Serum and urinary magnesium in young diabetic subjects in Bangladesh[1-3]

Laique A Khan, Abu MS Alam, Liaquat Ali, Anupam Goswami, Zahid Hassan, Soheli Sattar, Nani G Banik, and AK Azad Khan

ABSTRACT

Background: Magnesium imbalance, implicated in diabetes mellitus both as a cause and a consequence, has not yet been investigated in subgroups of subjects with malnutrition-related diabetes mellitus, which is prevalent in young patients in tropical developing countries such as Bangladesh.

Objective: The present study evaluated the serum and urinary magnesium concentrations in groups of young diabetic subjects in Bangladesh.

Design: Forty patients newly diagnosed with diabetes [13 with fibrocalculus pancreatic diabetes (FCPD), 13 with protein-deficient diabetes (PDDM), and 14 with type 2 diabetes mellitus] were studied along with 13 healthy control and 13 malnourished control subjects [body mass index (in kg/m^2) <19]. Magnesium was measured by atomic absorption spectrophotometry.

Results: Malnutrition itself was not related to the serum glucose (fasting: 3.68 ± 0.74 and 4.11 ± 0.29 mmol/L; postprandial: 6.30 ± 0.41 and 6.00 ± 0.24 mmol/L for healthy and malnourished control subjects, respectively) or serum or urinary magnesium (serum: 0.73 ± 0.03 and 0.75 ± 0.05 mmol/L; urinary: 232 ± 124 and 243 ± 88 mmol Mg/mol creatinine for healthy and malnourished control subjects, respectively) concentration. Subjects with FCPD and PDDM had significantly lower serum magnesium concentrations (PDDM: 0.68 ± 0.06 mmol/L, FCPD: 0.66 ± 0.07 mmol/L) than those in both control groups. In contrast with 0% of healthy and 7.7% of malnourished control subjects, 42.85% of type 2 diabetic subjects, 61.54% of those with PDDM, and 69.23% of those with FCPD were hypomagnesemic. Subjects with FCPD and PDDM had significantly higher urinary excretion of magnesium than the healthy and malnourished control subjects and the type 2 diabetic subjects. Hypermagnesuria paralleled hypomagnesemia.

Conclusions: Malnutrition may not itself give rise to glucose intolerance, and serum magnesium deficiency seems to be a consequence rather than a cause of diabetes mellitus.   *Am J Clin Nutr* 1999;69:70–3.

INTRODUCTION

Magnesium is known to play an important role in carbohydrate metabolism, and its imbalance has been implicated in diabetes mellitus both as a cause and a consequence (1–3). Hypomagnesemia has been observed in both animal (4) and human subjects with type 1 and type 2 diabetes mellitus (5–9). Low erythrocyte magnesium has also been reported in type 1 and type 2 diabetic subjects (5).

A substantial number of diabetic subjects in tropical, developing countries are young, nonketotic, and suffer from a type of diabetes termed "malnutrition-related diabetes mellitus" (MRDM) by the WHO Study Group on Diabetes Mellitus (10). MRDM is further subclassified into fibrocalculus pancreatic diabetes (FCPD) and protein-deficient diabetes mellitus (PDDM). About 55% (42% for PDDM and 13% for FCPD) of the diabetic patients in Bangladesh <30 y of age have MRDM (11). Although some clinical and biochemical peculiarities of these subjects have been recognized (12–15), the etiopathology of MRDM is still unclear. Even the role of malnutrition in this disease is disputed (16).

In light of the evidence of magnesium imbalance in diabetes mellitus, it is important to study magnesium metabolism in MRDM, which may be associated with malnutrition and consequent hypomagnesemia. No report has yet been published on the serum magnesium concentrations of subjects with MRDM. Moreover, no study has yet reported the serum and urinary magnesium concentrations of either the normal or diabetic population of Bangladesh. The objective of the present study was to investigate the serum and urinary magnesium status of early-onset diabetic subjects in Bangladesh with particular reference to MRDM patients.

SUBJECTS AND METHODS

Subjects

A total of 40 subjects newly diagnosed with uncomplicated diabetes, aged 15–30 y, were selected from the Under 30 Diabetic Clinic of the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) Hospital, Dhaka. Subjects' conditions were diagnosed and classified according to the WHO Study Group guidelines, taking body mass index (BMI; in kg/m^2) <19 as the cutoff point for MRDM (10). In the FCPD, PDDM, and type 2 diabetic groups there were 13 (4 female, 9 male), 13 (4 female, 9 male), and 14 (10 female, 4 male) subjects, respectively. No insulin or other treatments were given to the subjects until after postprandial blood samples were collected.

Twenty-six age- and sex-matched subjects of similar socioeconomic backgrounds with no family history of diabetes up to the second generation served as controls. Of the 26 control subjects selected, 13 (4 female, 9 male) with BMIs ≥ 19 served as healthy control subjects and 13 (5 female, 8 male) with BMIs <19 served as malnourished control subjects (10).

Diabetic persons with ketosis, microvascular complications, hypertension, or any other chronic diseases revealed by routine clinical and biochemical examinations were excluded from the study. Pregnant women were also excluded. None of the study subjects had taken any vitamin or mineral supplements in the recent past.

Collection of samples

Serum from overnight (12 h) fasting and a postprandial venous blood sample (2 h after a 75-g oral glucose load) were separated by centrifugation (1300 $\times$ g for 10 min) within 30 min after collection into capped, airtight polyethylene test tubes and were preserved at $-40\,°C$ for estimation of serum magnesium and other biochemical measures. After overnight urine was discarded, fasting urine samples were collected and preserved at $-40\,°C$ for estimation of urinary magnesium. All laboratory wares were washed properly beforehand by following a standardized procedure (17). All laboratory reagents used for determination of magnesium were prepared with distilled, deionized water.

Biochemical methods

Serum glucose was measured by using the glucose-oxidase method (Boehringer-Mannheim, Mannheim, Germany) method. Serum and urinary magnesium concentrations were estimated by atomic absorption spectrophotometry (model AA-680; Shimadzu, Tokyo) using an air-acetylene flame with a single hollow cathode lamp. Appropriate dilutions of both serum and urine samples were prepared by adding deionized water. Standard reference materials (Seronorm, trace elements, serum; Nycomed Pharma AS, Oslo) were analyzed for each batch to check the accuracy of the method. The reproducibility of the method was verified by analyzing 10 identical samples; the CV was 2.21% for magnesium.

Statistical methods

The differences between groups were analyzed by using analysis of variance (Duncan's new multiple-range test, significance set at $P < 0.05$) and the proportion test when applicable. Analysis of variance was calculated by using the SPSS package for Windows (SPSS Inc, Chicago).

RESULTS

Glycemic status

The mean BMI of the type 2 diabetic group was not significantly different from that of the healthy control subjects but was significantly higher than that of the malnourished control subjects. Although the degree of undernutrition in the malnourished control subjects was not different from that of the MRDM patients (groups with FCPD and PDDM), as reflected in their BMIs, their blood glucose concentrations, both fasting and 2-h postprandial, were in the normal range and were not significantly different from those of the healthy control group (**Table 1**).

Serum and urinary magnesium concentrations

Serum magnesium concentrations were not significantly different between the 2 control groups (**Table 2**). Because no difference was observed between the healthy and malnourished control groups, values for all the control subjects were pooled and a reference range for the population was calculated by taking the mean $\pm$ 3 SEMs as the limits. The range was found to be 0.70–0.76 mmol Mg/L.

The 2 control groups also did not differ in urinary magnesium concentration, and a calculation, similar to that for serum magnesium, gave a reference range of 128.04–334.98 mmol Mg/mol creatinine. Among the 3 diabetic groups, the subjects with FCPD and PDDM had significantly lower serum magnesium values than the control subjects. Subjects with FCPD had the lowest values but they did not differ significantly from those of the other 2 diabetic groups. In contrast with 0% of the healthy con-

TABLE 1
Age, BMI, and fasting and 2-hr postprandial serum glucose concentrations of the study subjects[1]

Study groups	Age	BMI	Serum glucose	
			Fasting	2-h Postprandial
	y	*kg/m²*	*mmol/L*	
Control				
Healthy ($n = 13$)	24.67 ± 3.17	21.56 ± 1.50[a]	3.68 ± 0.74[c]	6.30 ± 0.41[f]
Malnourished ($n = 13$)	24.17 ± 3.51	17.46 ± 0.84[b]	4.11 ± 0.29[c]	6.00 ± 0.24[f]
Diabetic				
Type 2 diabetes ($n = 14$)	24.53 ± 1.64	23.65 ± 3.49[a]	9.92 ± 4.67[d]	20.75 ± 7.48[g]
FCPD ($n = 13$)	24.23 ± 2.05	15.42 ± 2.03[b]	19.13 ± 5.85[e]	30.01 ± 4.01[h]
PDDM ($n = 13$)	24.64 ± 3.29	16.33 ± 1.13[b]	17.24 ± 6.27[e]	30.86 ± 7.32[h]

[1] $\bar{x} \pm$ SD. Values with different superscript letters in each column are significantly different, $P < 0.05$ (Duncan multiple-range test). FCPD, fibrocalculus pancreatic diabetes; PDDM, protein-deficient diabetes mellitus.

TABLE 2
Serum magnesium concentrations and urinary magnesium excretion of the study subjects[1]

Study group	Serum magnesium	Urinary magnesium
	mmol/L	*mmol Mg/mol creatinine*
Control		
Healthy ($n = 13$)	0.73 ± 0.03 [a,b]	232 ± 124 [d]
Malnourished ($n = 13$)	0.75 ± 0.05 [a]	243 ± 88 [d]
Diabetic		
Type 2 diabetes ($n = 14$)	0.70 ± 0.08 [b,c]	264 ± 163 [d]
FCPD ($n = 13$)	0.66 ± 0.07 [c]	625 ± 217 [e]
PDDM ($n = 13$)	0.68 ± 0.06 [c]	421 ± 133 [f]

[1]$\overline{x} \pm$ SD. Values with different superscript letters in each column are significantly different, $P < 0.05$ (Duncan's multiple-range test). FCPD, fibrocalculus pancreatic diabetes; PDDM, protein-deficient diabetes mellitus.

trol subjects and 7.7% of the malnourished control subjects, 42.85% of type 2 diabetic subjects, 61.54% of those with PDDM, and 69.23% of those with FCPD had hypomagnesemia (**Table 3**). The percentages in the 3 diabetic groups differed significantly from those in the healthy and malnourished control groups.

Subjects with FCPD and PDDM had significantly higher urinary excretion of magnesium than did the healthy and malnourished control subjects or the type 2 diabetic subjects. Among the 2 MRDM subgroups, the subjects with FCPD excreted significantly more magnesium than those with PDDM. The percentage distribution of hypermagnesuria closely paralleled the percentage distribution of hypomagnesemia (control subjects: 7.7%; type 2 diabetic subjects: 35.7%; subjects with PDDM: 84.62%; subjects with FCPD: 92.30%). The percentage of subjects with PDDM and FCPD who were hypermagnesuric was significantly higher than that of the healthy and malnourished control subjects or the type 2 diabetic group; however, the 2 MRDM groups were not different from each other (Table 3). In all diabetic subjects, serum magnesium did not show any significant correlation with either fasting serum glucose ($r = -0.068$, $P = 0.676$) or postprandial glucose ($r = -0.1975$, $P = 0.222$) concentrations.

DISCUSSION

When MRDM was considered as a third major type of diabetes by the WHO Study Group (9), there was an inherent

TABLE 3
Distribution of the study subjects with hypomagnesemia (Serum magnesium <0.70 mmol/L) and hypermagnesuria (urinary magnesium >334.98 mmol Mg/mol creatinine)[1]

Study group	Hypomagnesemia	Hypermagnesuria
	n (%)	*n (%)*
Control		
Healthy ($n = 13$)	0 (0)[a]	1 (7.7)[c]
Malnourished ($n = 13$)	1 (7.7)[a]	1 (7.7)[c]
Diabetic		
Type 2 diabetes ($n = 14$)	6 (42.85)[b]	5 (35.70)[c]
PDDM ($n = 13$)	8 (61.54)[b]	11 (84.62)[d]
FCPD ($n = 13$)	9 (69.23)[b]	12 (92.30)[d]

[1]Percentage values with different superscript letters in each column are significantly different, $P < 0.05$ (proportion test). FCPD, fibrocalculus pancreatic diabetes; PDDM, protein-deficient diabetes mellitus.

assumption that malnutrition plays an important role in the etiopathology of the disease. In the present study, malnourished control subjects had blood glucose values that did not differ from those of the healthy control subjects. The data suggest that malnutrition, characterized by low BMI, may not give rise to glucose intolerance in a straightforward way. However, the possibility of undernutrition in utero and in the early stages of life, as suggested by some authors as a cause of diabetes (18), is not excluded by this finding.

The current data also suggest that serum magnesium concentrations remain unchanged even in the face of weight loss in nondiabetic subjects. The finding of a highly significant reduction of serum magnesium in diabetic patients with similar BMIs (subjects with FCPD and PDDM) leads to the conclusion that serum magnesium deficiency is a consequence rather than a cause of diabetes in these patients. The conclusion is further substantiated by the fact that a significantly larger proportion of diabetic patients with much higher BMIs (type 2 diabetic group) showed significant hypomagnesemia.

The pathophysiologic mechanism of hypomagnesemia in diabetes mellitus has remained controversial, particularly the relative roles of hyperglycemia and insulin resistance (1, 2, 19–21). It may be difficult to show the relation between hyperglycemia and serum magnesium at a limited range of hyperglycemia. The present study had 2 groups of patients (those with FCPD and PDDM) with considerable hyperglycemia without ketosis and, thus, provided us with a unique opportunity to explore the relation between serum glucose and magnesium and also between serum glucose and urinary magnesium. Although serum magnesium and glucose concentrations (fasting and postprandial) did not show any significant correlation, the close parallelism between percentage of hypomagnesemic and hypermagnesuric cases in the various groups suggests a major role of hyperglycemia in the development of hypomagnesemia as a result of increased magnesium excretion. Detailed study with more reliable markers of glycemic status, such as glycated hemoglobin, may help to reveal the relation of serum magnesium to glucose concentrations in these subjects.

REFERENCES

1. American Diabetic Association. Magnesium supplementation in the treatment of diabetes—a consensus statement. Diabetes Care 1992;15:1065–7.
2. Paolisso G, Seheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. Diabetologia 1990;33:511–4.
3. Mooradian AD, Morley JE. Micronutrient status in diabetes mellitus. Am J Clin Nutr 1987;45:877–95.
4. Cadell JL. Magnesium in perinatal care and infant health. Magnes Trace Elem 1991–92;10:229–50.
5. Wester PO. Magnesium. Am J Clin Nutr 1987;45(suppl):1305–12.
6. Vanroelen WF, Van Gaal LF, Van Rooy PE, De Leeuw IH. Serum and erythrocyte magnesium levels in type I & type II diabetics. Acta Diabetol Lat 1985;22:185–90.
7. Nadler JL, Malayans S, Loung H, Shaw S, Nataranjan RD, Rude RK. Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in type-II diabetes mellitus. Diabetes Care 1992;15:835–41.

8. Mather HM, Levin GE. Magnesium status in diabetes. Lancet 1979;1:924 (letter).

9. Smith RG, Heise CC, King JC, Costa FM, Kitzmiller JL. Serum and urinary magnesium, calcium and copper levels in insulin dependent diabetic women. J Trace Elem Electrolytes Health Dis 1988;2:239–43.

10. World Health Organization. Diabetes mellitus. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1985;727:10–25.

11. Azad Khan AK, Banik NG, Mahtab H. Malnutrition-related diabetes mellitus in Bangladesh. In: Rifkin H, Colwell JA, Taylor SI, eds. Diabetes. Amsterdam: Elsevier Science Publishers, 1991:944–9.

12. Bajaj JS. Current concepts: classification, pathogenesis and diagnosis of malnutrition-related diabetes mellitus. IDF Bulletin 1988;33:17–21.

13. Mohan V, Ekoe JM, Ramachandran A, Snehalatha C, Viswanathan M. Diabetes in the tropics: differences from diabetes in the west. Acta Diabetol Lat 1986;23:91–8.

14. McMillan DE. Tropical malnutrition diabetes. Diabetologia 1986;29:127–8.

15. Hugh Jones P. Diabetes in Jamaica. Lancet 1955;11:891–7.

16. Rao RH. Diabetes in the undernourished: coincidence or consequence? Endocr Rev 1988;9:67–87.

17. Vanloon JC. Basic material. In: Elving PJ, Winefordner JD, Kolthoff IN. Selected method of trace metal analysis. Oxford, United Kingdom: A Wiley Interscience Publications, 1985:53–73.

18. Hales CN, Barker DJP, Clark PMS, Cox LJ, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at the age 64. BMJ 1991;303:1019–22.

19. Sheehan JP. Insulin resistance and hypomagnesaemia. Br Med J (Clin Res Ed) 1982;285:972 (letter).

20. Moles KW, McMullen JK. Insulin resistance and hypomagnesaemia: case report. Br Med J (Clin Res Ed) 1982;285:262.

21. Resnick LM, Gupta RK, Gruenspan H, Laragh JH. Intracellular free magnesium in hypertension: relation to peripheral insulin resistance. J Hypertens Suppl 1988;6:S199–201.