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Low plasma magnesium in type 2 diabetes

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Summary

Questions under study/principles: Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in type 2 diabetic patients. Low plasma magnesium concentration is a highly specific indicator of poor magnesium status. In the USA and some European countries, plasma magnesium concentrations have been found to be decreased in diabetics. The aim of this study was to compare plasma magnesium concentrations of type 2 diabetics and healthy controls in Switzerland.

Methods: Plasma magnesium concentrations were determined in 109 type 2 diabetics and 156 age- and sex-matched healthy controls.

Results: Mean (± SD) plasma magnesium concentrations of the diabetics and controls were 0.77 ± 0.08 and 0.83 ± 0.07 mmol/L, respectively ($p < 0.001$). Plasma magnesium concentrations were below the normal reference range in 37.6% of the diabetic patients and 10.9% of the control subjects ($p < 0.001$). Plasma magnesium was not correlated with glycemic control as measured by HbA_{1c}.

Conclusions: Lower plasma magnesium concentrations and poor magnesium status are common in type 2 diabetics in Zurich, Switzerland.

Key words: magnesium; diabetes; hypomagnesaemia; plasma magnesium

Introduction

Mg depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes [1, 2], as well as on the evolution of complications such as retinopathy, thrombosis and hypertension [3–5]. Moreover, low serum Mg is a strong independent predictor of the development of type 2 diabetes [6]. In the USA, 25 to 39% of outpatient diabetics have low concentrations of serum Mg [7], and several studies have shown lower serum Mg concentrations in type 2 diabetics compared to healthy controls [5, 8]. Although low serum Mg concentrations in diabetics have also been found in several European countries including Austria, Germany, Italy, France and Sweden [9–13], there are no reported data for Switzerland. Therefore, the aim of this study was to compare the plasma Mg concentrations of patients with type 2 diabetes and healthy controls in Switzerland.

Subjects, methods and materials

Subjects

One-hundred-and-nine type 2 diabetic patients and 156 non-diabetic controls matched for age and sex participated in the study (Table 1). The mean age (range) of the diabetics and controls was 61.3 (33–87) and 58.3 (46–74), respectively. The type 2 diabetics were recruited from the outpatient diabetes clinic at the University Hospital, Zurich (44.0%) and from a private endocrinologic practice in Winterthur (56.0%). Median (range) duration of diabetes was 10.7 years (0–37 years). Of the diabetics, 61.5% reported a history of hypertension and/or cardiovascular disease and 25.7% a history of dyslipidemia. Fifty-eight were using insulin, 29 were taking oral hypoglycemics, 14 were using both, and 8 were not prescribed any antidiabetic drugs (Table 2). Because loop diuretics are associated with higher urinary Mg excretion, patients taking loop diuretics were excluded. None were taking Mg supplements. Anonymous blood samples for control subjects were obtained from the local blood donation centre (Swiss Red Cross, Zurich) with specification of sex and year of birth for each subject. Exclusion criteria for blood donations included diabetes treated by insulin, infection, sexually transmittable diseases, cardiovascular diseases, cerebral incident, bleeding disorders, vascular diseases, chronic kidney diseases, autoimmunity diseases, epilepsy, cancer, hepatitis, and pregnancy. Written informed con-

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sent was obtained from each diabetic subject, and the study protocol was approved by the Ethical Committee of the University Hospital, Zurich.

Methods and materials

Venous blood samples from the subjects were drawn in heparinised 10 ml tubes (Vacutainer, Becton Dickinson, Meylan, France). Whether the subjects were in the fed or fasting state was not specified. Plasma was separated from blood cells by centrifugation at 3000 rpm for 15 minutes (Omnifuge 2.0 RS, Heraeus GmbH, Hanau, Switzerland) and stored in plastic vials at –25 °C until analysis.

Quantitative analysis of Mg in plasma was done by flame atomic absorption spectrometry (SpectrAA 400, Varian, Mulgrave, Australia) at 285.2 nm, using parameters recommended by the manufacturer [14]. Plasma samples were diluted 200-fold so that the Mg concentrations of the final diluted solutions were around 0.1 µg/mL. A commercial Mg standard (CertiPUR, Merck, Darmstadt, Germany) was used for internal calibration by standard addition to minimize matrix effects. Lanthanum nitrate (Fluka Chemie GmbH, Buchs, Switzerland) was added as a matrix modifier (5 mg La/mL in the final solutions), and 0.1% Triton X-100 solution (Fluka Chemie GmbH) to reduce the surface tension. Accuracy of the method was verified by analysing a serum control sample for Mg (Seronorm Trace Elements Serum, Nycomed, Oslo, Norway). All samples were analysed in duplicate and repeated if the difference between individual values relative to the mean was >10%. All chemicals used were analytic grade. Water used for analytical procedures was purified by ion exchange and reverse osmosis (18 MΩ) (RD2000, Renggli AG, Rotkreuz, Switzerland; Nanopure Cartridge System, Skan AG, Basel, Switzerland).

For all diabetic subjects, the most recent HbA_{1c} concentration was collected. For the patients from the university clinic, the HbA_{1c} was determined from the same blood sample as the plasma Mg concentration. For the remaining subjects, the most recent HbA_{1c} was recorded from the medical record. For all subjects but one, HbA_{1c} was obtained within 2 months of the plasma Mg determination.

Data processing and statistical analysis were done using Excel 2002 (Microsoft, Seattle WA, USA) and SPSS for Windows 11.0 (SPSS Inc., Chicago IL, USA). Normal distribution of data was verified by calculating the quotient of the skewness divided by its standard error; normal distribution was assumed if the quotient was between –2.5 and +2.5. Normally distributed data were expressed as arithmetic means ± SD. Variables not normally distributed were expressed as medians and ranges. Differences between groups were evaluated using unpaired Student's t-test and considered statistically significant at $p < 0.05$. ANOVA was done to test for associations with plasma Mg concentration as the dependent variable.

Table 1
Characteristics of the test subjects.

Characteristics	diabetics	controls
No of subjects	109	156
Sex	76 men / 33 women	112 men / 44 women
Age (y) ± SD	61.3 ± 10.3	58.3 ± 7.2

Table 2
Characteristics of the diabetic patients.

Characteristics		
Duration of diabetes [years][1]		10.7 (0–37)
Medication	Insulin-	53.2%
	Oral hypoglycaemics	26.6%
	Insulin and oral hypoglycaemics	12.8%
	Diet only	7.3%
Comorbidities	Hypertension	61.5%
	Dyslipidemia	25.7%

[1] median and range

Results

Mean (± SD) plasma Mg concentrations of the diabetics and the controls were 0.77 ± 0.08 and 0.83 ± 0.07 mmol/L, respectively ($p < 0.001$) (Figure 1). In 37.6% of the diabetic patients and 10.9% of the control subjects plasma Mg concentrations were below the normal reference range of 0.75 to 0.95 mmol/L (15). By ANOVA, sex and age were not significant predictors of plasma Mg in this sample. Median HbA_{1c} concentration (range) in the diabetic group was 7.1% (5.1–11.5%). By ANOVA, HbA_{1c} (Figure 2), duration of diabetes and diabetes treatment (medication) did not significantly predict plasma Mg concentration.

Discussion

Similar to findings from other countries in Europe and North America [5, 8], the mean plasma Mg concentration of the type 2 diabetics was significantly lower than in controls. The striking finding in this population was the high prevalence of low plasma Mg concentrations among the diabetic subjects. Plasma Mg concentrations of 37.6% of the diabetics were below the reference range, a

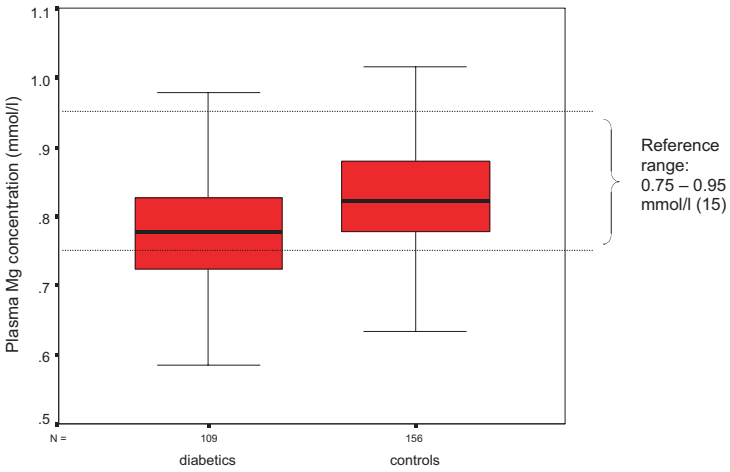

Figure 1
Plasma Mg concentrations of type 2 diabetics and controls. Box-whiskers plot showing medians, first and third quartiles, and minima and maxima.

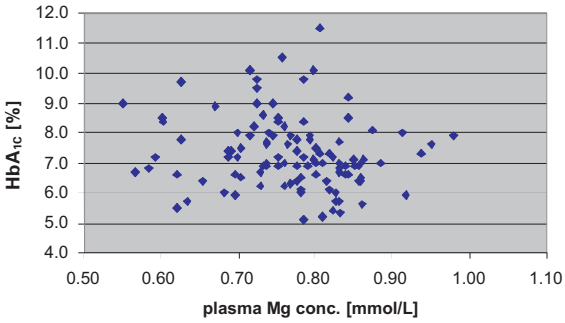

Figure 2
Relationship between plasma Mg concentration and glycaemic control measured as HbA_{1c} in 109 diabetic patients.

prevalence of low magnesium status that is similar to that reported in type 2 diabetics in outpatient clinics in the US [7]. Mg depletion has a negative impact on glucose homeostasis and insulin sensitivity in diabetic patients [1, 2] as well as on the evolution of complications such as retinopathy, thrombosis and hypertension [3–5]. Preventing low Mg status in diabetics may therefore be beneficial in the management of the disease.

The reasons for the high prevalence of Mg deficiency in diabetes are not clear, but may include increased urinary loss, lower dietary intake, or impaired absorption of Mg compared to healthy individuals. Several studies have reported increased urinary Mg excretion in type 1 and 2 diabetes [13, 16–18]. However, we have shown that low dietary intake does not appear to contribute to impaired Mg status in diabetics in Switzerland. A dietary assessment conducted in 97 type 2 diabetics and 100 healthy controls showed that only 5.4% of the diabetic group and 9.1% of the control group were predicted to have intakes of Mg below their individual requirements [19]. In addition, we have recently shown that type 2 diabetics in reasonable metabolic control and without nephropathy absorb dietary Mg to a similar extent as healthy controls, and have similar rates of urinary excretion [20]. Increased urinary Mg excretion due to hyperglycaemia and osmotic diuresis may contribute to hypomagnesaemia in diabetes [16–18]. Several authors have described a correlation between HbA_{1c} and plasma Mg in type 1 diabetics [11, 21]. However, no such correlation was found in type 2 diabetes [11, 22, 23], similar to our results.

Mg is mainly an intracellular cation, with less than 1% of total body content present in the extracellular fluids. The Mg concentration in serum represents not more than 0.3% of total body Mg [24]. Nevertheless, serum or plasma Mg measurement is the most readily available and widely used test of Mg status. In human studies, instituting a diet low in Mg produces a predictable decline in serum Mg [25–27]. However, there are a number of reports of low Mg values in various blood cells and tissues associated with normal serum/plasma Mg concentrations [24]. It appears therefore that plasma Mg concentration is an insensitive, but highly specific indicator of low Mg status. Of the total Mg in serum, around 55% is present as free ionised Mg^{2+}, 15% is complexed to anions (e.g. bicarbonate, citrate, sulfate) and 30% is bound to proteins, mainly albumin [28]. It could therefore be argued that in diabetics with microalbuminuria, serum Mg might be reduced because of lower serum albumin concentration. However, Pickup et al. [29] found no difference in serum Mg concentration between type 1 diabetics with microalbuminuria or clinical proteinuria compared to diabetics with normal albumin excretion. In contrast, Corsonello et al. [30] demonstrated significantly lower ionised serum Mg in type 2 diabetic patients with microalbuminuria or clinical proteinuria compared to a normoalbuminemic group. Free ionised serum Mg, however, is not associated with serum albumin levels. Moreover, microalbuminuria should not lower plasma albumin, because plasma contains macro-amounts (35–52 g/L) of albumin. Therefore, we did not exclude subjects with microalbuminuria.

In summary, we have demonstrated that low Mg status is common in type 2 diabetics in the Zurich region. Because Mg depletion reduces insulin sensitivity and may increase risk of secondary complications, it may be prudent in clinical practice to periodically monitor plasma Mg concentrations in diabetic patients. If plasma Mg is low, an intervention to increase dietary intakes of Mg may be beneficial.

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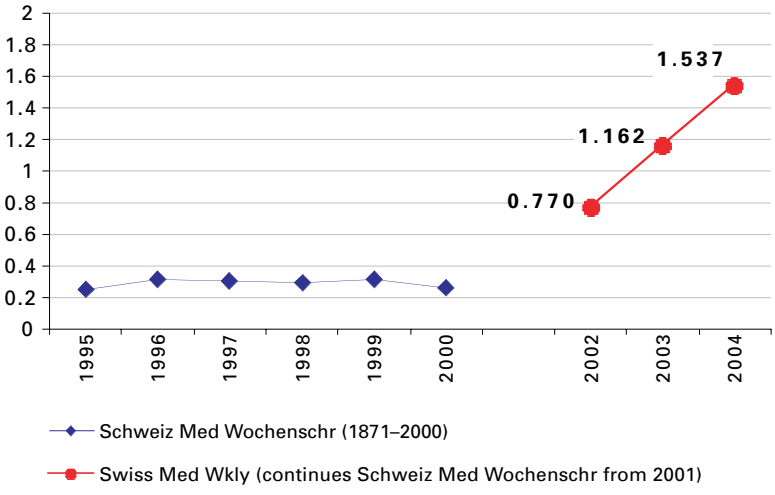

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