Magnesium levels and diabetic retinopathy*)

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Zusammenfassung

Bei 109 Diabetikern und 33 gesunden Probanden wurden mittels Atomabsorptionsspektrophotometrie die Magnesium (Mg)-Konzentrationen in Plasma, Erythrozyten und im Urin bestimmt. Für die Kontroll- bzw. Diabetikergruppe betrugen das Plasma-Mg: 1,65 ± 0,13 mEq/l (Mittelwert ± SD) gegenüber 1,59 ± 0,13 mEq/l ($p < 0,05$), das Erythrozyten-Mg: 4,93 ± 0,61 mEq/l gegenüber 4,77 ± 0,59 mEq/l und die Mg-Ausscheidung im Urin 4,01 ± 1,25 mEq/Tag gegenüber 5,59 ± 2,17 mEq/Tag ($p < 0,025$). Die Tendenz zu erniedrigtem Plasma-Mg und erhöhter Mg-Ausscheidung im Urin war am ausgeprägtesten in einer Untergruppe aus schlecht kontrollierten Diabetikern mit Blutzuckerwerten über 250 mg/dl. Andererseits waren Plasma-Mg und Erythrozyten-Mg am stärksten erniedrigt bei Patienten mit proliferativer diabetischer Retinopathie, selbst dann, wenn die Blutzuckerwerte im Bereich der Werte der anderen Diabetikergruppen mit oder ohne Retinopathie lagen.

Die Ergebnisse lassen vermuten, daß Störungen des Mg-Metabolismus eine Beziehung zur Auslösung und/oder der Entwicklung einer diabetischen Retinopathie haben können.

Summary

Magnesium (Mg) levels in plasma, erythrocyte and urine were determined, using atomic absorption spectrophotometry in 109 diabetic patients and 33 healthy subjects. Mg levels were 1.65 ± 0.13 mEq/l (mean ± SD) vs. 1.59 ± 0.13 mEq/l in plasma ($p < 0.05$), 4.93 ± 0.61 mEq/l vs. 4.77 ± 0.59 mEq/l in erythrocyte and 4.01 ± 1.25 mEq/day vs. 5.59 ± 2.17 mEq/day in urine ($p < 0.025$), for the control and diabetic groups respectively. The tendency toward reduced Mg level in plasma and increased urinary excretion was greatest in a subgroup of poorly controlled diabetics, whose fasting blood sugar levels were above 250 mg/dl. On the other hand, reduced Mg levels in plasma and erythrocyte was most pronounced in a group of patients with proliferative diabetic retinopathy, even when blood sugar was controlled to match that of the nonretinopathy group and of the background retinopathy group.

These results suggest that derangement of Mg metabolism may have some relationship to the onset and/or development of diabetic retinopathy.

Resumé

Les taux du magnésium dans le plasma, les érythrocytes et l'urine ont été déterminés en utilisant la spectrophotométrie d'absorption atomique chez 109 patients diabétiques et chez 33 sujets sains. Les taux du magnésium ont été de 1,65 ± 0,13 meq/l (moyenne ± ES) au lieu de 1,59 ± 0,13 meq/l dans le plasma ($p < 0,05$), de 4,93 ± 0,61 meq/l au lieu de 4,77 ± 0,59 meq/l dans les érythrocytes, et de 4,01 ± 1,25 meq/j au lieu de 5,59 ± 2,17 meq/j dans l'urine ($p < 0,025$), pour le groupe de contrôle et le groupe diabétique respectivement. La tendance à un taux de magnésium réduit dans le plasma et à une excrétion urinaire accrue a été la plus élevée dans le sous-groupe des diabétiques mal contrôlés, dont les taux de sucre sanguin à jeun ont été supérieures à 250 mg/dl. D'autre part, les taux réduits de magnésium dans le plasma et les érythrocytes ont été les plus marqués dans un groupe de patients avec une rétinopathie diabétique proliférative même quand le sucre sanguin a été contrôlé de façon semblable à celle du groupe sans rétinopathie diabétique et à celle du groupe de base avec rétinopathie.

Ces résultats suggèrent que la perturbation du métabolisme du magnésium peut avoir certains rapports avec l'apparition et/ou le développement de la rétinopathie diabétique.

Introduction

Hypomagnesemia has been reported to occur in diabetics in the course of recovery from ketoacidosis [5], as well as during insulin maintenance therapy [3,9]. Moreover, the hypomagnesemia in patients with diabetic retinopathy has also been reported in recent studies [7]. However, it is well known that serum magnesium level does not always accurately reflect true total body magnesium content. In the present study, magnesium (Mg) levels in plasma, erythrocyte and urine were determined in patients with diabetes mellitus. The relation to the degree of diabetic retinopathy was also investigated.

Patients and Methods

109 diabetics aged 17 to 77 (mean 48.5 years) were selected and were divided into three groups on the basis of retinal finding: (1) diabetics with normal fundi (Group I, n = 63), (2) those with background diabetic retinopathy (Group II, n = 33) and (3) those with proliferative diabetic retinopathy (Group III, n = 13). None of patients had marked renal damage and had taken magnesium drugs or hypotensive diuretics.

The control group consisted of 33 healthy subjects ranging from 15 to 80 years of age (mean 51.8 years).

Each subject was fasted for more than twelve hours prior to study. The morning dose of insulin

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was withheld in insulin treated diabetics. Venous blood samples were taken into heparinized tubes. Lysed blood samples for erythrocyte measurement were prepared by adding 3 ml of deionized water to 2 ml of blood. 5 ml of 0.75 % EDTA was then added to 0.2 ml of this mixture. After standing for 30 minutes, the solution was centrifuged and a supernatant was used for the assay [4]. Mg concentrations were measured by atomic absorption spectrophotometry, using the Hitachi 170-50A.

Erythrocyte Mg concentration was calculated from plasma and whole blood concentration, using the following formula:

Erythrocyte Mg (mEq/l packed cells)

$= A - B \times (1 - Ht/100) \times 100/Ht.$

[A = Mg in whole blood (mEq/1),

B = Mg in plasma (mEq/1)].

The platelet aggregation was determined on the basis of the decrease of absorbance of 660 nm measured with Lumi-Aggregometer (Chronolog Co., Ltd.,) when 2 μM of ADP (Sigma Chemical Co., Ltd.,) was added to platelet rich plasma (PRP). Statistical analysis was carried out applying the Student's t-test.

Results

Mg levels in plasma and erythrocyte were shown in Figure 1. The average concentration of plasma Mg in the diabetic group (1.59 ± 0.13 mEq/l, mean ± S.D.) was lower than that of the control group (1.65 ± 0.13 mEq/l) ($p < 0.05$). Erythrocyte Mg levels in the diabetic group and in the control group were 4.77 ± 0.59 mEq/l and 4.93 ± 0.61 mEq/l, respectively. The difference was not statistically significant. The level of urinary Mg was significantly higher in the diabetic group (5.59 ± 2.17 mEq/24hrs) than in the control group (4.01 ± 1.25 mEq/24hrs) ($p < 0.025$).

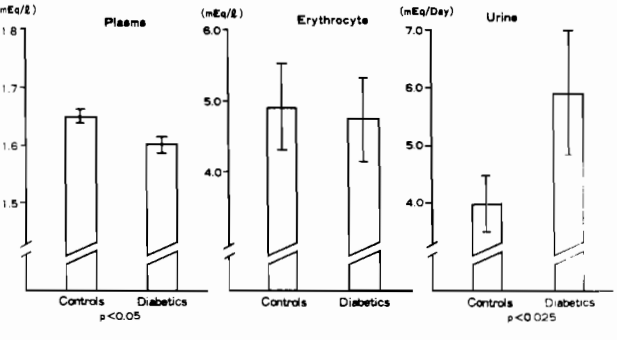

Figure 1: Mg levels in plasma erythrocyte and urine in 33 healthy control and 109 diabetics. The value represents the mean ± S.D.

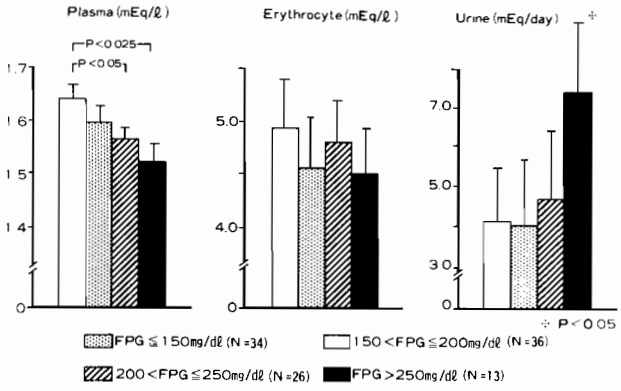

Figure 2: The relationship between Mg levels and the diabetic control state. FPG: Fasting Plasma Glucose (mg/dl). Each value represent the mean ± S.D.

Figure 2 showed the relationship between Mg levels and the diabetic control states judged by the fasting plasma glucose (FPG) level. The tendency toward reduced plasma Mg and increased urinary Mg was most significant in a subgroup of poorly controlled diabetics, whose FPG was above 250 mg/dl. However, no correlation between the erythrocyte Mg level and the dia-

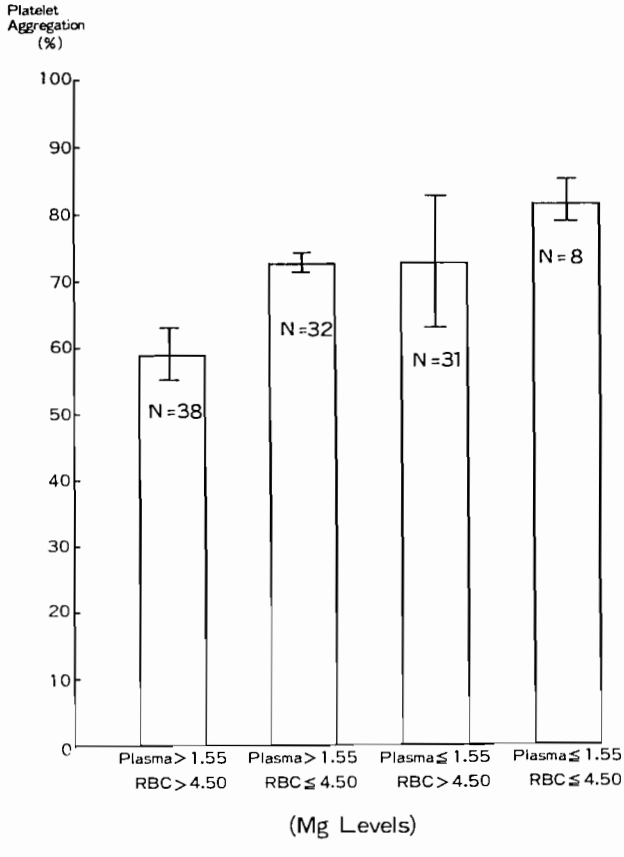

Figure 3: The relationship between platelet aggregation and Mg levels (mEq/l) in diabetics (n = 109, Mean ± S.D.)

betic control state was found. On the other hand diabetics whose Mg level in plasma and erythrocyte were low (below 1.55 mEq/l and 4.50 mEq/l, respectively) showed the tendency of increased platelet aggregation (Figure 3). Table 1 shows the relationship among Mg levels, degree of diabetic retinopathy and platelet aggregation. Although no significant differences were observed in FPG levels and in platelet aggregation among the three groups, reduced Mg levels in plasma and erythrocyte were most pronounced in group III diabetics.

Table 1: The Relationship between Magnesium Levels and the Degree of Diabetic Retinopathy, and Platelet Aggregation in Diabetics.

Subjects	FPG (mg/dl)	Mg Levels Plasma (mEq/l)	Erythrocyte (mEq/l)	Urine (mEq/day)	Platelet Aggregation(%)
Group I (n=63)	167.8 ±32.6	1.61 ±0.12[a)]	4.78 ±0.62[b)]	5.09 ±2.72[c)]	58.24 ±12.95
Group II (n=33)	158.6 ±33.0	1.61 ±0.13	4.78 ±0.48	4.76 ±1.96	72.67 ±12.22
Group III (n=13)	171.0 ±36.6	1.53 ±0.12[a)]	4.63 ±0.35[b)]	6.60 ±3.84[c)]	80.67 ± 8.09

Group I; No diabetic retinopathy. Group II; Background diabetic retinopathy. Group III; Proliferative diabetic retinopathy.
Each value represents the mean±SD. a) $p<0.01$. b),c) $p<0.05$

Discussion

The precise mechanism of diabetic hypomagnesemia still remains unknown. It has been reported in recent years that a definitely low plasma Mg level had been found in insulin treated diabetic patients, with no evidence of hypocalcemia or secondary hyperparathyroidism [7]. In the present study, reduced plasma Mg and increased urinary Mg were found in poorly controlled diabetics. Furthermore the positive correlation between Mg excretion/GFR and plasma glucose level was also found ($r = 0.68$, $p < 0.025$). These results indicate that increased urinary loss of Mg caused by osmotic diuresis may contribute to diabetic hypomagnesemia.

On the other hand plasma Mg is not necessarily a reliable index of the tissue Mg content [4, 6, 11]. Concerning the clinical significance of erythrocyte Mg, a low erythrocyte Mg content was observed with Mg depletion by *Wallach* et al. [10]. It has been also suggested that lesser degrees of Mg deficiency, if prolonged, can cause profound drops in erythrocyte Mg [2]. Recently, there have been reports that Mg depletion could cause atherogenesis and hypercoagulability [1, 8]. In fact we observed in the present study, the tendency of increased platelet aggregation in diabetics with low Mg levels in plasma and erythrocyte, as shown in Figure 3. Furthermore, we found that reduced Mg levels in plasma and erythrocytes were pronounced in diabetics with proliferative retinopathy even though no significant difference of plasma glucose levels was found compared with diabetics without marked retinopathy. Further study is needed to obtain other evidence of tissue Mg depletion in these cases. However, the present study suggests that total body Mg may be significantly depleted in some diabetics, especially with advanced retinopathy, and that changes in Mg levels may play some roles in the development or aggravation of diabetic retinopathy.

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