Evidence for a disturbed magnesium metabolism in diabetes mellitus*)

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Zusammenfassung

Serum-Mg ist erniedrigt bei Diabetes mellitus (DM), und diese Hypomagnesämie soll einen Risikofaktor für die Entwicklung der diabetischen Retinopathie darstellen. Besteht ein Mg-Mangel bei DM?

Probanden: 45 Insulin-bedürftige Patienten mit DM, der über zehn Jahre bestand. Ausschlußkriterien waren: Schwangerschaft, Niereninsuffizienz, Nierensteine, Alkoholabusus, Malabsorption. Die ermittelten Daten wurden mit denen entsprechender gesunder Kontrollen (K) verglichen.

Ergebnisse: Bei DM war das Serum-Mg erniedrigt (0,74 ± 0,05 gegenüber 0,84 ± 0,05 mmol/l) und das Urin-Mg erhöht (5,1 ± 1,6 gegenüber 4,0 ± 1,2 mmol/24 h). Urin-Mg war positiv korreliert mit Harn-Zucker und Urin-Ca. Die Mg- und die K-Konzentrationen der Skelettmuskulatur waren bei DM erniedrigt; Serum-K und Urin-K waren normal.

Schlußfolgerung: Bei lange mit Insulin behandelten Diabetikern wird ein Mg-Mangel angenommen, möglicherweise aufgrund von Magnesium-Verlusten im Urin infolge erhöhten osmotischen Druckes bei Glukosurie.

Summary

Serum magnesium (Mg) is low in patients with diabetes mellitus (DM) and hypomagnesemia is proposed as a risk factor for diabetic rethinopathy. Does this suggest Mg deficiency in DM?

Subjects. 45 insulin-treated patients with DM during more than 10 years were studied. Pregnancy, renal insuff., urolithiasis, alcohol abuse, malabsorption were criteria for exclusion. Data were compared with those from sex- and age-matched healthy subjects (C).

Results. Serum Mg was lower in DM than in C (0.74 ± 0.05 vs 0.84 ± 0.05 mmol/l) and urinary Mg was increased in DM (5.1 ± 1.6 vs 4.0 ± 1.2 mmol/24 h). Urinary Mg was pos. correlated to both urinary glucose and calcium. Intracellular conc. in muscle Mg as well as potassium (K) was decreased, whereas serum and urinary K was normal.

Conclusions. These data suggest a Mg deficiency in diabetics treated during long-term with insulin, possibly due to increased urinary loss of Mg sec. to the osmotic action of urinary glucose.

Résumé

Le magnésium sérique est faible chez les patients avec diabète sucré (DS) et l'hypomagnésémie est proposée en tant que facteur de risque de la rétinopathie diabétique. Ceci suggère-t-il un déficit magnésique dans le D.S.?

Sujets: 45 avec D.S., traités par l'insuline pendant plus de 10 ans, ont été étudiés. La grossesse, l'insuffisance rénale, l'urolithiase, l'abus d'alcool, la malabsorption ont été des critères d'exclusion. Les données ont été comparées avec celles de sujets en bonne santé d'âge et de sexe comparables (C).

Résultats: Le magnésium sérique a été plus faible dans le D.S. que dans C (0,74 ± 0,05 au lieu de 0,84 ± 0,05 nmol/l) et le Mg urinaire a été accru dans le diabète sucré (5,1 ± 1,6 au lieu de 4,0 ± 1,2 nmol/24 h). Le Mg urinaire a présenté une corrélation positive à la fois avec le glucose et le calcium urinaire. La concentration intracellulaire du Mg dans le muscle, ainsi que celle du K, a été réduite, alors que le K sérique et urinaire ont été normaux.

Conclusions: Ces données suggèrent un déficit magnésique chez les diabétiques traités au cours d'un long terme par l'insuline peut-être dû à une perte urinaire accrue du Mg, secondairement à l'action osmotique du glucose urinaire.

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Introduction

Patients with diabetes mellitus have been shown to have a higher risk of developing cardiovascular complications [11]. It has been suggested to exist a causal relationship between disturbances in the magnesium metabolism and cardiovascular disease [2]. Further, it has been shown that diabetic patients often have a low concentration of magnesium in the serum [9] and *McNair* and co-workers [10] proposed hypomagnesemia to be an additional risk factor in the development and progress of diabetic rethinopathy.

It has been proposed that especially insulin-treated patients with diabetes may have magnesium deficiency [9]. The magnesium content has also been demonstrated to be reduced in trabecular bone, suggesting a magnesium deficiency [7]. These results could not, however, be reconfirmed when the magnesium concentration was measured in erythrocytes or leucocytes [5, 8]. These observations prompted us to investigate the magnesium metabolism and to compare the results with those obtained from an age- und sexmatched control group.

Material

Subjects. 45 (23 men, 22 women) consecutive insulin-treated patients with diabetes mellitus were investigated at our out-patient clinic. There mean age was 45 ± 13 years (range 22 — 78 years). All patients had had the disease for more than ten years and had during these years

*) Results presented at the 3rd International Symposium on Magnesium, Baden-Baden, 22.—28. 8. 1981.

been dependent on insulin. Following criteria were used for exclusion of patients: serum-creatinine > 115 µmol/l, ketoacidosis during the last twelve months, gastrointestinal malabsorption, pregnancy, renal stone disease, alcoholism, diseases of the liver and pancreas and malignant diseases. Patients using litium, diuretics, other hormones than insulin, antacids and antaconvulsant drugs were also excluded from the study.

Control groups. Apparently healthy subjects recruited from a general health survey together with members of the medical staff formed a control group. The groups were matched for age and sex when the results of serum and urinary electrolytes were compared. Data from the whole control group of 106 subjects have been presented previously [3].

Methods

Serum and urinary magnesium and calcium were measured by atomic absorption. Urine was collected during 24 h in plastic bottles containing no additives. Muscle magnesium was determined in muscle specimens according to a technique described earlier [3]. Serum and urinary glucose was calculated as the mean value of the four last determinations. Glucose and creatinine were analyzed by standard techniques at the clinical chemistry laboratory of the hospital. Immunoreactive parathyroid hormone (PTH) concentrations in serum were measured by a radio-immuno assay measuring intact human PTH and C-terminal ⅔ of the molecule [13].

Results

Laboratory data are summarized in Table 1.

Serum magnesium concentration was decreased in comparison with the values found in the sex- and agematched control group (Table 1).

In the diabetics, but not in the control group, the serum magnesium was negatively correlated to the serum calcium concentration ($r = -0.55$, $p < 0.001$).

Urinary magnesium excretion was higher in the diabetics also when the clearance of magnesium was corrected for by the clearance of creatinine (Table 1). Urinary magnesium was positively correlated to urinary calcium excretion and negatively correlated to age, in both diabetics and controls. Urinary magnesium was also positively correlated to urinary glucose excretion ($r = 0.41$, $p < 0.01$).

Tab. 1: Laboratory data in healthy subjects and patients with diabetes mellitus. When comparing data for serum and urinary electrolytes, the subjects were matched for age and sex.

	Controls	Diabetes mellitus
Serum magnesium (mmol/l)	0.84 ± 0.05	0.74 ± 0.06***
Urinary magnesium (mmol/24 h)	4.0 ± 1.2	5.4 ± 2.0***
Mg clear/creatinine clear	0.033 ± 0.009	0.050 ± 0.017***
Urinary calcium (mmol/24 h)	5.0 ± 1.5	4.4 ± 2.0
Muscle magnesium (mmol/100 g FFS)	3.7 ± 0.5	3.4 ± 0.5*
Serum calcium (mmol/l)	2.39 ± 0.07	2.42 ± 0.06
Serum PTH (arbitrary units/l)[1])		0.44 ± 0.14

*** $p < 0.001$ compared with controls
* $p < 0.05$ compared with controls
[1]) reference values: 0.22 — 0.50 arbitrary units/l

Muscle magnesium concentration. The intracellular concentration of magnesium in muscle cells was low in diabetics compared with controls (Table 1). However, the muscle magnesium did not correlate to serum or urinary magnesium or to the duration of the diabetic disease.

Serum and urinary calcium. All values for serum calcium fell within the normal range and there was no difference regarding the mean value in the diabetics and the controls (Table 1). Urinary calcium was positively correlated to urinary glucose excretion ($r = 0.50$, $p < 0.01$) but in contrast to the urinary magnesium, the urinary calcium excretion was rather low in the diabetics compared with controls.

Glucose metabolism. Serum glucose concentration showed a great variation with a range of 2.9 — 21.5 mmol/l (11.5 ± 4.5 mmol/l; mean ± SD). Urinary glucose excretion varied between 3 and 430 mmol/24 h.

Discussion

In accordance with other studies [9, 10], this study also disclosed a lower serum magnesium concentration in insulin-treated diabetics as compared with a matched control group. However, no correlation could be found between serum magnesium and age or sex in the diabetics, in contrast to the findings by *Mather* [9] on diabetics with or without insulin therapy. This lack of correlation is

in agreement with our [3] and others experience in healthy subjects [1, 12].

The release of parathyroid hormone (PTH) from the parathyroid glands rather than its biosynthesis or storage has earlier been shown to be dependent on the serum concentration of magnesium [12]. The relevance of the observed inverse correlation between the serum values of magnesium and calcium is somewhat obscure, but a possible explanation might be a common action of the ions on the parathyroid glands during hypomagnesemia in these diabetics. However, the serum PTH was found to be normal, when analyzed in the diabetics.

The osmotic action of the hyperglucosuria might contribute to the increased urinary excretion of magnesium found in the diabetics compared to the age- and sexmatched controls. The hyperglycemia per se is also known to depress the tubular reabsorption of magnesium in the kidneys [6], thus aggrevating the hypermagnesuria. During longterm these effects may deplete the body stores of magnesium. As serum magnesium does not necessarily reflect the main stores of magnesium in the body, the intracellular concentration of magnesium in muscle specimens was analyzed and found to be decreased in comparison with controls. This finding with a low serum magnesium and muscle magnesium concentration suggests a magnesium deficiency in these patients with insulin-treated diabetes mellitus. Thus, a poor diabetic control with a high glucosuria appears to be an important factor for depletion of the body stores of magnesium.

The magnesium deficiency could concievable be an aethiological factor in the increased incidence and morbidity of ischemic heart disease, and perhaps the vascular calcification, seen in diabetics. Supplements with magnesium during longterm might be of benefit in these patients, but evaluation of any possible effect will present difficulties.

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