Renal hypomagnesaemia in human diabetes mellitus.

Its relation to glucose homeostasis.

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Zusammenfassung

Die Beziehungen zwischen Mg und Glucose-Metabolismus wurden bei 215 insulinbedürftigen ambulanten Diabetikern im Alter von 7 bis 70 Jahren untersucht. Alle hatten normale Serum-Kreatinin-Werte (unter 115 μmol/l), und keiner hatte Erkrankungen oder erhielt Medikamente, die mit dem Mineralhaushalt interferieren. Eine eindeutige Hypomagnesaemie (HS) (< Normalwert - 2 SD) und Hypermagnesurie (HU) (> Normalwert + 2 SD) wurde bei 38,6% bzw. 55% der Patienten beobachtet. In Gegenwart von HU war das Serum-Mg invers korreliert mit der Urin-Mg-Ausscheidung (r = -0,23, p < 0,02).

Serum-Mg korrelierte invers sowohl mit dem Nüchtern-Blutzucker (r = -0,32, p < 0,001) und der Glucose-Ausscheidung im Urin (r = -0,22, p < 0,005). Die Urin-Mg-Ausscheidung korrelierte direkt mit diesen Variablen (r = 0,27, p < 0,001 und r = 0,58; p < 0,001). Diese Befunde zeigen, daß die tubuläre Nett окруgresorption von Mg bei Diabetikern vermindert ist in Gegenwart von Hyperglykämie, die zu HU und HS führt.

Summary

Interrelations between Mg and glucose metabolism were studied in 215 insulin-treated diabetic out-patients aged 7—70 years. All had normal serum creatinine concentrations (below 115 μmol/l) and none had other diseases or received drugs known to interfere with mineral metabolism.

A definite hypomagnesaemia (HS) (< normal mean - 2 SD) and hypermagnesuria (HU) (> normal mean + 2 SD) occurred in 38.6% and 55% of the patients. In the presence of HU serum Mg was inversely correlated to the urinary Mg excretion (r = -0.23, p < 0.02).

Serum Mg correlated inversely with both fasting blood glucose (r = -0.32, p < 0.001) and the urinary glucose excretion rate (r = -0.22, p < 0.005). The urinary Mg excretion rate correlated directly with the same variables (r = 0.27, p < 0.001 and r = 0.58, p < 0.001, respectively).

These data indicate that the net tubular reabsorption of Mg is decreased in diabetic patients in presence of hyperglycaemia, leading to HU and HS.

Résumé

Des interrelations entre les métabolismes du magnésium et du glucose ont été étudiées chez 215 patients non hospitalisés diabétiques traités par l'insuline, âgés de 7 à 70 ans. Tous présentaient des concentrations sériques normales (inférieures à 115 μmol/l) et aucun d'entre eux n'avaient d'autres maladies ou ne recevaient des médicaments connus comme interférant avec le métabolisme minéral.

Une hypomagnésémie (< à la moyenne normale - 2 ES) et une hypermagnésurie (> à la moyenne normale + 2 ES) définies sont survenues chez 38,6 % et 55 % des patients. En présence d'une hypermagnésurie, la concentration de Mg sérique a présenté une corrélation inverse avec le taux de l'excrétion urinaire du Mg (r = -0,23 p < 0,02).

Le Mg sérique a présenté une corrélation inverse à la fois avec le glucose sanguin à jeun (r = -0,32 p < 0,001) et avec le taux de l'excrétion urinaire du glucose (r = -0,22 p < 0,005). Le taux de l'excrétion urinaire du Mg a présenté une corrélation directe avec les mêmes variables (r = 0,27 p < 0,001, et r = 0,58 p < 0,001 respectivement).

Ces données indiquent que la réabsorption tubulaire nette du magnésium est réduite chez les patients diabétiques en présence de l'hyperglycémie, ce qui entraîne une hypermagnésurie et une hypomagnésémie.

Introduction

Decreased serum concentration of magnesium has been recognized in patients with diabetes mellitus during recovery from ketoacidosis [11], during maintenance insulin therapy in hospital [5, 18], and also during daily life when studied as out-patients [14]. An association between the hypomagnesaemia and the severity of diabetic retinopathy has been observed [14]. There is, however, little information about the relation between indices of metabolic control and the hypomagnesaemia of diabetic man [6, 13]. As the reason for diabetic hypomagnesaemia is obscure [1], the aim of the present study was to explore pathogenetic factors of diabetic hypomagnesaemia.

Patients and controls

The cross-sectional study comprised 215 insulin-treated diabetic out-patients, aged 7—70 years. The patients were asked to participate by a written invitation sent to their home address, stating the purpose and procedure of the study. All patients had normal serum creatinine (below
115 μmol/l) and none had gastro-intestinal, hepatic or renal disorders; drug treated heart diseases or hypertension; endocrine illness except diabetes mellitus; nor received drugs known to interfere with mineral metabolism. Further details are presented elsewhere [15]. The patients were studied on their habitual diet, e.g. on free intake of magnesium. The clinical data of the patients are given in table 1.

Tab. 1: Clinical data of 215 insulin treated diabetic outpatients.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36</td>
<td>7-70</td>
</tr>
<tr>
<td>Age at diabetes onset (years)</td>
<td>26</td>
<td>0-67</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>10</td>
<td>0-29</td>
</tr>
<tr>
<td>Insulin dose (IU/kg/day)</td>
<td>0.56</td>
<td>0.05-1.14</td>
</tr>
<tr>
<td>Fasting blood glucose (g/l)</td>
<td>2.27</td>
<td>0.46-5.34</td>
</tr>
<tr>
<td>Glycosuria (g/g creatinine)</td>
<td>69</td>
<td>0-483</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>97.2</td>
<td>31.7-174.0</td>
</tr>
</tbody>
</table>

Blood samples were drawn at 8—9 a.m. after at least 8 hours fasting and tobacco abstinence before the administration of insulin. A 24 hour urine collection was completed in the morning at the start of the study. All but 9 urine samples were free from ketone bodies, when tested with "Ketostix®". Proteinuria was detectable in 6 (3 %) patients (Albustix®). Two hundred and thirty healthy school children (aged 7—20 years) and 194 blood-donors (aged 21—70 years) gave normal reference values for serum magnesium. Reference values for urine magnesium were obtained from the literature [7, 16], but were identical with measurements in 28 normal persons investigated in our department.

Methods

Magnesium concentration in serum and urine was determined by atomic absorption spectrophotometry (Perkin Elmer 403), and serum values were corrected for individual variation in serum protein concentration to a protein level of 70 g/l [3].

Glucose, creatinine and protein were measured by methods routinely used in the laboratory.

Insulin dosage was in each patient calculated as IU/kg body weight/day at the time of the study.

The clearance of creatinine was determined from the 24-hour urine collection. The excretion rates of glucose and magnesium in urine were calculated per gram creatinine in order to eliminate variations due to incomplete collection. Furthermore, the age and sex dependency of the magnesium excretion rate is minimized by this calculation [16].

The following tests were used for statistical evaluation of the results: Student’s unpaired t-test concerning differences between means and proportions, the Spearman rank correlation test and trivariate correlation analysis for the determination of coefficients of correlation.

Results

The mean serum magnesium concentration in the diabetic patients (± SD) was 18.08 ± 1.29 mg/l, which was significantly reduced compared with normal mean (x̄ = 20.3 ± 1.30 mg/l; P < 0.001). Fig. 1A shows the distribution of the diabetic patients according to their serum magnesium concentrations, in relation to normal mean and normal standard deviation. Two hundred and six patients (95.6 %) had serum concentrations below normal mean, and 83 patients (38.6 %) had serum magnesium levels below the normal range (x̄ - 2 SDn), which is significantly more than the expected 2.5 % (P < 0.001). The diabetic patients had hypermagnesiuria (mean ± SD: 125 ± 42 mg/g creatinine) compared with normal (75 ± 21 mg/g creatinine [9, 10], P < 0.001). Fig. 1B shows the distribution of diabetic patients according to their urinary magnesium excretion rate, in relation to normal mean and SD. The urinary excretion rate of magnesium was above normal mean in 194 patients (90.2 %), and above 127 mg/g creatinine (normal mean + 2 SD) in 119 patients (55.3 %, P < 0.001).

When the patients were grouped according to duration of diabetes the following pattern was observed: During the first 4 years of diabetes serum magnesium decreased to a minimum of 17.4 mg/l (fig. 2A), the urinary excretion rate increased to 145 mg/g creatinine (fig. 2B) and the fasting blood glucose and glycosuria (fig. 2C and 2D) rose to 2.5 g/l and to 90 g/g creatinine, res-
pectively. After 4—5 years of diabetes, serum magnesium and the urinary magnesium excretion rate remained stable at about 18,2 mg/1 and 120 mg/g creatinine (fig. 2A and 2B, respectively). The hyperglycaemia and the glycosuria gradually declined to about 2,2 g/l and 70 g/g creatinine (fig. 2C and 2D, respectively). The clearance of creatinine did not vary as a function of diabetes duration.

Serum magnesium correlated inversely with the degree of hyperglycaemia (R = -0.32, P < 0.001) and with the amount of glycosuria (R = -0.22, P < 0.005). The urinary magnesium excretion rate correlated directly with both fasting blood glucose and the glycosuria (R = 0.27, P < 0.001, and R = 0.58, P < 0.001, respectively), see table 2 and figure 3.

No significant correlation was observed between serum magnesium and the insulin dosage (R = -0.12, P = 0.09), but the urinary excretion rate of magnesium was positively associated

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**Fig. 1:** Distribution of 215 insulin treated diabetic patients (hatched) according to serum magnesium concentration and urinary magnesium excretion rate, in relation to normal mean and SD. The expected normal distributions are indicated.

- **SERUM MAGNESIUM**
- **URINE MAGNESIUM**

**Fig. 2:** Serum magnesium (A), urine magnesium (B), fasting blood glucose (C), and glycosuria (D) in 215 insulin treated diabetic patients grouped according to the duration of diabetes mellitus. Each point present mean ± SEM.
Tab. 2: Serum concentration and urinary excretion rate of magnesium in 215 insulin treated diabetic patients grouped according to fasting blood glucose. Values are given as mean ± SEM.

<table>
<thead>
<tr>
<th>Blood glucose g/l</th>
<th>Number of patients</th>
<th>Serum magnesium mg/l</th>
<th>Urine magnesium mg/g creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0,99</td>
<td>16</td>
<td>18,8±0,5</td>
<td>101,7± 7,5</td>
</tr>
<tr>
<td>1,00-1,49</td>
<td>33</td>
<td>18,9±0,2</td>
<td>116,4± 6,5</td>
</tr>
<tr>
<td>1,50-1,99</td>
<td>34</td>
<td>18,1±0,2</td>
<td>118,0± 5,1</td>
</tr>
<tr>
<td>2,00-2,49</td>
<td>40</td>
<td>18,1±0,2</td>
<td>119,3± 5,5</td>
</tr>
<tr>
<td>2,50-2,99</td>
<td>40</td>
<td>17,8±0,2</td>
<td>121,2± 6,8</td>
</tr>
<tr>
<td>3,00-3,49</td>
<td>36</td>
<td>17,7±0,2</td>
<td>142,3± 8,2</td>
</tr>
<tr>
<td>3,50-</td>
<td>16</td>
<td>17,3±0,3</td>
<td>162,2±14,3</td>
</tr>
</tbody>
</table>

Fig. 3: Serum magnesium (A) and urine magnesium (B) in 215 insulin treated diabetic patients grouped according to their degree of glycosuria. Mean ± SEM is shown.

with the daily insulin dose (R = 0.34, P < 0.001, see fig. 4). The insulin dosage was related to the severity of glycosuria (R = 0.29, P < 0.001). The association between the insulin dosage and the excretion rate of magnesium in urine was not totally explained by covariation with the glycosuria, since trivariate correlation analysis including urinary excretion of magnesium, glycosuria and dosage of insulin showed a significant partial correlation coefficient between urinary magnesium excretion rate and the dosage of insulin (R = 0.22, P < 0.001).

The biphasic relationship between the serum magnesium concentration and urinary magnesium excretion rate is presented in fig. 5. At relatively low excretion rates of magnesium, i.e. within normal levels, serum concentrations of magnesium tend to increase with rising urinary excretion rates of magnesium. When the urinary losses of magnesium exceed about 120 mg/g creatinine the serum magnesium decrease (R = -0.23, n = 111, P < 0.02).

Fig. 4: Serum magnesium (A) and urine magnesium (B) in 215 insulin treated diabetic patients grouped according to daily insulin dosage. Each point presents mean ± SEM.
Triple correlation analysis with the duration of diabetes as the third parameter gave no further information, the correlation coefficients being virtually unchanged. The same patterns were observed when the urinary magnesium excretion rate was corrected for differences in creatinine clearance. There were no significant correlations between serum or urine magnesium and the age or the age at onset of diabetes. The six patients (3%) with detectable proteinuria during the 24 hours before the study did not significantly differ from the rest of the patients regarding indices of either glucose or magnesium metabolism.

Discussion

The present study demonstrates that hypomagnesaemia and hypermagnesiuria occur frequently in insulin treated diabetic patients studied in their usual diabetic state. The prevalence of hypomagnesaemia almost 40%, and 55% had increased urinary excretion rates of magnesium. These disturbances are related to the metabolic control of diabetes, as shown by their correlations with both fasting blood glucose and glycosuria. The patients were studied in the morning before the administration of insulin, because insulin injection may aggravate the hypomagnesaemia [10].

The patients were selected to be free of medications with a known influence on renal handling of magnesium (except for insulin) and to have a normal serum creatinine concentration. There was, however, a rather wide range in the calculated clearances of creatinine, 15 patients having clearances below 60 ml/min. An analysis of the individual data of these patients showed that the main reason for the low clearances was a very low 24 hour excretion rate of creatinine, in average 50% of the excretion rate in all the diabetics. Consequently the 24 hour urine collection must have been incomplete in these patients, resulting in falsely low creatinine clearances. This is further supported by a virtually identical mean serum creatinine in the 15 patients and in the whole group.

In normal man glucose ingestion, alone or combined with insulin administration, increases the urinary excretion rates of magnesium and calcium, probably through an inhibition of the tubular reabsorption of these ions [8, 9]. In parallel to this we observed that the serum magnesium concentration decreased and the urinary magnesium excretion rate rose with increasing blood glucose and glycosuria in diabetic patients. This indicates that the tubular reabsorption of magnesium decreases in the presence of hyperglycaemia. Pronounced hypermagnesiuria despite decreased serum magnesium levels suggests that insulin dependent diabetics develop magnesium depletion.

This is in accordance with the observation of De Leeuw et al. [4] that the bone magnesium content was 30% below normal in diabetic patients treated with insulin. As the skeleton normally contains more than 50% of the total body magnesium [19], the total deficit of magnesium may well be pronounced.

So far, however, there is no evidence of soft tissue magnesium depletion: A normal concentration of magnesium has been reported in erythrocytes [6] and leucocytes [12] of diabetic patients.

There is no obvious explanation for the rise in urinary magnesium excretion rate with increasing insulin dosage, which did not affect the serum concentration of magnesium. This change may be explained if there is an association between high levels of insulin dosage and calory intake. High calory intake is possibly associated with high intake and absorption of magnesium. This would lead to increased urinary excretion rates of magnesium with unchanged serum magnesium.
concentration [16]. Another explanation may be, that insulin changes the renal handling of magnesium. This would be in accordance with the findings in normal man, that the administration of insulin alone or with glucose produced increased urinary excretion rates of magnesium without glycosuria [9].

The long-term consequences of diabetic hypomagnesaemia are largely unsettled [1]. It appears to be a risk factor in diabetic retinopathy [14]. As magnesium depletion can cause atherosclerosis in experimental animals and perhaps also in man [2, 17, 19] it may also be involved in the development of other vascular complications in diabetes mellitus [2].

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References


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