversely related to glycosylated hemoglobin (measured only in the diabetic subjects) and fasting glucose concentrations (all subjects; Fig. 5). Plasma magnesium was also inversely related to the fasting insulin concentration ($r = -0.70$; $P < 0.001$). The decrement in plasma magnesium during the prandial insulin infusion correlated positively with glucose disappearance in all subjects ($r = 0.55$; $P < 0.01$; Fig. 6). On the other hand, the decrement in magnesium showed no relationship to suppression of hepatic glucose release (data not shown).

Discussion

People with NIDDM are resistant to insulin (24–26). The present studies indicate that this resistance not only impairs the ability of insulin to stimulate glucose uptake, but it also impairs the ability of insulin to lower the plasma magnesium concentration. Although glucose disappearance was considerably greater during the hyperglycemic experiments than

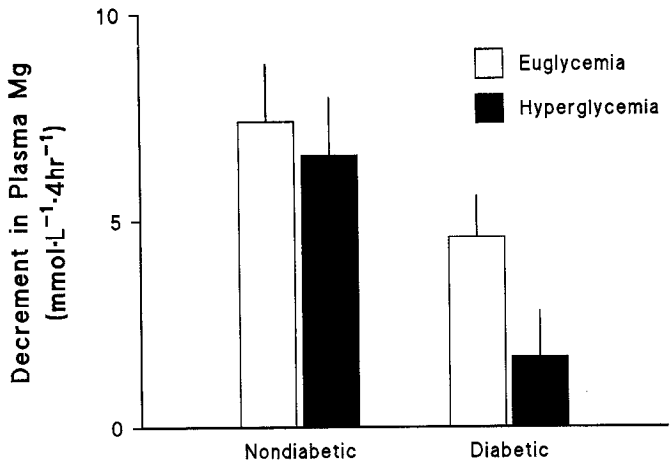

FIG. 4. Decrement in plasma Mg below the baseline in diabetic and nondiabetic subjects during the euglycemia and hyperglycemic experiments.

that during the euglycemic experiments in both the diabetic and nondiabetic subjects, the decrement in plasma magnesium did not differ on the 2 study days. The correlation between insulin-induced increases in tissue glucose uptake and insulin-induced decreases in plasma magnesium concentration is consistent with the regulation of both processes via a common proximal step.

Magnesium has recently attracted considerable interest because of its potential role in the pathogenesis of disease states such as hypertension, coronary heart disease, and diabetic complications (4–6, 27). Magnesium appears to be an important determinant of vascular tone (28) and is a cofactor in numerous intracellular enzymatic reactions, including some critical to glucose metabolism (1). Diabetic patients are susceptible to magnesium depletion (29, 30). Consistent with previous studies (31, 32), we noted that the plasma magnesium concentration is decreased in diabetic subjects and is inversely correlated with both glycosylated hemoglobin and fasting glucose concentration. Although the cause of the low plasma magnesium concentration in diabetic individuals has not been fully established, it is highly probable that glycosuria contributes to magnesium deficiency by causing excessive urinary loss (10). However, other factors may be involved, as Schnack *et al.* (33) recently reported that magnesium deficiency persisted in a group of patients with NIDDM despite improved long term glycemic control. The present studies show that restoration of euglycemia produced by an overnight iv insulin infusion also does not return plasma magnesium concentrations to nondiabetic levels.

The present studies confirm previous reports (34) that plasma insulin and magnesium concentrations are inversely correlated. Such a relationship could occur if insulin resistance impaired tissue uptake of glucose, but not magnesium. In this circumstance, insulin resistance would lead to increased insulin secretion and higher insulin concentrations. If insulin's effects on magnesium transport were intact, the higher insulin concentrations presumably would decrease plasma magnesium by shifting magnesium into insulin-sensitive cells. The present studies do not support this sequence of events, as the insulin-induced decrease in the magnesium concentration and the increase in glucose uptake were proportionate to one another. The lesser fall in magnesium concentration in the diabetic subjects is unlikely to be simply due to their lower rates of glucose disposal, because insulin action, rather than the absolute rate of disposal, appears to be the primary determinant of magnesium transport. Thus, further stimulation of glucose disposal by means of hyperglycemia did not cause a greater fall in the magnesium concentration in either the diabetic or nondiabetic subjects than did the same dose of insulin given in the presence of euglycemia. If anything, the decrement in plasma magnesium tended to be slightly less during the hyperglycemic than euglycemic experiments. *In vitro* experiments have shown that hyperglycemia can decrease intracellular magnesium concentrations in red blood cells through an insulin-independent pathway (35). Thus, the hyperglycemia-induced stimulation of glucose uptake in the present experiment, by increasing intracellular glucose concentrations, may have enhanced the cellular release of magnesium back into the extracellular space. This, in turn, could have offset the insulin-induced decrement in the plasma magnesium concentration.

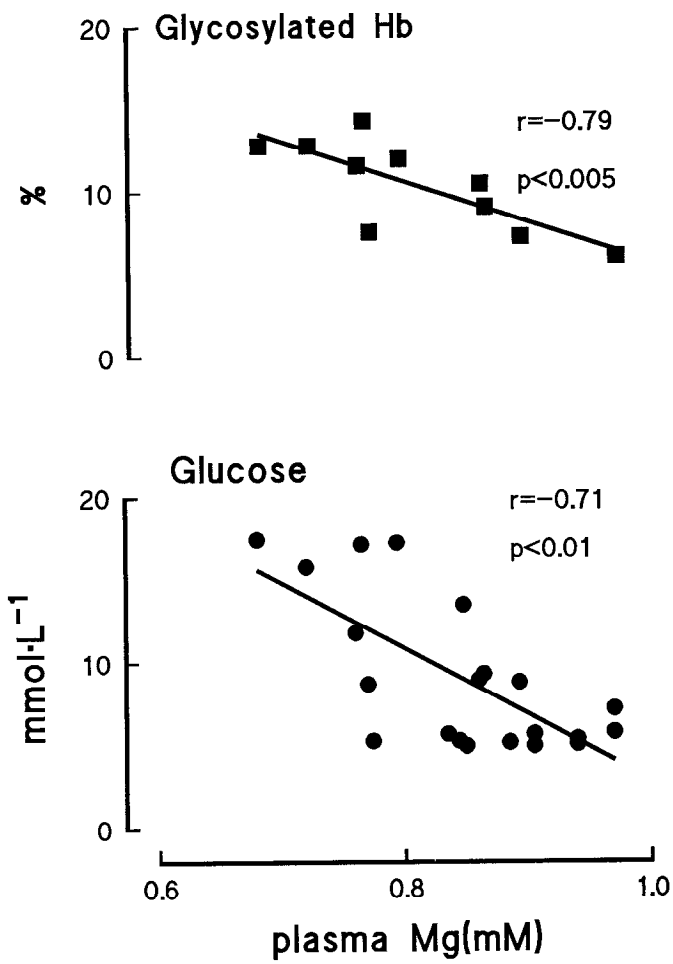

FIG. 5. Relation of fasting Mg concentration to glycosylated hemoglobin-A_1 (*upper panel*; diabetic subjects only) and fasting plasma glucose concentrations (*lower panel*) in diabetic and nondiabetic individuals.

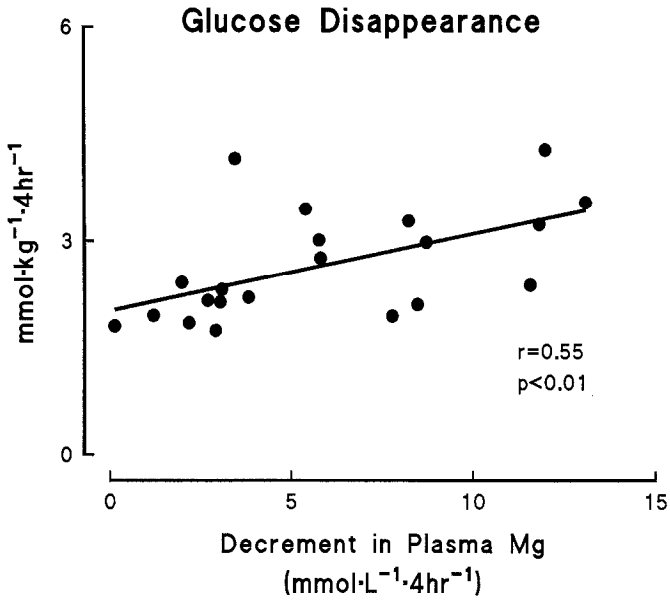

FIG. 6. Relation of decrement in plasma Mg to rates of glucose disposal during the euglycemic studies.

The observation that insulin produced a lesser decrement in plasma magnesium in diabetic than nondiabetic subjects is consistent with *in vitro* studies which have shown that erythrocytes obtained from diabetic people take up less magnesium when incubated with insulin than do erythrocytes obtained from nondiabetic controls (14). These data also suggest that the lesser fall in plasma magnesium after glucose ingestion in subjects with glucose intolerance is due to defects in insulin action as well as alterations in insulin secretion (36).

As discussed in detail previously (3, 29), decreased magnesium transport has intriguing implications regarding the mechanism of insulin resistance and the pathogenesis of chronic diabetic complications. Both calcium and magnesium are transported by adenosine triphosphatase-dependent processes (2, 11). Calcium and magnesium appear to have opposite effects on a variety of intracellular processes (6). Draznin *et al.* (37) reported that insulin increases intracellular calcium concentrations and that excessive intracellular calcium can cause insulin resistance. If magnesium uptake is impaired, then insulin could result in a disproportionate influx of calcium into insulin-sensitive tissues. In this circumstance, intracellular magnesium deficiency presumably could cause or exacerbate insulin resistance in NIDDM. This speculation is supported by the demonstration by Nadler *et al.* (4) that diet-induced magnesium deficiency produces insulin resistance. If, indeed, magnesium deficiency causes insulin resistance, then one could argue that lower total body magnesium (as reflected by lower fasting plasma magnesium concentrations) in the diabetic subjects not only impaired insulin-induced stimulation of glucose uptake, but also inhibited its own uptake. Intracellular magnesium deficiency may have a variety of other effects, including alteration of thromboxane synthesis (4), platelet aggregatibility (38), vascular contractility (28), and angiotensin-mediated aldosterone synthesis (4). However, the extent to which these *in vitro* observations pertain to human physiology remains to be determined.

As with all studies, the present experiments have limitations. Plasma concentrations were measured rather than free Mg levels within the cells of insulin-sensitive tissues. Thus, although we have shown a clear defect in the ability of insulin to lower plasma magnesium concentrations in diabetic subjects, we have not directly assessed magnesium transport in specific tissues. Therefore, the present experiments cannot determine whether insulin's effects on magnesium uptake are equally impaired in all insulin-sensitive cells, nor is it known whether this defect is intrinsic to NIDDM or is secondary to the associated metabolic abnormalities (*e.g.* hyperinsulinemia).

In summary, the present studies demonstrate that the ability of insulin to lower plasma magnesium levels is impaired in people with NIDDM. The insulin-induced fall in plasma magnesium is not accentuated by hyperglycemia, implying that insulin *per se*, rather than enhanced glucose disposal, stimulates magnesium transport. Additional studies will be required to determine whether abnormal magnesium transport leads to and/or is caused by insulin resistance.

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