Differences in Serum Ionized and Total Magnesium Values During Chronic Renal Failure Between Nondiabetic and Diabetic Patients

A cross-sectional study

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Magnesium (Mg) is known to play a fundamental role in carbohydrate metabolism by influencing glucose catabolism and insulin sensitivity (1–2) and may be associated with the development of diabetes complications (3). However, to the best of our knowledge, there is currently no study that has evaluated the value of either serum total Mg (t-Mg) or ionized Mg (i-Mg) in diabetic patients with chronic renal failure (CRF). This is rather unexpected considering the dramatic increase in the prevalence of diabetic nephropathy, which represents one of the most serious chronic complications among patients with diabetes (4).

Therefore, the aim of the present study was to investigate serum i- and t-Mg during CRF (as measured by creatinine clearance [C_{Cr}]) in diabetic patients and to compare them with values found in nondiabetic patients.

RESEARCH DESIGN AND METHODS

— Subjects were 55 ambulatory nondiabetic patients from the renal division of the Ghent University Hospital and 73 ambulatory diabetic patients from the renal and endocrinological divisions of the same hospital, both with varying degrees of renal failure. Patients treated with diuretics, $NaHCO_3$, or polystyrene sulfonate were excluded. Written informed consents were obtained from the patients in accordance to the instructions of the ethics committee of the Ghent University Hospital.

Serum sample preparation

Blood for determination of Mg was sampled into plain evacuated glass tubes with glycerine caps (Venoject VT-100SU; Terumo Europe, Leuven, Belgium), while Vacutainer tubes (Becton Dickinson, Erembodegem, Belgium) were used for the other analytes. The samples were allowed to coagulate for at least 30 min at room temperature and were then centrifuged for 20 min at 3,000 rpm.

Analytical measurements

Measurements of t-Mg were performed using an ion chromatography reference method (5,6). The i-Mg values were determined with an ion-selective electrode system 988-4 from AVL List (Graz, Austria) immediately after centrifugation. The reported value of i-Mg was normalized to pH 7.4. Reference intervals for t- and i-Mg were taken from previous studies (7,8).

Routine clinical and metabolic characteristics (creatinine, total protein, potassium, sodium, chloride, calcium, urea, phosphate, cholesterol, glucose, and bicarbonate) were determined with a Hitachi 747 instrument (Roche Diagnostics, Basel, Switzerland) (serum creatinine was determined with the Jaffé method). The C_{Cr} was determined by the Cockcroft-Gault equation and normalized for the respective body surface area.

Statistical evaluation was performed using the CBstat software (version 4.3.2; K. Linnet, Risskov, Denmark). It consisted of the Anderson-Darling test for the probability of a normal distribution of Mg values, the *F* test, Student's unpaired *t* test, and logarithmic regression and correlation analysis for investigating the relationship between serum i- and t-Mg levels and C_{Cr}. All values are reported as means ± SD.

RESULTS

— The mean age, weight, and body surface area were not significantly different between the two groups, as was the total protein value, indicating a comparable state of nutrition between the diabetic and nondiabetic patients. Moreover, approximately one-half of the participating patients in each group were being treated with an ACE inhibitor and/or an angiotensin 2 receptor antagonist. No differences in renal function were observed between the two groups, as measured by C_{Cr} values. This is an important consideration since it is known that Mg value increases with the progression of renal failure, at least in patients without diabetes.

We observed a significant decrease in Na and Cl concentrations in the diabetic

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Abbreviations: C_{Cr}, creatinine clearance; CRF, chronic renal failure; i-Mg, ionized magnesium; t-Mg, total magnesium.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

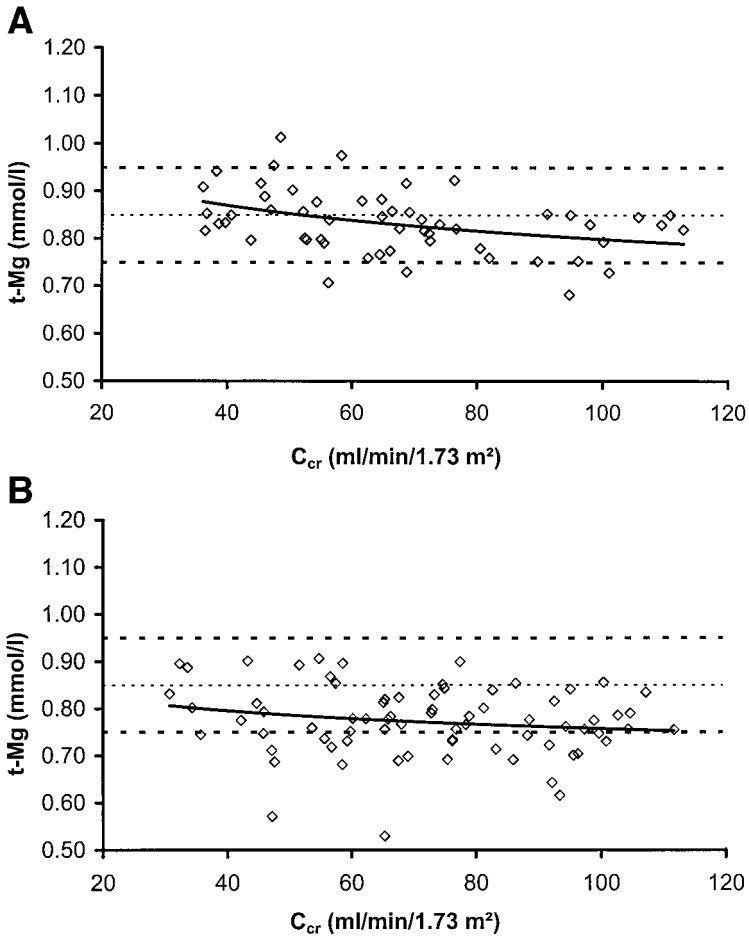

Figure 1—*Distribution of serum t-Mg values as a function of the C_{Cr} in nondiabetic* (A) *and diabetic* (B) *subjects. Also indicated are the reference interval (7) (broken lines represent the mean and bold broken lines represent upper and lower limits) and the course of t-Mg, as predicted from C_{Cr} by regression analysis (solid line).*

patients ($P < 0.001$ and $P < 0.05$, respectively) and an expected higher at-random glycemia level ($P < 0.001$) than the nondiabetic population.

Comparison of the Mg values between the nondiabetic and diabetic patients

Statistical analyses demonstrated that t- and i-Mg were normally distributed in both groups (Andersen-Darling test: $P > 0.05$) and that the distributions had equal variances (F test: $P > 0.05$). The mean i- and t-Mg values in the nondiabetic group (0.534 ± 0.05 and 0.834 ± 0.07 mmol/l, respectively), however, were significantly higher than in the diabetic group (0.489 ± 0.05 and 0.773 ± 0.07 mmol/l, respectively) (unpaired t test: $P < 0.001$). In the nondiabetic patients, serum i- and t-Mg increases significantly when C_{Cr} decreases from 115 to 30 ml · min^{-1} · 1.73 m^{-2} ($y = -0.077 \ln[x] + 0.8552$, $r = -0.52$, $P < 0.001$; $y = -0.078 \ln[x] + 1.1577$, $r = -0.38$, $P < 0.001$, respectively), whereas declining C_{Cr} was not accompanied by increases in serum i- or t-Mg ($y = -0.038 \ln[x] + 0.6486$, $r = -0.23$, $P > 0.05$; $y = -0.042 \ln[x] + 0.9505$, $r = -0.18$, $P > 0.05$, respectively) in the diabetic group (Fig. 1) (only the data for t-Mg are presented).

CONCLUSIONS

— The occurrence of hypomagnesemia is well established in patients with diabetes without CRF (see refs. 9–12 for t-Mg 13,14 for i-Mg). Therefore, our findings of significantly lower serum t- and i-Mg values in diabetic patients with CRF than in the nondiabetic patients with CRF were not unexpected. However, no significant correlation of the i- and t-Mg values with C_{Cr} was found in the observed C_{Cr} range (>30–115 ml · min^{-1} · 1.73 m^{-2}) in the diabetic patients, which was in sharp contrast to the findings for the nondiabetic patients. Thus, in patients with diabetes, the combination of initial significantly lower Mg values, without consequential increase of the Mg levels during the progression of renal failure, exacerbates the risk of worsening hypomagnesemia in comparison with the nondiabetic patients. In light of this finding, taken together with the emerging role of Mg (especially inherent hypomagnesemia) in the pathogenesis of cardiovascular diseases (15), a strict follow-up of Mg levels is recommended in diabetic patients under treatment with Mg-lowering side effects (such as diuretics or polystyrene sulfonate), while also considering the preexisting increased cardiovascular risk factors in this group of patients. In addition, our findings reinforce the recommendations by the American Diabetes Association to supplement diabetic patients with magnesium early (16–18). Finally, it should be noted that although the prevalence of hypomagnesemia was somewhat higher when i-Mg was considered, this finding does not really warrant sufficient clinical importance in order to justify systematic determination of serum i-Mg in patients with CRF.

Additionally, our results show significantly lower Na and Cl levels in the diabetic group. On one hand, this possibly correlates with the higher glycemia levels in this population; however, on the other hand, this may reflect defects in the Na^+/Mg^{2+} exchanger (19–21) and/or the Na-K cation pump, leading to accumulation of intracellular Na^+ and water (22).

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