Fasting plasma magnesium concentrations and glucose disposal in diabetes

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Abstract

Fasting plasma concentrations of magnesium were measured by neutron activation analysis in 30 non-diabetics and 87 diabetics (55 non-insulin-treated, 32 insulin treated). Plasma concentrations of magnesium were lowest in the insulin treated group (mean 0·84 (SEM 0·01) mmol/l; 2·0 (0·02) mg/100 ml), intermediate in the non-diabetics (mean 0·89 (SEM 0·01) mmol/l; 2·2 (0·02) mg/100 ml), and highest in the non-insulin-treated diabetics (mean 0·95 (SEM 0·02) mmol/l; 2·3 (0·05) mg/100 ml). In all diabetics plasma magnesium concentrations were inversely related to plasma glucose values ($r_s = -0.33$; $p < 0.01$) and in non-insulin-treated patients to plasma insulin concentrations ($r_s = -0.28$; $p < 0.05$), the former confirming previous observations. In 67 of the diabetics the K_G constant for disposal rate of glucose during a standard intravenous glucose tolerance test was directly related to fasting plasma magnesium concentrations, and this relation persisted after controlling for age, sex, body mass index, type of treatment, and glucose and insulin values.

This direct relation of plasma magnesium concentration with glucose disposal was unexplained by its influence on insulin secretion but was related to insulin sensitivity; hence magnesium may be an important determinant of insulin sensitivity in maturity onset diabetes.

Introduction

Magnesium is an essential element[1] and is a cofactor in both glucose transporting mechanisms of cell membranes[2] and various enzymes important in carbohydrate oxidation.[3] It also plays a part in mechanisms for energy transfer mediated by phosphate bonds.[3] The concentrations of magnesium in the serum of healthy people are remarkably constant.[4] Diabetic patients may develop hypomagnesaemia,[5 6] possibly because excessive urinary loss of magnesium accompanies glycosuria.[7 8] Hypomagnesaemia has been claimed as a risk factor for diabetic retinopathy[9] and to produce insulin resistance after diabetic ketoacidosis.[10] A deficient supply of magnesium in areas with soft water may be a risk factor for ischaemic heart disease.[11 12]

From random clinic samples[6] and diurnal profiles of diabetics and non-diabetics,[13] Mather et al discovered an inverse correlation between plasma concentrations of magnesium and glucose. We do not know, however, whether plasma magnesium affects the disposal of glucose loads from the blood, nor whether it is related to the plasma insulin concentration. We have therefore studied plasma magnesium concentrations in diabetic patients, both fasting and after intravenous glucose.

Subjects and methods

Table I gives clinical and laboratory data on the 87 diabetics and 30 non-diabetics who agreed to cooperate in the study. Thirty two diabetic subjects were receiving insulin at the time of study; of the remaining 55, non-insulin-treated diabetics, 43 were taking oral sulphonylureas and 12 were being managed by diet alone. All subjects had normal liver function values, two had a plasma creatinine concentration above 150 μmol/l (1·7 mg/100 ml), but none had clinically detectable proteinuria. Three patients were receiving thiazide diuretics.

TABLE I—Basic information on subjects studied. Values are means (SEM in parentheses)

	Non-diabetics (n = 30)	Insulin treated diabetics (n = 32)	Non-insulin-treated diabetics (n = 55)	All diabetics (n = 87)
Age (years)	46·5 (2·3)	45·9 (2·7)	59·7 (1·1)**	54·7 (1·4)**
Men (%)	56	59	76*	70*
Body mass index (weight in kg/height in m²)	22·9 (0·8)	25·5 (0·9)*	27·2 (0·6)**	26·7 (0·5)**
Glucose (mmol/l)		12·9 (1·0)	8·1 (0·4)	9·8 (0·5)
Insulin (mU/l)			8·1 (0·7)	
HbA₁c(%)		12·2 (0·6)	10·0 (0·4)	10·8 (0·4)
K_G†		0·55 (0·05)	0·80 (0·05)	0·70 (0·04)
Magnesium (mmol/l)	0·89 (0·01)	0·84 (0·01)**	0·95 (0·02)**	0·91 (0·01)

All concentrations except HbA₁c measured in fasting blood plasma.
Compared with non-diabetics: *$p < 0.05$; **$p < 0.01$.
†K_G = Rate constant for decrease of glucose during intravenous glucose tolerance test.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. Magnesium: 1 mmol/l ≈ 2·4 mg/100 ml.

Blood samples from fasting subjects were collected in special lithium heparin containers for elemental analysis and separately for glucose, insulin, and "metabolite" measurements. Patients did not take their antidiabetic treatment on the morning of the test. Sixty seven of the diabetics were given an intravenous glucose tolerance test, 50% glucose solution (20 g glucose/m² body surface) being injected intravenously over two minutes. This test was done three or five years after diagnosis as part of a prospective study on a larger group of diabetics.

Plasma magnesium concentration was determined by neutron activation analysis using the ²⁷Mg nuclide (half life 9·5 minutes, γ ray energies 843, 1014 keV) after the elimination of sodium with hydrated antimony pentoxide.[14] The coefficient of variation for 10 replicate analyses of "pooled" blood plasma was 7%, and there was 101% recovery of magnesium added to the pooled sample at a concentration of 0·82 mmol/l (2·0 mg/100 ml). Fasting plasma samples were similarly collected for elemental analysis from 30 non-diabetics for comparison.

Plasma glucose concentration was measured on an autoanalyser by the glucose oxidase (gum guaiac) method of Technicon Instruments (Tarrytown, USA), and metabolites were measured as described.[15] Plasma insulin was measured by radioimmunoassay.[16] Haemoglobin A₁c (HbA₁c) was measured by an isoelectrofocusing method with a five hour incubation of the dialysed sample at 37°C to exclude short term glucose adducts.[17] The rate constant (K_G) for decline in blood glucose during an intravenous glucose tolerance test was calculated from plasma glucose values from 10 to 60 minutes after intravenous injection of glucose.[18] The insulin resistance factor was calculated

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from fasting glucose and insulin values[19]; this factor is a quantitative expression of a person's resistance to the action of insulin, an arbitrary scale being used on which normal, non-diabetic subjects have a value of 1 or less.

Results are expressed as means and SEM and were analysed either by Student's *t* test (unpaired or paired) or non-parametrically by Spearman's correlation coefficient (r_s). Multiple linear regression analysis was performed on an ICL 2980 computer according to the program of the statistical package for the social sciences,[20] the data having been normalised as necessary by appropriate mathematical conversions.

Results

The fasting plasma magnesium concentration was lower in the insulin treated and higher in the non-insulin-treated diabetics than in the non-diabetic subjects (table I). Magnesium concentration was positively correlated with age when results for both groups of diabetics were pooled (table II); among the non-insulin-treated patients women had a lower magnesium concentration than men (p < 0·05). The plasma magnesium concentrations in two subjects with raised plasma creatinine values and three subjects receiving thiazide diuretics were comparable to those of the rest of the group.

TABLE II—*Correlation of fasting magnesium values with other factors*

	Non-diabetics	Insulin treated diabetics	Non-insulin-treated diabetics	All diabetics
Age (years)	0·11	0·33	0·02	0·33**
Sex	0·13	0·22	−0·28*	−0·17
Glucose (mmol/l)		−0·28	−0·21	−0·33**
HbA$_{1c}$(%)		−0·55**	−0·25	−0·44***
Insulin (mU/l)			−0·28*	
Insulin A$_{0-90}$†			−0·002	
KG‡		0·09	0·22	0·31**
3-Hydroxybutyrate (mmol/l)		0·06	−0·10	−0·23*
Acetoacetate (mmol/l)		−0·07	−0·14	−0·27*
Free fatty acids (mmol/l)		0·13	−0·06	−0·12
Insulin resistance factor§			−0·36**	

Metabolites refer to fasting concentrations in blood plasma for glucose, insulin, free fatty acids, and magnesium, and whole blood for 3-hydroxybutyrate and acetoacetate.
Inverse correlation with sex denotes lower values in women.
*p < 0·05; **p < 0·01; ***p < 0·001 (Spearman's correlation coefficient).
†Insulin A$_{0-90}$ refers to total area under insulin *v* time curve for 90 minutes after intravenous injection of glucose.
‡KG = Rate factor for disappearance of glucose from plasma.
§Insulin resistance factor calculated according to Turner *et al*.[19]
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml. 3-Hydroxybutyrate: 1 mmol/l ≈ 10·4 mg/100 ml. Acetoacetate: 1 mmol/l ≈ 10·2 mg/100 ml. Free fatty acids: 1 mmol/l ≈ 25·6 mg/100 ml.

Plasma concentrations of magnesium and glucose were inversely correlated, as were those of magnesium and HbA$_{1c}$ (table II). In the whole diabetic group there was a direct correlation between magnesium and the rate of decrease in glucose after its injection (as measured by the K_G rate constant) (see figure). This relation between magnesium and K_G was not secondary to the original relation between magnesium and glucose and the known inverse relation between fasting glucose and K_G because it remained significant, even when the interaction of each factor with glucose had been allowed for (r = 0·32; p < 0·01).

Plasma magnesium concentration was inversely related to the fasting plasma insulin value in non-insulin-treated patients (table II) but not to the total secretion of insulin during the intravenous glucose tolerance test. The relation with fasting insulin was in part secondary to the relation of both to the degree of obesity. The plasma concentration of magnesium was inversely related to those of the ketone bodies 3-hydroxybutyrate and acetoacetate. It was, however, not related to free fatty acid concentrations.

Because of the interrelations of the various factors listed above multiple linear regression analysis of the K_G rate constant was performed. For all the diabetics the link between plasma magnesium concentration and the K_G rate factor remained significant (p < 0·05), even with allowance for interactions with the mode of treatment of diabetes, age, sex, body mass index, and the concentrations of glucose and ketone bodies.

The plasma magnesium concentration fell by about 4% during the intravenous glucose tolerance test but this was not statistically significant.
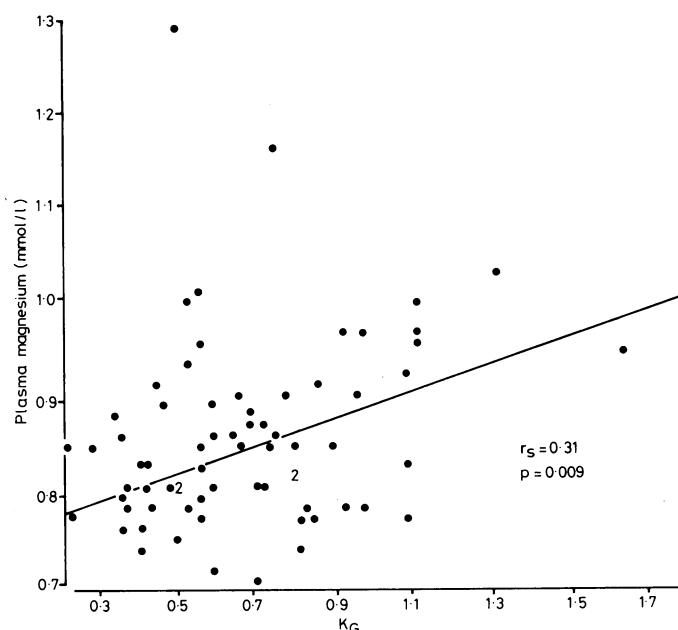
Plot of K_G against fasting magnesium values in insulin dependent and non-insulin-dependent diabetics.
Conversion: SI to traditional units—Magnesium: 1 mmol/l ≈ 2·4 mg/100 ml.

Discussion

Plasma magnesium concentrations have been reported to be lower,[5 6 9] similar,[21] or higher[22] in diabetic than in non-diabetic subjects. We found no significant difference in plasma magnesium concentrations between the non-diabetic controls and all the diabetic subjects taken together. There were significant differences, however, when insulin treated and non-insulin-treated diabetics were considered separately. Insulin treated diabetics had lower and non-insulin-treated diabetics higher plasma magnesium concentrations than non-diabetic subjects. Among the diabetics plasma magnesium concentration was related directly to age, and men had significantly higher concentrations than women in the non-insulin-treated group. Greater age and male preponderance possibly contributed to the higher plasma magnesium concentrations in our non-insulin-treated diabetic group.

Our findings confirm for fasting morning samples the inverse relation between the plasma concentrations of magnesium and glucose previously observed in random clinic samples[6] as well as throughout the diurnal cycle.[13] We also found a strong and inverse relation between plasma concentrations of magnesium and HbA$_{1c}$. The inverse relation between magnesium and the concentrations of 3-hydroxybutyrate and acetoacetate probably reflects the association of a higher plasma magnesium value with better general metabolic control.

A direct relation was observed between the fasting plasma magnesium concentration and the rate of disappearance of intravenously injected glucose. Arguably these related features were both consequences of the severity of hyperglycaemia, with higher urinary losses of magnesium in the more hyperglycaemic and so lower plasma magnesium concentrations in those with the lower K_G values. The correlation between plasma magnesium and K_G, however, was even stronger among those with a fasting glucose concentration below 7·0 mmol/l (126 mg/100 ml) (r_s = −0·53; p < 0·01), refuting that possibility.

The relation with glucose disappearance rate may be because higher plasma magnesium values are linked with either greater insulin secretion by the pancreatic β cells in response to the glucose stimulus or increased sensitivity of the tissues to the hypoglycaemic action of insulin. The inverse relation between fasting magnesium and insulin, and even more the lack of relation between the plasma magnesium concentration and the

total insulin secretion in the intravenous glucose tolerance tests, argue against a prime link with insulin supply. The relation of plasma magnesium persisted with the K_G rate constant but not with the fasting blood glucose value when interactions between the latter two were allowed for, which further supports an effect mediated by glucose disposal. A factor expressing the resistance to the action of insulin in lowering blood glucose concentrations may be calculated,[19] and this correlated strongly and inversely with the plasma concentration of magnesium ($r_s = -0.36$; p <0.01). This gives direct support to emphasis on an improvement of the sensitivity of tissues to the action of available insulin in explaining how magnesium acts.

If a fault in diabetes mellitus were to impair the usual intracellular binding of magnesium the plasma magnesium concentration would tend to increase, depending on both the renal handling of magnesium and the total body magnesium value. When extracellular magnesium is high the efflux from cells would diminish, lessening the reduction in intracellularly active magnesium; this might explain the higher glucose disappearance rate.

Insulin resistance makes a variable but significant contribution to the pathogenesis of non-insulin-dependent diabetes mellitus. This resistance may reside at receptor or postreceptor level. Ionic imbalance of the type we describe might contribute significantly to postreceptor resistance. The increased rate of disposal of intravenously injected glucose, when the plasma magnesium concentration is higher, is compatible with the role of magnesium as a cofactor in glucose transporting mechanisms of the cell membrane[2] and important intracellular enzymes of carbohydrate metabolism—for example, pyruvate dehydrogenase. It also accords with (but does not necessarily explain) the glucose intolerance of malnutrition and of diuretic treatment, in either of which there may be hypomagnesaemia.[23] [24] It is probably relevant that glucose intolerance of these two conditions is said to be due to relative insulin resistance. In a recent review glucose intolerance was considered to be a disadvantage of diuretic treatment additional to potassium and magnesium abnormalities[23]; perhaps it should rather be considered as another expression of these ionic imbalances.

This implication of magnesium as an important factor in glucose metabolism might at least partially explain its postulated role in diabetic retinopathy and large vessel disease. Cardio-vascular disease is a major cause of illness and death in diabetics, and it is intriguing to speculate whether the elemental disturbance described here reflects an abnormality similar to that linking heart disease with softness of the local water supply, where tissue magnesium concentrations may be lowered as a result of reduced intake.

Magnesium supplementation improves blood pressure control[25] and retention of concomitantly administered potassium supplements in patients receiving diuretics.[26] One of the most abundant of earth's metallic elements and quantitatively the fourth most plentiful cation in vertebrates, magnesium may have wider metabolic implications than suspected hitherto. It will be important to determine whether oral magnesium supplementation of diabetics increases plasma magnesium concentrations and whether this will lower the K_G rate constant.

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