HYPOMAGNESEMIA IN ETHIOPIANS WITH DIABETES MELLITUS

Berhane Seyoum, MD, MPH; Elias S. Siraj, MD; Christopher Saenz, MA; Jemal Abdulkadir, MD

Background: Magnesium, the second most abundant intracellular cation, plays a key role in cellular metabolism. Even though hypomagnesemia has been demonstrated in patients with both type 1 and type 2 diabetes elsewhere, limited information exists from African patients with diabetes mellitus.

Methods: This was a cross-sectional study to assess the prevalence of hypomagnesemia in Ethiopian patients with type 1 and type 2 diabetes. A total of 159 subjects were included in the study (44 patients had type 1 diabetes, 69 patients had type 2, and 46 were nondiabetic controls).

Results: The mean age (±standard error of the mean) of the subjects with type 1 diabetes, type 2 diabetes, and controls was 30.6±1.6, 51.3±1.3, and 29.0±1.7 years, respectively ($P<.001$). Patients with type 2 diabetes were significantly older than those with type 1 diabetes and controls. Basal C-peptide level and body mass index were also significantly higher in patients with type 2 diabetes ($P<.001$). The mean magnesium level was significantly lower in patients with diabetes than in controls (.84±.12 mmol/L vs 1.02±.17 mmol/L, $P<.001$). Hypomagnesemia was seen in 65% of the patients with diabetes.

Conclusion: The study showed that patients with diabetes mellitus have lower levels of magnesium and are therefore at increased risk of complications related to magnesium. In light of these potential complications, we recommend periodic determination of magnesium levels and appropriate magnesium replacements. (*Ethn Dis*. 2008;18:147–151)

Key Words: Magnesium, diabetes mellitus

From the Division of Endocrinology, Diabetes and Metabolism (BS), Department of Psychology and Community Medicine (CS), Wayne State University School of Medicine, Detroit, Michigan; Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic Foundation, Cleveland, Ohio (ESS); Endocrine/Diabetes Unit, Department of Internal Medicine, Addis Ababa University, Addis Ababa, Ethiopia (JA).

Address correspondence and reprint requests to: Berhane Seyoum, MD, MPH; Wayne State University; Division of Endocrinology, Diabetes and Metabolism; UHC-4H, 4201 St Antoine; Detroit, MI 48201; 313-993-0903 (fax); bseyoum@med.wayne.edu

INTRODUCTION

Magnesium, the second most abundant intracellular cation, plays a key role in cellular metabolism. Approximately 50% of total body magnesium is found in bone. The other half is found predominantly inside cells of tissues and organs. Only 1% of magnesium is found in blood.[1] Hypomagnesemia has been demonstrated in patients with both type 1 and type 2 diabetes mellitus,[2,3] with an incidence of 25%–39%.[4,5]

Magnesium deficiency in diabetes is caused primarily by renal magnesium wasting secondary to glucosuria-induced osmotic diuresis. The degree of magnesium depletion correlates positively with serum glucose concentration and the degree of glucosuria.[6] Hypomagnesemia may increase the risk of cardiovascular abnormalities, such as cardiac arrhythmia, ischemic heart disease, and myocardial infarction.[7,8] Although magnesium is used in the treatment of some cardiovascular disorders,[9–11] the beneficial effect of magnesium replacement in preventing cardiovascular complications in patients with diabetes mellitus has not been proven in long-term studies. Moreover, hypomagnesemia might indicate the development of diabetes in groups known to be at high risk, although correction of low magnesium levels has not been shown to reduce this risk.[12]

…the beneficial effect of magnesium replacement in preventing cardiovascular complications in patients with diabetes mellitus has not been proven in long-term studies.

No studies of magnesium levels have been conducted in patients with diabetes in Africa; therefore, we conducted a cross-sectional study in Ethiopian patients with type 1 and type 2 diabetes to determine the prevalence of hypomagnesemia.

METHODS

The study was performed at the diabetes clinic of the Tikur Anbessa Hospital, Addis Ababa University, Ethiopia. Forty-four subjects with type 1 diabetes, 69 subjects with type 2 diabetes, and 46 nondiabetic controls were included in the study. The classification and diagnosis of diabetes mellitus were made according to World Health Organization criteria.[13] Tikur Anbessa Hospital is the main national referral and teaching hospital in the capital of Ethiopia, Addis Ababa. The diabetes clinic has more than 2000 registered patients with diabetes. All subjects with either type 1 or type 2 diabetes who volunteered to participate in the study and were available for laboratory examination were included. None of the subjects took their morning dose of insulin or oral agents on the day of examination. Apart from hypertension, no other significant co-morbidities were observed in those patients, and none were smokers.

Information regarding age, type of diabetes, duration of diabetes, and type of treatment was collected. Weight and height were measured for all patients and were recorded to the nearest kilogram and centimeter. Blood pressure was measured on the right arm in the sitting position with a standard mercury sphygmomanometer. Informed consent was obtained from each participant according to the guidelines of the Helsinki convention.

Table 1. Characteristics of patients with diabetes and controls

Variable	Type 1 (*n*=44)	Type 2 (*n*=69)	Controls (*n*=46)	*P* value
Age (years)	30.6±1.6†	51.3±1.3†,‡	29.0±1.7‡	<.001
Duration of diabetes (years)	7.3±.9	8.9±.8	-	NS
Systolic BP (mm Hg)	116.3±3.0†	133.2±2.3†,‡	119.6±2.8‡	<.001
Diastolic BP (mm Hg)	78.1±3.0	81.4±1.3	78.2±1.6	NS
Basal C-peptide	.14±.05†,‡	.69±.05†	.56±.05‡	<.001
BMI (kg/m^2)	20.2±.5†	23.9±.4†,‡	20.2±.5‡	<.001
Waist-to-hip ratio	.88±.01†	.94±.01†	.83±.01†	<.001
Cholesterol (mmol/L)	5.7±.3	5.2±.2	4.8±4.2	NS
HDL (mmol/L)	.97±.09	.88±.07†	1.25±.19†	.006
Triglycerides (mmol/L)	1.6±.2	2.1±.1†	1.3±.2†	.006
LDL (mmol/L)	3.4±.3	3.2±.2	2.8±.2	NS
Magnesium (mmol/L)	.82±.02†	.86±.02‡	1.02±.02†,‡	<.001

* Matching superscripts (†‡) across the row indicates Tukey HSD planned comparisons were significant at the $P<.05$ level. All values are mean±SE. Differences regarding age, systolic blood pressure, basal C-peptide, BMI, waist/hip ratio, HDL cholesterol, triglycerides, and magnesium were significant, as well as their planned comparisons.

We collected 5–10 mL of venous blood from each subject in the fasting state. After centrifugation of the blood samples, the sera were isolated and then frozen at −20°C. The samples were then transported to Germany on dry ice at temperatures reaching 0°C. Within 24 hours, the specimens reached their destination and were stored at −20°C until analyzed.

Lipid values (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides) were measured with a Beckman DU-640 Spectrophotometer (Beckman Coulter Company, Fullerton, Calif, USA). The method used for the lipid panel was an enzymatic method from Boehringer-Mannheim company (Monotest Cholesterol Boehringer-Mannheim Company, Ingelheim, Germany). Magnesium levels were measured with a Flame Atomic Absorption Spectrophotometer (Perkin-Elmer Company, Waltham, Mass, USA). After measurement of magnesium levels, 50 µL serum was diluted with 1.25 mL of .1 molar HCl. Acetylene was used as fuel gas. The determination was done with reference curve software. The normal range for plasma magnesium level is .70–1.00 mmol/L.

SAS software (SAS Institute, Inc., Cary, NC) was used for all statistical analyses. Data were analyzed as means plus or minus standard errors of mean (SEM) for continuous variables and as frequency and percentage of study sample for categorical variables. In evaluating univariate differences, analysis of variance was used to compare continuous variables such as age and duration of diabetes; χ^2 tests were used

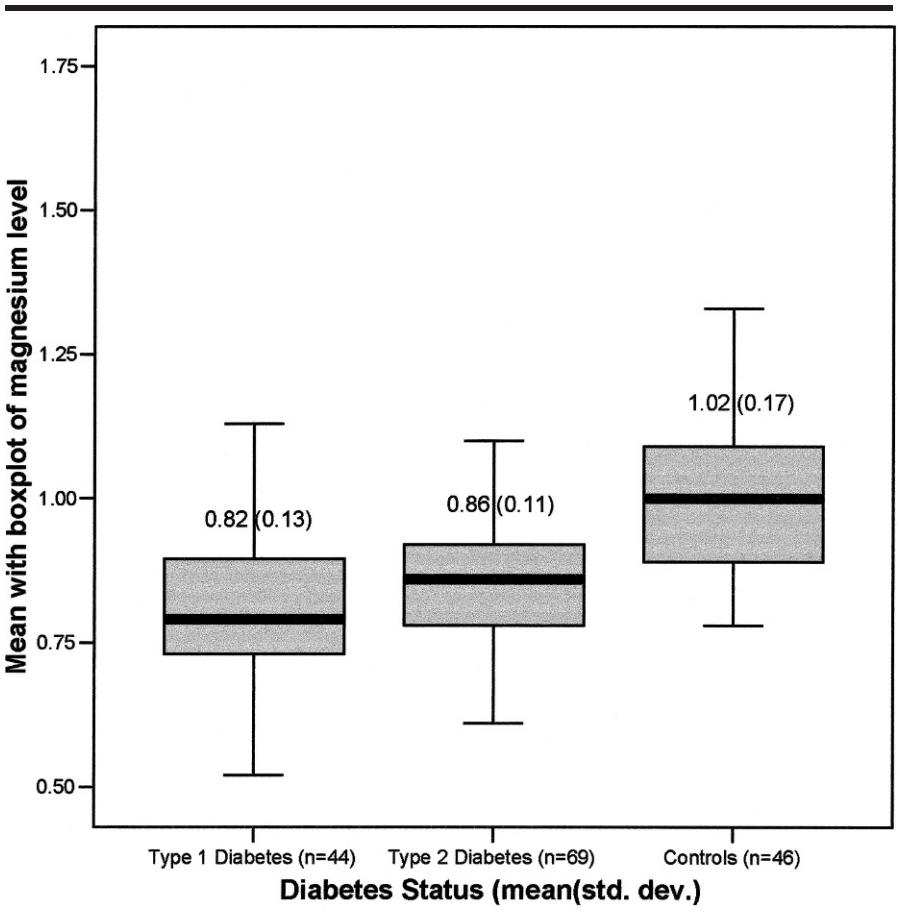

Fig 1. Magnesium levels in patients with diabetes mellitus and controls. Note: Controls have significantly higher magnesium than both type 1 and type 2 patients with diabetes, *F*=28.77 (2, 156), *P*<.001

Table 2. Characteristics of 113 patients with diabetes with different levels of magnesium

		Type 1 Diabetes			Type 2 Diabetes			
Magnesium levels (mmol/L)		**<0.7 *n*=7**	**0.7–0.9 *n*=26**	**>0.9 *n*=11**	**<0.7 *n*=5**	**0.7–0.9 *n*=39**	**>0.9 *n*=25**	***P* value**
Age (years)	±SE	*23.14*	31.81	32.1	50.80	*52.59*	49.32	<0.001
		1.06	2.27	3.60	3.38	*2.08*	1.68	
Gender (% female)		57.14	38.46	40.40	80.00	58.97	64.00	NS
Duration of diabetes (years)	±SE	6.57	7.69	6.70	11.60	8.23	9.28	NS
		1.04	1.38	2.06	3.70	0.94	1.35	
Systolic BP (mmHG)	±SE	*108.33*	118.00	123.75	124.00	133.55	*134.40*	.006
		3.07	2.65	14.01	5.10	3.43	*4.00*	
Diastolic BP (mmHG)	±SE	*71.67*	79.40	81.25	73.60	80.26	*84.60*	.024
		1.67	1.64	4.41	2.23	1.61	*1.87*	
BMI (kg/m^2)	±SE	20.93	20.44	*19.27*	*24.70*	24.48	23.13	<0.001
		1.15	0.58	*1.03*	*2.74*	0.68	0.72	
Waist/hip ratio	±SE	*0.85*	0.89	0.89	0.92	*0.94*	0.93	0.002
		0.02	0.01	0.02	0.02	*0.01*	0.01	
Cholesterol (mmol/L)	±SE	5.89	5.69	5.38	5.22	5.27	5.20	NS
		0.62	0.51	0.55	0.82	0.26	0.25	
HDL (mmol/L)	±SE	1.02	1.02	0.80	1.10	0.83	0.90	NS
		0.08	0.08	0.08	0.13	0.05	0.10	
Triglyceride (mmol/L)	±SE	1.03	1.51	2.38	1.74	1.90	2.36	NS
		0.23	0.14	0.86	0.40	0.19	0.26	
LDL (mmol/L)	±SE	3.52	3.37	3.32	3.13	3.25	3.20	NS
		0.64	0.42	0.52	0.67	0.19	0.24	

Notes: All values are expressed as mean±SE.

For significant main effect ANOVAs, the highest and lowest values are denoted in *italics*. Considering the low sample sizes in some cells, the data are more descriptive in nature, and significance levels should be interpreted with caution.

to explore the univariate relationships among categorical variables.

RESULTS

Type 2 diabetes patients were significantly older than were patients with type 1 diabetes and controls (Table 1). Systolic blood pressure was significantly higher in patients with type 2 diabetes, but diastolic blood pressure was similar in all groups. Basal C-peptide levels, body mass index, and the waist-to-hip ratio were significantly higher in patients with type 2 diabetes. Similarly, serum triglyceride and HDL cholesterol levels were significantly higher in type 2 patients, but LDL cholesterol and total cholesterol were not.

The mean magnesium level was significantly lower in patients with diabetes than in controls (.84±.12 mmol/L vs 1.02±.17 mmol/L, $P<.001$). The levels in type 1 and type 2 patients were similar (.82±.13 mmol/L and .86±.02 mmol/L, respectively) (Figure 1). The overall prevalence of hypomagnesemia was 65% in patients with diabetes.

When the different characteristics were compared among patients with diabetes, magnesium levels, age, systolic blood pressure, diastolic blood pressure, and waist-to-hip ratio were significantly lower in patients with type 1 diabetes with the lowest magnesium level ($P<.005$). All other variables were similar among the different magnesium level categories. The duration of diabetes, sex, and lipid profile of the patients with diabetes were similar in the different categories of magnesium levels (Table 2).

DISCUSSION

We found a high rate of hypomagnesemia among patients with diabetes; these findings concur with those of other studies,[3,14,15] but the magnitude of hypomagnesemia in our patients is roughly twice what was observed in these studies (65% vs 25%–39%).

Diabetes mellitus is one of the most common causes of magnesium deficiency,[16] although the mechanism is not

We found a high rate of hypomagnesemia among patients with diabetes; these findings concur with those of other studies,[3,14,15] but the magnitude of hypomagnesemia in our patients was roughly twice what was observed in these studies …

completely known. Hypomagnesemia is related to poor metabolic control, which is attributed to increase in urinary magnesium loses,[6] and although we did not determine glycosylated hemoglobin levels in our patients, poor diabetic control might be an additional factor for their hypomagnesemia. Other factors, however, including vomiting, diarrhea, low sodium intake, and diuretic use may play a role in magnesium deficiency in diabetes.

Recent evidence suggests that insulin, enhances the transport of magnesium into cells; thus, lack of insulin may result in an intracellular magnesium deficit.[17,18] However, in states of insulin resistance, insulin-induced cellular entry of magnesium is impaired.[19–21] A recent study showed that pioglitazone, an insulin sensitizer, increases free magnesium concentration in insulin-responsive tissues such as adipocytes.[22] However, whether hypomagnesemia precedes or follows insulin resistance is not clear.[23,24] Additionally, reduced magnesium intake may contribute to magnesium deficiency in patients with diabetes. A large portion of the US population consumes less magnesium than is recommended.[25] Similarly, 80% of patients with diabetes in Denmark consume less magnesium than is recommended.[26] In Ethiopia, a country with a widespread famine and drought, a large portion of the population is malnourished. Therefore, a magnesium-deficient diet might have contributed to the high prevalence of hypomagnesemia observed in our patients.

Magnesium levels have been shown to be inversely related to both systolic and diastolic blood pressure.[27] Contrary to this finding, diastolic blood pressure in our patients was significantly lower in those with diabetes and low magnesium levels, and systolic blood pressure showed a similar trend.

Low magnesium is linked to a higher incidence of ischemic heart disease and cardiac death,[5,6,28] and magnesium deficiency in skeletal muscle has been observed in patients who had a myocardial infarction.[29] Intravenous magnesium therapy during acute myocardial infarction has been shown to significantly reduce cardiac arrhythmias.[30] Diabetes patients with magnesium deficiency are at an increased risk of cardiovascular death, but none of these cardiac complications were seen in our patients, and although hypomagnesemia is associated with low HDL cholesterol, high total cholesterol, and triglyceride levels,[31,32] hypomagnesemia was not associated with dyslipidemia in our study. We were unable to determine calcium, phosphate, and vitamin D levels in our patients.

In conclusion, our patients with diabetes have significant magnesium deficiency and thus might be at increased risk of related complications. We recommend periodic determination of magnesium levels and appropriate magnesium replacement. To examine the effect of magnesium replacement on outcomes, a long-term prospective study is needed.

REFERENCES

1. Rude RK. Magnesium deficiency: a cause of heterogeneous disease in humans. *J Bone Miner Res*. 1998;13(4):749–758.
2. Rude RK. Magnesium deficiency and diabetes mellitus: causes and effects. *Postgraduate Medicine*. 1992;92(5):217–224.
3. Nadler JL, Rude RK. Disorders of magnesium metabolism. *Endocrinol Metab Clin North Am*. 1995;24(3):623–641.
4. Fujii S, Takemura T, Wada M, Akai T, Okuda K. Magnesium levels in plasma erythrocyte and urine in patients with diabetes mellitus. *Horm Metab Res*. 1982;14(3):161–162.
5. de Valk HW. Magnesium in diabetes mellitus. *Neth J Med*. 1999;54(4):139–146.
6. Djurhuus MS, Skott P, Vaag A, et al. Hyperglycemia enhances renal magnesium excretion in type 1 diabetic patients. *Scan J Clin Lab Invest*. 2000;60(5):403–409.
7. Altura BM, Altura BT. New perspectives on the role of magnesium in the pathophysiology of the cardiovascular systems. *Magnesium*. 1985;4(5–6):226–244.
8. Chadda KD. Clinical hypomagnesemia, coronary spasm and cardiac arrhythmia. *Magnesium*. 1986;5(1):47–52.
9. Morton BC, Smith FM, Mckibbon TG. Magnesium therapy in acute myocardial infarction. *Magnesium Bull*. 1981;3(1): 192–194.
10. Morton BC, Smith FM, Nair RC, Mckibbon TG, Poznanski WJ. The clinical effects of magnesium sulfate treatment in acute myocardial infarction. *Magnesium*. 1984;3(4–6): 346–352.
11. Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomized trials. *BMJ*. 1991;303(6816): 1499–1503.
12. Yokota K. Diabetes mellitus and magnesium. *Clin Calcium*. 2005;15(2):203–212.
13. WHO Study Group. Diabetes mellitus—technical report series 727. Geneva: World Health Organization; 1985.
14. Mather HM, Nisbet JA, Burton GH, et al. Hypomagnesemia in diabetes. *Clin Chim Acta*. 1979;95(2):235–242.
15. McNair P, Christiansen C, Madsbad S, et al. Hypomagnesemia, a risk factor in diabetic retinopathy. *Diabetes*. 1978;27(Suppl 1): 1075–1077.
16. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbol I. Renal hypomagnesemia in human diabetes mellitus: its relation to glucose homeostasis. *Eur J Clin Invest*. 1982; 12(1):81–85.
17. Barbagallo M, Gupta RK, Resnick LM. Cellular ionic effects of insulin in normal human erythrocytes: a nuclear magnetic resonance study. *Diabetologia*. 1993;36(2):146–149.
18. Hwang Dl, Yen CF, Nadler JL. Insulin increases intracellular magnesium transport in human platelets. *J Clin Endocrinol Metab*. 1993;76(3):549–553.
19. Alzaid AA, Dinneen SF, Moyer TP, Rizza RA. Effects of insulin on plasma magnesium in non insulin dependent mellitus: evidence for insulin resistance. *J Clin Endocrinol Metab*. 1995;80(4):1376–1381.
20. Paolisso G, Ravussin E. Intracellular magnesium and insulin resistance: results in Pima Indians and Caucasians. *J Clin Endocrinol*. 1995;80(4):1382–1385.
21. Paolisso G, Sgambato S, Giugliano D, et al. Impaired insulin induced erythrocyte magnesium accumulation is correlated to impaired insulin mediated glucose disposal in type 2 (non insulin dependent) diabetes patients. *Diabetologia*. 1988;31(12):910–915.
22. Nadler JL, Scott S. Evidence that pioglitazone increases intracellular free magnesium concentration in freshly isolated rat adipocytes. *Biochem Biophys Res Commun*. 1994;202:416–421.
23. Palisso G, Scheen A, D'Onofrio FD, LeFebere PJ. Magnesium and glucose homeostasis. *Diabetologia*. 1990;33(9):511–514.
24. Schnack C, Bauer I, Pregant P, Hopmeier P, Schernthaner G. Hypomagnesemia in type 2

diabetes mellitus is not corrected by improvement of metabolic long term control. *Diabetologia*. 1992;35(1):77–79.
25. Morgan KJ, Stampley GL, Zabik ME, Fischer DR. Magnesium and calcium dietary intakes of the US population. *J Am Coll Nutr*. 1985;4(2):195–206.
26. Djurhuus MS, Klitgaard NA, Pedersen KK, et al. Magnesium reduces insulin stimulated glucose uptake and serum lipid concentrations in type 1 diabetes. *Metabolism*. 2001;50(12): 1409–1417.
27. Resnick LM, Gupta RK, Gruenspan H, Alderman MH, Laragh JH. Hypertension and peripheral insulin resistance: possible mediating role of intracellular free magnesium. *Am J Hypertens*. 1990;3(5 pt 1):373–379.
28. Karppanen H. Epidemiological aspects of magnesium deficiency in cardiovascular diseases. *Magnesium Bull*. 1986;8:199–203.
29. Rasmussen HS, McNair P, Goransson L, Balslov S, Larsen OG, Aurup P. Magnesium deficiency in patients with ischemic heart disease with and without acute myocardial infarction uncovered by an intravenous loading test. *Arch Intern Med*. 1988;148(2):329–332.
30. Rasmussen HS, Suenson M, McNair P, Norregard P, Balslev S. Magnesium infusion reduces the incidence of arrhythmias in acute myocardial infarction: a double blind placebo controlled study. *Clin Cardiol*. 1987;10(6): 351–356.
31. Guerrero-Romero F, Rodriguez-Moran M. Hypomagnesemia is linked to low serum HDL cholesterol irrespective of serum glucose values. *J Diabetes Complication*. 2000;14(5): 272–276.
32. Baydas B, Karagoz S, Meral I. Effects of oral zinc and magnesium supplementation on serum thyroid hormone and lipid levels in experimentally induced diabetic rats. *Biol Trace Elem Res*. 2002;88(3):247–253.

AUTHOR CONTRIBUTIONS

Design concept of study: Seyoum, Siraj, Saenz, Abdulkadir
Acquisition of data: Seyoum, Siraj, Saenz, Abdulkadir
Data analysis and interpretation: Seyoum, Siraj, Saenz, Abdulkadir
Manuscript draft: Seyoum, Siraj, Saenz, Abdulkadir
Statistical expertise: Seyoum, Siraj, Saenz, Abdulkadir
Acquisition of funding: Seyoum, Siraj, Saenz, Abdulkadir
Administrative, technical, or material assistance: Seyoum, Siraj, Saenz, Abdulkadir
Supervision: Seyoum, Siraj, Saenz, Abdulkadir