Original Article

Hypomagnesemia in type 2 diabetes mellitus

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ABSTRACT

Introduction: Hypomagnesemia is reported in type 2 diabetes; magnesium deficiency may play a role in the development of endothelial dysfunction and altered insulin function. **Objective:** To assess the incidence of hypomagnesemia among noncritically ill patients of Type 2 diabetes mellitus and to evaluate the relation of hypomagnesemia to glycemic control and various long-term complications of diabetes mellitus. **Materials and Methods:** One hundred and fifty, noncritically ill (APACHE score < 10) type 2 diabetes mellitus patients, who were admitted in the Departments of Medicine and Endocrinology, GMCH for uncontrolled hyperglycemia and/or various diabetic complications were studied. Serum magnesium was assessed at admission and rechecked in those found to be deficient. **Results:** Hypomagnesemia (Se magnesium < 1.6 mg/dl) was documented in 17 (11.33%) patients with a female:male ratio of 9:8. Mean HbA1c was 11.9% in the hypomagnesemic patients compared with 9.8% in controls (P =0.0016). Retinopathy, microalbuminuria, macroalbuminuria, foot ulceration, and neuropathy was present in 64%, 47%, 17.64%, 58.8%, and 82.35%, respectively, of the patients with hypomagnesemia as compared with 45.8% (P =0.118), 38.34% (P =0.704),15.03% (P =0.566), 22.55% (P =0.011) and 82.7% (P =0.976) without hypomagnesemia. Coronary artery disease was less common in the hypomagnesemia group (17.6% vs 39%), but comparable in the subgroup < 50 years (27% vs 25%) (P =0.796). **Conclusion:** Hypomagnesemia in diabetes was associated with poorer glycemic control, retinopathy, nephropathy, and foot ulcers.

Key words: Diabetic complications, glycemic control, hypomagnesemia, type 2 diabetes

Introduction

Recently there has been an emerging interest regarding the important roles played by magnesium in various cell processes in the body.[1]

Studies have shown that magnesium levels are lower in patients with diabetes compared with nondiabetic controls.[2-4] The association of hypomagnesemia with poor glycemic control and also with various long-term complications of diabetes mellitus have been reported.[2] This study was conducted to evaluate the relation of hypomagnesemia to glycemic control as also to the various microvascular and macrovascular complications.

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Materials and Methods

This was a cross sectional study conducted over 6 months from January 2010 to June 2010. One hundred and fifty (93 male and 57 female), noncritically ill (APACHE score < 10) patients of type 2 diabetes mellitus, of all ages, admitted in the Departments of Endocrinology, Medicine and Surgery, Gauhati Medical College and Hospital, Guwahati(GMCH), were included in the study. The reference range of magnesium was taken between 1.6 and 2.2 mg/dl. The patients with hypomagnesemia were taken as cases and the patients with normal magnesium levels were taken as controls. Serum magnesium was assessed by photometric method. (Vitros, Ortho clinical Diagnostics, CV-10%.)

Patients on drugs known to affect magnesium levels [Table 1], with a Se creatinine > 1.5 mg/dl, with acute or chronic diarrheal/malabsorption states, with thyroid or

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adrenal dysfunction, h/o alcohol intake, h/o vitamin or mineral supplements in the recent past, recent metabolic acidosis, pregnancy, lactation, or sepsis were excluded from the study.

SPSS window package 19 (IBM) was used for analysis of data. All parametric variables were expressed as mean +/- SD. The comparison between groups was made by unpaired *t*-test and *P* values < 0.05 were considered significant.

Results

Seventeen out of 150 subjects (11%) had hypomagnesemia (Se magnesium < 1.6 mg/dl) whereas 133 (89%) were found to have normal levels of magnesium. The mean duration of diabetes in the patients with hypomagnesemia was 6.8 years. All the patients assessed were admitted in the general wards of the Departments of Endocrinology, Medicine and Surgery, Gauhati Medical College and Hospital, Guwahati. The various causes of admission are enumerated in Table 2. The characteristics of the cases and controls and the results of the study are given in Tables 3 and 4, respectively.

After adjusting for HbA1c values and doing a multivariate analysis the association of hypomagnesemia was found to be significant only with foot ulcer (*P* 0.01).

Discussion

Among the endocrine and metabolic disorders associated with magnesium deficiency, diabetes mellitus is the most common. Many studies have shown that mean plasma levels are lower in patients with both type 1 and type 2 diabetes compared with nondiabetic control subjects. Significant negative correlations between magnesium and fasting plasma glucose, HbA1c, HOMA-IR have been shown.[3,5] The various causes of low magnesium in diabetics include diets low in magnesium,[6] osmotic diuresis causing high renal excretion of magnesium, insensitivity to insulin affecting intracellular magnesium transport and thereby causing increased loss of the extracellular magnesium,[7] rampant use of loop and thiazide diuretics promoting magnesium wasting, diabetic autonomic neuropathies,[2] and reduced tubular reabsorption due to insulin resistance.[8] In the present study hypomagnesemia was found in 11% of diabetics. Studies have reported incidence rates of 13.5–47.7% in diabetic subjects.[2] The lower incidence of hypomagnesemia in our study could perhaps be attributed to stricter exclusion criteria followed in the study and to the dietary habits of the region where whole grain rather than milled grain is more commonly consumed.

Table 1: Drugs known to affect magnesium status

Aminoglycosides
Amphotericin B
Cetuximab
Cyclosporine
Digoxin
Diuretics (loop, thiazide, osmotic)

Table 2: Causes of admission

Uncontrolled hyperglycemia	64
Diabetic foot	40
Diabetic microvascular complications	35
Diabetic macrovascular complications	9
Quadriparesis	2

Table 3: Characteristics of cases and controls

	Hypomagnesemia	Normal magnesium	*P*-value
No. of patients (%)	17(11)	133(89)	
Mean age (years)	45 (±5.8)	58 (±5.3)	<0.0001
Female:Male ratio	1.12:1	0.56:1	0.07

Intracellular magnesium plays a key role in regulating insulin action, insulin-mediated glucose uptake, and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action, and worsening of insulin resistance in diabetic patients.[8,9] Cellular magnesium is a critical cofactor for the activities of various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATPase and adenylate cyclase enzymes.[1] Chronic magnesium deficiency has also been associated with elevated concentrations of TNF-alpha, and this may also contribute to postreceptor insulin resistance.[10]

We found statistically poorer glycemic control in the hypomagnesemia patients as compared with the normomagnesemia patients. The Health Professionals Follow-Up Study and the Nurse's Health Study showed that subjects in the highest quintile of magnesium intake had a 33% lower risk of developing type 2 diabetes mellitus (T2DM) than those in the lowest quintile of magnesium intake.[11] A recent meta-analysis found that of the 13 selected studies, 9 showed a statistically significant inverse association between magnesium intake and diabetes risk and concluded that decreased magnesium intake is significantly associated with risk of type 2 diabetes in a dose-response manner.[12]

The mean duration of diabetes in the patients with hypomagnesemia was 6.8 years. Haquea *et al*. found a mean diabetic duration of 8.85 years in hypomagnesemic patients and concluded that serum magnesium level has no

Table 4: Comparison of results between cases and controls

	Hypomagnesemia	Normal magnesium	*P*-value	Odds ratio
Average Mg levels (mg/dl)	1.023 (±0.315)	1.97±1.11	0.0001	
Mean FBS (mg/dl)	339±90.66	278±85.22	0.011	
HbA1c	11.9%±2.26%	9.8%±2.1%	0.0016	
Retinopathy	11(64%)	61 (45.8%)	0.118	2.164
Neuropathy	14 (82.35%)	110 (82.70%)	0.816	0.976
Microalbuminuria	8 (47%)	51 (38%)	0.704	1.429
Macroalbuminuria	3 (17.60%)	20 (15.03%)	0.566	1.211
Coronary artery disease	3 (17.6%)	52 (39%)		
Subgroup < 50 years	3 (27%)	21 (25%)	0.796	1.125
Foot ulcer	10 (58.80%)	30 (22.55%)	0.011	4.90

direct relationship with diabetic duration if the diabetes is well controlled.[13]

Increased endothelial dysfunction in hypomagnesemia has been attributed to thrombogenesis via increased platelet aggregation and vascular calcifications.[14] Hypomagnesemia may also lead to the induction of proinflammatory and profibrogenic response, cause reduction of protective enzymes against oxidative stress, cause induction or augmentation of vasoconstriction and hypertension, interfere with normal cell growth and apoptosis, and cause stimulation of aldosterone, among others.[2]

Incidence of retinopathy was higher in the hypomagnesemia group (64% vs 45.8%) in our study. The existence of a close relationship between impaired magnesium balance and retinopathy was established by Fujii *et al*., who found a marked depletion in plasma and erythrocyte magnesium levels in diabetic patients with advanced retinopathy.[15] A study from Brazil with type 1 and type 2 diabetics, however, did not demonstrate a significant correlation between the severity of retinopathy and Mg concentration in the plasma.[16]

Neuropathy was comparable in both groups (82.35% vs 82.70%). Studies have found that intracellular magnesium levels are lower in patients with diabetic peripheral neuropathy[17] with improvement in the nerve conduction following supplementation.[18]

Both microalbuminuria and macroalbuminuria were found at a higher incidence in the hypomagnesemia group compared with the normomagnesemia group. Corsonello *et al*. demonstrated that diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized magnesium compared with normoalbuminuria group.[19]

Low circulating magnesium levels have been related to elevated blood pressure, dyslipidemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease.[20,21] In our study, however, incidence of coronary artery disease was lower in the hypomagnesemia patients (17.6% vs 39%). However, as there was gross discrepancy (*P* value < 0.0001) in the mean age of both the population groups, which could account for the increased incidence of coronary artery disease in the higher age group normomagnesemic group, we further analyzed a subgroup of < 50 years. In the subgroup < 50 years coronary artery disease was slightly more in the hypomagnesemia group (27% vs 25%). Atherosclerosis Risk in Communities (ARIC) Study, a multicenter, prospective cohort study lasting 4 to 7 years and involving 13,922 middle-aged adults who were free of coronary heart disease at baseline, showed an inverse association between serum magnesium and the risk for coronary heart disease among men with diabetes.[22]

The incidence of foot ulcer was significantly more in the hypomagnesemia group (58.80% vs 22.55%). Rodríguez-Morán *et al*. also reported that serum magnesium depletion is present in subjects with type 2 diabetes and shows a strong relationship with foot ulcers.[23]

Hypomagnesemia has been mentioned as a reversible cause of muscle weakness in diabetes.[24] Two patients presented with severe hypomagnesemia (Se magnesium: 1 mg/dl), quadriparesis with refractory hypokalemia and hypocalcemia. Extensive relevant investigation did not reveal any other cause of hypokalemia, hypocalcemia, or quadriparesis. Complete clinical and biochemical improvement occurred only after correction of hypomagnesemia. Hypomagnesemia causes hypokalemia via the action on renal outer medullary potassium (ROMK), the inwardly rectifying K channel in the distal nephron, required for the back-leak of K^+. A low intracellular Mg^{2+} increases ROMK efflux activity and thereby K^+ wasting.[25] Hypomagnesemia causes hypocalcemia via inappropriately low parathyroid secretion and parathyroid hormone resistance[26] and decreased action of 1,25,hydroxylase.

Conclusion

Hypomagnesemia was found to be associated with poor glycemic control and increased incidence of retinopathy, nephropathy, and foot ulcers. However, statistically significant association was found only with foot ulcers. Hypomagnesemia may be a cause of muscle weakness in diabetic patients and must be kept in mind while evaluating for neuromuscular dysfunction in diabetics. Thus it is prudent to monitor magnesium levels in all type 2 diabetic patients regularly. Further studies on the role of magnesium supplementation in T2DM in the Indian population are recommended.

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