ORIGINAL ARTICLE

Associations of serum Magnesium levels with diabetes mellitus and diabetic complications

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Abstract

Background: Magnesium (Mg) deficiency is a common problem in diabetic patients. Deficiency of Mg may increase the incidence of diabetes mellitus (DM) and occurrence of diabetic complications. In this study, our aim was to evaluate an association between serum Mg level, glycemic regulation, and diabetic complications.

Material-Methods: In this retrospective study 673 diabetic patients were evaluated. According to Mg levels, the patients were divided into two groups; as normomagnesemic patients and hypomagnesemic patients.

Results: Among the patients, 57.8% were men and 42.2% were women. Mean age was 55.6 years and the mean duration of diabetes was 81 ± 86.9 months. The mean glycosylated hemoglobin (HbA1c) was 9.0 ±2.4 % (4.5-18); mean magnesium level was 1.97 ± 0.25 (1.13 to 3.0) mg / dl. There were 55 patients (8.2%) with diabetic retinopathy and 95 patients (14.1%) with diabetic neuropathy. Five hundred patients (74.3%) had normoalbuminuria; 133 patients (19. 8%) had microalbuminuria (MA) and 40 patients (5.9%) had overt proteinuria. One hundred and seventy one patients (25.4%) had HbA1c levels equal or below 7%; and 502 patients (74.6%) had HbA1c levels above 7%. There was no statistical difference in age or duration of diabetes between the groups formed according to Mg levels. Although there were no differences between the groups for retinopathy and neuropathy, MA was more common in hypomagnesemic patients (p =0.004). HbA1c levels did not differ between the groups (p =0.243). However there was a weak negative correlation between serum Mg and HbA1c levels (r =-0.110, p =0.004) and also between serum Mg and urine protein level (r =-0.127, p =0.018).

Conclusion: Mg depletion is a common problem in patients with DM. It affects both glycemic regulation and the occurence of complications. Also, poor glycemic regulation affects serum Mg levels. Hippokratia 2015; 19 (2):153-157.

Keywords: Hypomagnesemia, poor glycemic control, diabetic complication

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Introduction

Magnesium (Mg) has a critical role in the actions of important enzymes and is the fourth most abundant cation in the human body[1]. It is claimed that there is an inverse relationship between Mg intake and incidence of diabetes mellitus (DM)[2]. Mg deficiency is common in diabetic patients. The incidence of hypomagnesemia varies between 11 and 47.7%[3-7]. Compared with the control group, incidence of hypomagnesemia in newly diagnosed diabetes is 10.5-fold and in patients with previously diagnosed diabetes is 8.5-fold more common[8].

Microalbuminuria (MA) was first described in diabetic patients in 1982[9]. It was shown to be associated with increased risk of cardiovascular morbidity and mortality in diabetic patients[10-12]. At the same time, it is accepted as an indicator for the presence of diabetic retinopathy/ neuropathy, cardiovascular and peripheral vascular disease and increased mortality[11,12]. The presence of MA and overt proteinuria in non-insulin dependent diabetes mellitus (NIDDM) is an indicator of poor glycemic control. As well as poor glycemic control; insulin resistance and low Mg level strongly associated with increased the prevalence of MA[13].

There have been controversial views on the relationship between MA and Mg deficiency. Some studies demonstrated that MA and overt proteinuria do not affect plasma Mg level[4,14].

On the other hand, in other studies a significant reduction in serum Mg level in diabetic cases with MA and proteinuria were reported[3,5,15-17]. When compared with normomagnesemic people; increased urinary albumin excretion was reported in type 1 DM patients with hypomagnesemia[15]. A negative correlation between serum Mg and glycosylated hemoglobin (HbA1c) levels was noted[4].

The aim of this study was to evaluate whether glycemic regulation and diabetic complications could be changed between normomagnesemic and hypomagnesemic patients.

Material and Methods

Patients

Our study consisted of 673 NIDDM patients, subdivided into three groups according to their 24-hour urinary albumin excretion rate (UAER): normoalbuminuria (<30 mg/day), MA (30-300 mg/day) and overt proteinuria (>300 mg/day). Cases were also stratified by their serum Mg levels: Low Mg level of ≤1.8 mcg/dl and normal range of 1.9-2.6 mcg/dl. All patients were questioned for age, gender, disease duration, medical history, family history, smoking history, usage of alcohol and concomitant diseases.

Measurement

Height, body weight and body mass index (BMI), which was calculated with the formula weight/height^{square} (kg/m^2), were recorded for each patient. Fat mass and total body water measured by TANITA device [Body Composition Analyzer Model TBF-300 (Tanita Corporation, Tokyo, Japan)] were also recorded. A venous blood sample was collected from each subject in the morning after 12-hour fasting, to evaluate fasting glucose [hexokinase with enzymatic reference methods, (Roche Diagnostics GmbH, Mannheim, Germany)]; low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), sodium, potassium, magnesium [Colorimetric end point methods with ksilidil blue (Roche Diagnostics GmbH, Mannheim, Germany)], creatinine [kinetic colorimetric assay based on the Jaffe methods (Roche Diagnostics GmbH, Mannheim, Germany)], HbA1c [HPLC-high performance liquid chromatography- Biorad Variant II Turbo (Biorad Medical Diagnostics, California, USA)], glomerular filtration rate (GFR) was calculated with the following equation [(140-age) x weight in kg] / (72 x serum creatinine in mg/dl) for male patients. For female patients, the value was reduced to 85% of that estimated with this equation[16].

Diagnosis of diabetic neuropathy was confirmed by a detailed medical history, and neurological examination. Blood pressure and heart rate measurement, pinprick sensation test, perception with monofilaments, vibration and position, and reflexes were performed in all patients. Rarely electrophysiological test were needed.

Diabetic retinopathy was diagnosed with fundus examination, performed by an ophthalmologist.

Exclusion criteria were: patients on drugs that affect Mg levels (diuretics, aminoglycosides, amphotericin B, etc), malabsorption or diarrhea, alcohol consumption, vitamin or mineral supplements in recent past, pregnancy, lactation or sepsis.

Statistical Methods

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics for numeric variables as mean ± standard deviation and median (minimum-maximum) and categorical structure of data was expressed as numbers and percentages. Categorical differences were examined between groups, in terms of structure variables with the Chi-square test. One-way ANOVA test was used for comparison of the normal and low magnesium group. Quantitative variables with normal distribution were compared between two groups using parametric tests, otherwise the Mann-Whitney U test was used. The relationship between two numerical variables was examined using Spearman's correlation analysis. Results were evaluated in 95% confidence interval, and p value of <0.05 was considered as significant.

Results

In this study, a total of 673 patients with type 2 diabetes mellitus who were recorded in diabetes outpatient clinic of our hospital, were included. Among these patients, 57.8 % (n: 389) were men, and 42.2% (n: 284) were women. Mean age was 55.6 ± 10.4 years and mean duration of diabetes was 81 ± 86.9 months. Mean BMI was 31.48 ± 5.8 kg/m^2.

The mean HbA1c was 9.0 ± 2.4 % (range 4.5-18), mean serum creatinine was 0.83 ± 0.22 mg/dl (0.3-1.5), and mean magnesium level was 1.97 ± 0.25 (1.13 to 3.0) mg/dl. Mean glomerular filtration rate (GFR) was 117.88 ± 31.18 ml/minute, mean LDL-C was 127.86 ± 39.3 mg/dl (45-330), mean HDL-C was 42 ± 11.4 mg/dl (26-101), and mean TG was 187.10 ± 129.8 mg/dl (31-710). There were 55 patients (8.2%) with diabetic retinopathy and 95 patients (14.1%) with diabetic neuropathy. Five hundred patients (74.3%) had normoalbuminuria, 133 patients (19. 8%) had MA, and 40 patients (5.9%) had overt proteinuria. A total of 171 patients (25.4%) had an HbA1c levels equal or below 7%, and 502 patients (74.6%) had HbA1c levels above 7%.

According to the serum level of Mg, patients were classified into two groups: low Mg (Group 1, n: 65, 9.7%) and normal Mg group (Group 2, n: 608, 90.3%); there were no statistical differences between two groups in terms of age (p =0.292). Compared with the normomagnesemic group, those in the hypomagnesemic group were more likely to be females (p =0.006). Also, the duration of diabetes was similar in both groups (p =0.058). In both groups BMI (body mass index) and fat mass were similar (p =0.145 and p =0.268) (Table 1).

There were no correlation between BMI and Mg (r =-0.071, p =0.069) , and between Mg and fat mass (r =-0.068, p =0.116). We did not observe a correlation between Mg and LDL-C (r =-0.049, p =0.207), HDL-C (r =-0.044, p =0.253), or TG (r =-0.027, p =0.487).

There was no difference between the groups for retinopathy and neuropathy (p =0.597 for retinopathy, p =0.297 for neuropathy). However MA was more common in group 1 (p =0.004) (Table 1).

Logistic regression analysis was performed between the two groups, consisted of low and normal Mg levels, according to clinical characteristic and variables. In univariate analysis, a statistical significance was shown between sex, duration of DM and MA (p <0.05). In multivariate analysis a significant and independent relationship was shown between sex and MA (p <0.05) (Table 2).

HbA1c levels did not differ between the groups (p

Table 1: Demographic and laboratory features of the two (low and normal Mg) groups according to serum Mg levels.

Feature	All patients (n=673)	Mg low (n=65)	Mg normal (n=608)	p value
Age(year)	55.6 ± 10.4	56.71 ± 10	55.44 ± 10	0.292
Gender (F/M)	284/389	48/17	341/267	0.006
DM time (month)	81 ± 86.9	103 ± 95	78 ± 85	0.058
BMI(kg/m^2)	31.48 ± 5.8	32.8 ± 5.5	31.3 ± 5.8	0.145
HbA1c(%)	9.0 ± 2.4	9.3 ± 2.2	8.9 ± 2.4	0.243
MA(mg/day)	172.91 ± 510.66	557.28 ± 1032	133.20 ± 406	0.004
MA(-) (<30 mg/day)	500	39	461	
MA(+) (30-300 mg/day)	133	17	116	0.016
OP(+) (>300 mg/day)	40	9	31	
Cre (mg/dl)	0.83 ± 0.22	0.84 ± 0.29	0.84 ± 0.31	0.820
GFR (ml/min)	117.88 ± 31.18	115.3 ± 3.7	118 ± 1.3	0.817

DM: diabetes mellitus, BMI: body mass index, F: female, M: male, HbA1c: glycosylated hemoglobin, Cre: Creatinine, MA: microalbuminuria, OP: overt protenuria, GFR: glomerular filtration rate, p value is refered to two groups: Mg low and Mg normal groups.

Table 2: Logistic regression analysis of the two (low and normal Mg) groups according to serum Mg levels.

	Univariate Model				Multivariate Model			
		95% CI		p		95% CI		p
	OR	Low	High		OR	Low	High	
Age	0.99	0.96	1.01	0.375				
Sex	2.21	1.24	3.93	**0.007**	2.33	1.30	4.18	**0.005**
BMI	0.96	0.92	1.00	0.054				
Duration of DM	1.00	0.99	1.00	**0.033**				
Retinopathy	0.71	0.31	1.64	0.423				
Neuropathy	1.69	0.71	4.02	0.239				
HbA1c	0.94	0.85	1.04	0.226				
LDL-C	1.00	1.00	1.01	0.595				
HDL-C	0.99	0.97	1.01	0.211				
TG	1.00	1.00	1.00	0.420				
MA Group	0.55	0.38	0.80	**0.002**	0.53	0.36	0.77	**0.001**

BMI: body mass index, DM: diabetes mellitus, HbA1c: glycosylated hemoglobin, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, TG: triglyceride, MA: microalbuminuria, OR: odds ratio.

=0.243) (Table 1); however, there was a weak negative correlation between serum Mg and HbA1c levels (r =-0.110, p =0.004) which means that when serum Mg level decreases, HbA1c levels increase. To strengthen the link between HbA1c and Mg, we calculated the median Mg value and found to be 1.97 mg/dl. HbA1c values were higher in the group in which Mg <1.97 mg/dL and were lower in the group in which Mg >1.97 mg/dl (p =0.044). At the same time, there was a weak correlation between serum Mg and urine proteinuria (r =-0.127, p =0.018).

Patients were divided into two groups according to HbA1c levels; one group with HbA1c ≤7% and the other with HbA1c >7%. In the group with HbA1c ≤7%, serum Mg level was lower than in the HbA1c >7% group. Also, MA was more common in the group with HbA1c ≤ 7% (Table 3).

Table 3: Serum magnesium levels and urinary proteinuria according to HbA1c.

Feature	HbA1c ≤7% (n=171)	HbA1c >7% (n=502)	p value
Mg(mg/dl)	2.0 ± 0.22	1.95 ± 0.26	0.031
Microalbuminuria grup			
Microalbumunuria(-)	138	362	
Microalbumunuria(+)	25	108	0.045
Overt protenuria	8	32	

HbA1c: glycosylated hemoglobin, Mg: Magnesium.

Discussion

In this study, we found that MA was common in the hypomagnesemic group compared to the normomagnesemic group regardless of age and duration of diabetes. Also, there was a weak negative correlation between serum Mg and HbA1c levels and between serum Mg and urine proteinuria. Hypomagnesemia is not rare in patients with diabetes mellitus. It may affect both glycemic regulation and nephropathy.

Diabetes mellitus is the most common disorder among endocrine disorders that are associated with hypomagnesemia. So far many studies have shown that Mg levels are lower in diabetic patients[2,7,17]. According to CARDIA Study (Coronary Artery Risk Development in young Adults) there was an inverse relationship between Mg intake and the incidence of diabetes[2].

Mg depletion may cause an insulin-resistant state[18,19], poor glycemic control[4,15,20] and disordered lipid metabolism in diabetic patients[21]. Furthermore, poor glycemic control in diabetic patients is a well-known risk factor for Mg depletion[20]. Significant negative correlation between Mg and fasting plasma glucose, HbA1c and Homa Insulin resistant Index (HOMA-IR) have been shown[2,17]. Similarly, we found a negative correlation between serum Mg level and HbA1c level. Marhalle et al[22] have found that diabetes, dyslipidemia, and hypertension were inversely related with serum Mg levels. But we did not observe any correlation between serum Mg and LDL-C, HDL-C and TG levels.

Some authors have suggested that reduced Mg level could have a role in the pathogenesis of microvascular complications of diabetes[23,24]. Serum Mg depletion has been reported in diabetic patients who had advanced retinopathy and poor glycemic control[25]. However we did not find any difference in the presence of retinopathy and neuropathy between the two groups.

The association between MA and depletion of Mg is controversial[17,26-28]. In a study on type 1 diabetic patients, hypomagnesemia has been associated with poor glycemic control and urine albumin excretion[27]. Similarly, we also found a negative correlation between Mg level and urine protein excretion. On the other hand, Zargar et al[28] suggested that glycemic control and presence of MA did not affect serum Mg levels. Other studies also, have not found any association between Mg and MA in Type 1 and Type 2 diabetes[17,28]. In another study with adolescents and young adults, serum Mg levels had differed in diabetic patients based on persistent MA level[14].

One of the possible mechanisms explaining the relation between MA and Mg deficiency is insulin resistance. Mg can act as a mild calcium antagonist. In patients with Mg deficiency, intracellular calcium is increased. Increased calcium may interrupt response of skelatal muscles and adipocytes to insulin and lead to insulin resistance[29]. Intracellular Mg plays a role in regulating insulin action, insulin-dependent glucose uptake, and vascular tone. Deficiency of Mg can reduce tyrosine-kinase activity, postreceptorial activity and eventually it may contribute to the development of insulin resistance[30,31]. On the other hand, insulin deficiency and resistance can effect tubular reabsorption of Mg[32]. According to other hypotheses, oxidative stress is important in complications of diabetes[2]. The antioxidative capacity of Mg have also been reported[26]. Another hypothesis is that by influencing the activity of Na^+/K^+-ATPase reduction of Mg favors the onset and the progression of diabetic microangiopathy[33,34].

In hypomagnesemia endothelial dysfunction occurs due to increased platelet aggregation and vascular calcification[35]. A relationship between high cholesterol and low serum Mg has been shown in animal studies in which Mg supplementation has also decreased the severity of vascular plaque[36]. In NIDDM, Mg supplementation reduced serum total cholesterol, and LDL-C and increased HDL-C[37]. In another study, a negative correlation between serum cholesterol levels and triglyceride levels was reported[38]. Corica et al[39] have found an association of hypomagnesemia with dyslipidemia, high waist circumferences, high blood pressure, MA and overt proteinuria. In another study, no relationship was found between serum lipids and Mg levels[3]. Also in our study, we did not find any difference in serum lipid levels between hypomagnesemic and normomagnesemic groups. Serum Mg levels is reported to be lower in females than in males but there is not an association between hypomagnesemia and age, BMI, HDL, TG, smoking or alcohol history[13]. Similarly in our study female gender was more common in the hypomagnesemic group than in the nomomagnesemic group. Furthermore we did not find any assosiation between serum Mg and age, BMI, LDL-C, TG or HDL-C.

Limitation of the current study was the fact that the number of patients in the two groups was not equal. Also, neuropathy was only assessed clinically.

Conclusion

Serum Mg was found to be inversely associated with the prevalence of MA. Hypomagnesemia was found to be associated with poor glycemic control. Large-scale clinical trials are needed in order to determine whether the correction of Mg deficiency could be effective to reduce the incidence of MA and to further elucidate the association between serum Mg and MA.

Conflict of interest

Authors declared no conflict of interest.

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