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Serum and Urine Levels of Magnesium in Adult Males with Type 2 Diabetes Mellitus in Jeddah, Saudi Arabia

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ABSTRACT

The present study aimed to investigate the association of serum and urine magnesium (Mg) levels of the patients living in Jeddah, Saudi Arabia, with type 2 diabetes mellitus (T2 DM) without complications. The effect of Mg deficiency on the prevalence of DM and its related complications has received great attention. Serum and urine Mg, fasting serum glucose (FSG), glycated hemoglobin (HbA1c), and urine creatinine (Creat) levels were determined in 68 diabetic subjects and 62 age-matched nondiabetic subjects (controls) using auto-analyzer and atomic absorption spectrometer. Body mass indices (BMI) of the subjects were also determined. The serum Mg levels in the patients with T2 DM were significantly lower than that in controls. BMI and the levels of FSG, HbA1c, and urine Mg were significantly higher and urine Creat level lower in diabetic subjects compared with nondiabetic subjects. Significantly lower serum Mg and significantly higher urinary Mg levels were observed in diabetic subjects with poor glycemic control (HbA1c >7%) compared with the nondiabetic population. The present correlation study revealed a highly significant correlation between FSG and HbA1c ($r = 0.846$, $P = 0.000$). Aging and increasing duration of DM alter the metabolism of Mg by decreasing its serum concentration and increasing its urinary excretion. This study also showed a significant negative association between serum Mg and FSG ($r = –0.408$, $P = 0.039$ and HbA1c ($r = –0.478$, $P = 0.043$). Also, a significant negative association was observed between serum Mg and age of both patients with T2 DM ($r = –0.787$, $P = 0.044$) and controls ($r = –0.798$, $P = 0.041$). Again, a significant negative correlation ($r = –0.452$, $P = 0.018$) was observed between serum Mg and urine Mg levels of the diabetic population of the study. DM and poor glycemic control alter the metabolism of Mg by increasing its urinary excretion and lowering its serum levels. Its clinical implications were discussed in this study.

Key words: Diabetes and glycemic control, magnesium, serum, urine

INTRODUCTION

Diabetes mellitus (DM) is a growing public health concern across the world, particularly in developing countries. The prevalence of type 2 DM (T2 DM) is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. This is true in most countries, and 6 of the top 10 countries with the highest rates are in Asia (1). The prevalence of DM in Saudi Arabia is at an alarming level. More than 25% of the adult population is suffering from DM, and this figure is expected to be more than double by 2030 (2). Half of the people more than 30 years of age are prone to DM. Saudi Arabia ranks seventh worldwide and the first in the gulf in terms of DM prevalence rates (3). T2 DM is the major problem and accounts for more than 90% of the cases. It is reported that around 9% of patients with DM die annually. Beyond the devastating humanitarian costs, DM threatens to subvert the gains of economic development globally as a consequence of spiraling costs of medical care (4).

Glycated hemoglobin (HbA1c) is considered a good method of assessing glycemic control. The higher the percentage of circulating HbA1c in DM, the poorer the mean diabetic control. Achieving near-normal HbA1c levels has been shown to reduce long-term complications. The HbA1c assay is recommended to determine whether treatment is adequate and to guide adjustments (5,6). Accumulating evidence indicates that the metabolism of several trace elements is altered in DM. Deficiency and efficiency of some essential trace elements may play a role in the development of DM (7). Magnesium (Mg)

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is known to play an important role in carbohydrate metabolism. Its imbalance has been implicated in DM, both dietary Mg and low serum Mg levels. These are recently implicated as risk factors for hypertension, DM, and coronary artery disease. Hypomagnesemia occurs frequently in patients with DM, especially those with poor glycemic control (8 -12).

Although some limitations may apply, serum Mg concentration is still used as the standard for evaluating Mg status in patients. Another approach for assessing Mg status is urinary Mg excretion. The results provide etiological information: while a high urinary excretion indicates renal wasting of Mg, a low value suggests an inadequate intake or absorption (10, 13,14).

This study aimed to determine the serum and urine levels of Mg in diabetic and nondiabetic subjects with different states of glycemic control to know the status of this element and explore any association of FSG and HbA1c with Mg concentrations.

MATERIALS AND METHODS

Selection of subjects

This study was conducted among 68 male subjects with T2 DM (DM group) and 62 age-matched, nondiabetic male subjects (control group) within age range 35–65 years. All of them worked at the King Abdulaziz University. The patients attended the clinic of the University regularly. They were all urban residents of Jeddah city, Saudi Arabia. Before the start of the study, all control subjects and patients with DM were informed about the aim of the study via the distributed questionnaire, and all agreed to participate and signed the form. The study protocol was approved by the Research Ethics Committee of the University.

The inclusion and exclusion criteria were the same as those mentioned in previous reports (15,16).

Sixty-two apparently healthy, nondiabetic subjects of similar socioeconomic status, who had routine medical checkups in the clinic, were recruited as control. No clinical or laboratory disorders were observed in the control group. Body weight and height were measured and used to calculate the body mass index (BMI), which was used as a measure of relative body weight. Following enrollment, both patients and controls were instructed not to change their lifestyle or their dietary habits and not to take any dietary supplements. The diet was not monitored.

Sample collection and preparation

Fasting blood samples were collected into labeled centrifuge tubes from the subjects by venipuncture after an 8- to 12-h overnight fast. The blood samples were centrifuged at 2000 rpm for 10 min using a desktop centrifuge, and the serum was separated and kept in labeled sample bottles at −70°C until further analysis.

Serum urea and creatinine levels were also assayed to test for renal function. Fasting spot urine samples were also collected into sterile chemically clean universal containers for urine Mg determination and also for urine creatinine estimation to correct for urine flow rate of individuals. A certain amount of urine samples was taken into a metal-free glass tube and mixed with concentrated nitric acid to remove interfering of organic compounds. The resulting solution was then centrifuged.

Instrumentation

The sera were analyzed for HbA1c and fasting serum glucose (FSG) using an auto-analyzer (Roche Modular P-800, Germany). The trace concentrations of Mg in serum and urine samples were measured using the Graphite Furnace Atomic Absorption Spectrometer (Varian, Model Spectra AA 30P, Australia) by a calibration method. The accuracy of determination was evaluated by measuring the metal contents of certified biological reference materials (Seronorm Trace Elements Serum; Nycomed Pharma, Oslo, Norway) (15,16).

Statistical analysis

The results were presented as mean ± standard deviation (SD). The significance of difference between the groups was tested using the t test. Association between variables was determined using the Pearson's correlation analysis on Microsoft Excel and SPSS software version 16 (SPSS, IL, USA). Statistical significance was determined at a P value less than 0.05.

RESULTS

A total of 130 male subjects were included in this study; 68 of them were patients with T2 DM and 62 age-matched nondiabetic healthy control subjects. The patients and controls were aged between 35 and 65 years. BMI was calculated using the standard formula (weight in kilograms/height in square meters, kg/m^2). General characteristics and laboratory findings of the population studied are shown in Table 1. The mean age ± SD of the patients and control subjects was 60.08 ± 6.29 and 58.05 ± 5.88 years, respectively. The patients with DM were generally heavier than the control subjects. The BMI of patients with DM was also found to be more compared with that of the controls (Table 1). The results of the BMI indicated that

TABLE 1: Descriptive data and laboratory findings of diabetic and nondiabetic subjects.

Data	Diabetic subjects (n = 68)	Nondiabetic subjects (n = 62)	P value
Sex	Male	Male	
Age (year)	60.08 ± 6.29	58.05 ± 5.88	0.038
Duration of diabetes (year)	5.73 ±3.06		
BMI (kg/m^2)*	28.96 ± 1.86	24.58 ± 1.52	0.018
Fasting serum glucose (mmol/L*	10.16 ± 3.59	4.36 ± 0.21	0.001
HbA1c (%)*	9.34 ± 2.16	5.12 ± 1.07	0.004
Creatinine (mg/dL)*	0.98 ± 0.25	0.90 ± 0.24	0.005
Urine creatinine (mg/dL)*	117.63± 60.21	141.11± 56.52	0.006
Serum Mg (mg/L)*	14.10 ± 3.89	18.51± 4.86	0.003
Urine Mg (mg/g Creat)*	11.67 ± 5.49	5.78± 3.62	0.043

*Significant difference in the mean.

the diabetic subjects were overweight. A significant difference in the BMI of the patients with DM was found compared with the control group (Table 1). The FSG, HbA1c were significantly higher in diabetic than in nondiabetic subjects (Table 1). Urine creatinine was significantly higher in nondiabetic than in diabetic subjects (Table 1).

A significant decrease in serum Mg was noted in diabetic subjects compared with controls (Table 1). The urinary Mg levels were found to be significantly higher in the diabetic compared with the control population (Table 1).

Table 2 shows the serum and urine Mg levels in diabetic subjects with poor glycemic control (HbA1c >7%) and nondiabetic subjects. The serum Mg was significantly lower while urine Mg levels were significantly higher in diabetic subjects with poor glycemic controls than in nondiabetic controls (Table 2).

The present study also showed a significant negative association between serum Mg and age of both patients with DM and controls ($r = -0.787$, $P = 0.044$; $r = -0.798$, $P = 0.041$).

The results showed that the serum Mg levels decreased significantly ($r = -0.267$, $P = 0.037$) and urinary excretion increased ($r = 0.385$, $P = 0.015$) with the duration of DM.

This correlation study revealed a highly significant correlation between FSG and HbA1c ($r = 0.846$, $P = 0.000$) for patients with DM. Moreover, a significantly negative correlation was observed between serum Mg and FSG ($r = -0.408$, $P = 0.039$) (Fig. 1) and HbA1c ($r = -0.478$, $P = 0.043$) (Fig. 2) for patients with DM. A significant positive correlation ($r = 0.356$, $P = 0.013$) was observed between HbA1c and urinary loss of Mg in patients with T2 DM (Fig. 3). A significant negative correlation ($r = -0.452$, $P = 0.018$) was observed between serum and urine Mg levels of patients with DM (Fig. 4).

DISCUSSION

Accumulating evidence indicates that the metabolism of several trace elements is altered in DM (8). Mg is known to play an important role in carbohydrate metabolism. Its imbalance has

TABLE 2: Serum and urine Mg levels in different states of glycemic control in diabetic and nondiabetic subjects.

Control state	Serum Mg (mg/L)	Urine Mg (mg/g Creat)
Good HbA_{1c} (<7%) (n = 13)	18.60 ± 4.57	10.74 ± 4.99
Poor HbA_{1c} (>7%) (n = 55)	13.81 ± 3.96	11.93 ± 6.98
P value	0.039	0.055
Poor HbA_{1c} (>7%) (n = 55)	13.81 ± 3.96	11.93 ± 6.98
Nondiabetic subjects (n = 62)	18.51 ± 4.86	5.78 ± 3.62
P value	0.038	0.044

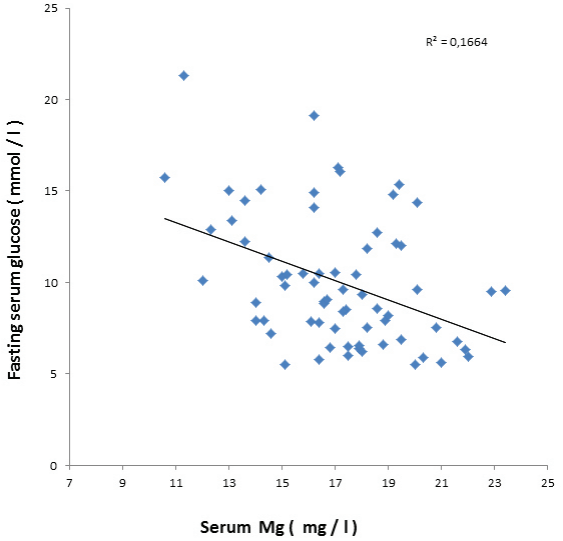

FIGURE 1: Correlation between serum Mg and FSG of patients with DM.

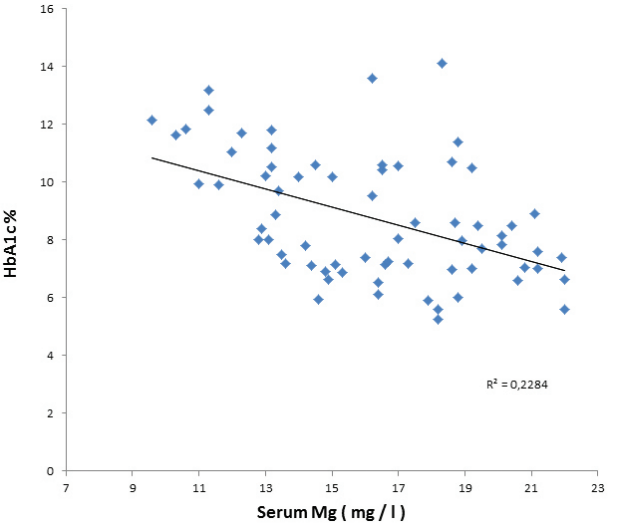

FIGURE 2: Correlation between serum Mg and HbA1c of patients with DM.

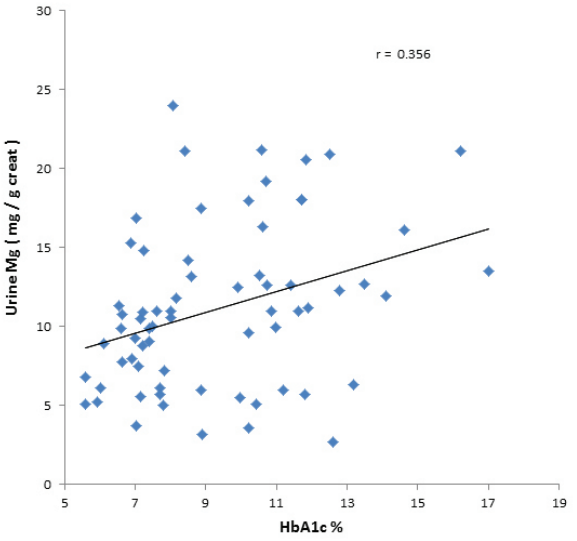

FIGURE 3: Correlation graph of HbA1c and urine Mg of patients with DM.

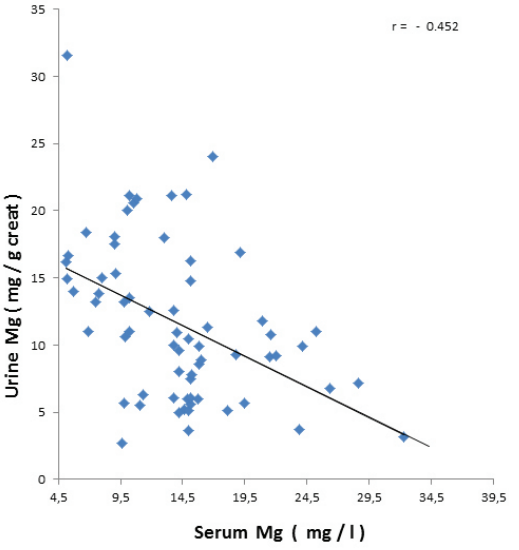

FIGURE 4: Correlation between serum Mg and urine Mg of patients with DM.

been implicated in DM, as a cause and a consequence (6,14). The interest in the important roles played by Mg in various cell processes in the body has increased recently (11, 17). Studies have shown that Mg levels are lower in patients with DM compared with nondiabetic controls. The association of hypomagnesemia with poor glycemic control and various long-term complications of DM has been reported (17-20). The serum and urine levels of Mg in diabetic subjects and in different states of glycemic control, as determined by HbA1c levels, were determined in this study. The possible correlation of age and duration of DM with serum and urine levels of Mg was also examined.

The BMI, FSG, and HbA1c were significantly higher in the diabetic population compared with the nondiabetic population of the study. The higher values of BMI, FSG, and HbA1c recorded for patients with DM in this study were consistent with previous reports (21-25). This study demonstrated a good agreement between FSG and HbA1c in the assessment of glucose metabolism in DM. A significant positive correlation was found in both patients with DM and control subjects ($r = 0.846$ and 0.878, respectively, $P = 0.000$), which was consistent with the findings of other studies (22,24,25). The main use of HbA1c is to assess long-term glycemic control in managing patients with DM, provide

valuable information about the average blood glucose levels in the previous 1–2 months, and monitor compliance of patients to treatment regimens (21,23-26). Apart from classical risk factors such as dyslipidemia, elevated HbA1c has now been regarded as an independent risk factor for cardiovascular disease (CVD) in subjects with or without DM. The estimated risk of CVD has been shown to be increased by 18% for each 1% increase in the absolute HbA1c value in the diabetic population (21,22, 25-27).

The result of the present study revealed a significant lowering of serum Mg level in T2 DM (Table 1) compared with healthy controls, which was consistent with the findings of other studies (6, 27-29). The present study results demonstrated some degree of variability in the serum and urine concentrations of Mg with age and duration of DM. A significant inverse correlation of serum Mg with age in both patients with DM and normal controls was observed, which was similar to the findings of previous studies (24, 30-32, 37). A number of surveys have shown Mg, zinc (Zn), selenium (Se), and chromium intakes by old persons to be lower than the corresponding nutrient intakes; this may be attributed to changes in mineral bioavailability with aging. Aging has been previously associated with low intracellular Mg concentration, which is probably the consequence of insulin resistance due to aging (30, 33-35).

This study showed a significant negative correlation of serum Mg with FSG and HbA1c. The results demonstrated that serum Mg concentrations were dependent on the degree of glucose control as determined by correlation analysis between HbA1c and Mg concentrations. The findings suggested that the patients with poorly controlled DM had a decreased level of Mg, potentiating the risk for DM-related complications. The association of hypomagnesemia with poor glycemic control and various long-term complications of DM has been reported (10,29,36,37,38). Mg deficiency has also been argued as a probable causal factor of dyslipidemia, which constitutes an alert for the chronic complications of DM, such as atherosclerosis (6,29,37,39).

Urine concentrations of Mg were observed to be significantly higher in patients with DM than in the nondiabetic population in the present study. El-Yazigi et al. (40) made similar observations on the effects of the diabetic state and related disorders on the urinary excretion of Mg in patients, where higher urinary excretion of this element was demonstrated in the diabetic state. Different authors also reported increased urinary Mg loss in diabetic subjects (22,29,41). This study also observed decreased serum Mg and increased urinary Mg loss with increasing age and duration of DM in the diabetic population. Hypermagnesuria in diabetic subjects has been attributed to osmotic diuresis. Glycosuria, which accompanies the diabetic state, impairs renal tubular reabsorption of Mg from the glomerular filtrate. An increased urinary loss of Mg may be attributed to reductions in renal function with aging and duration of DM (30,38). Low Mg, Se, and Zn status has also been reported in the elderly population (30,43).

Hypomagnesemia is common among patients with DM, especially those with poor metabolic control (6,34). Polyuria caused by hyperglycemia, coupled with hyperinsulinemia, tended to increase renal excretion of Mg or decrease renal reabsorption of Mg, thereby resulting in hypomagnesemia in T2 DM. An inadequate intake of dietary Mg in patients with diabetes may also cause hypomagnesemia. Hypomagnesemia occurs at an incidence of 13.5%–47.7% among patients with T2 DM. The increased incidence of hypomagnesemia among patients with T2 DM presumably is multifactorial (10,21,28,39).

Clinically, hypomagnesemia may be defined as a serum Mg concentration $\leq$1.6 mg/dL or $>$2 SD below the mean of the general population (10,29,32). The present study demonstrated that 38% of the patients with DM had significant hypomagnesemia with the serum Mg level less than 1.6 mg/dL. Studies have reported incidence rates of 13.5%–47.7% in diabetic subjects (10,28,29,32). Jeddah has a hot and humid climate year-round. Summer temperatures are very hot, often crossing the 43oC (109oF) mark in the afternoon and dropping to 30oC (86oF) in the evening. The highest temperature ever recorded in Jeddah was 52°C (125.6°F). The average temperature in Jeddah is 28.4°C (83°F). The high temperature in Jeddah (especially in summer, April to November) might also be a contributing factor to the higher incidence of hypomagnesemia in the present study. A possible correlation between Mg deficiency and climate variations is speculated, contributing to the increase in deaths due to heart disease and DM. High temperatures would increase sweat losses. Consequently, among the minerals, Mg would be the most affected because the losses would not be compensated by the diet and water intake, thereby increasing the risk of these diseases (6,39,44).

Duration of DM also seems to exert a significant effect on the serum and urine Mg concentration of the diabetic population studied. Serum Mg levels decreased with the increasing duration of, and their urinary excretion increased with the increasing duration of DM. The decreased serum levels may be attributed

to the increased urinary loss of this trace element. Reduction in renal functions with the increasing duration of DM has been implicated in the urinary loss of trace elements (38,45). The strong correlation of Mg with duration of disease suggests that elderly diabetic patients are more susceptible to develop Mg deficiency (30,37).

Higher urine Mg concentrations and lower serum Mg concentrations were seen in diabetic subjects with poor glycemic control compared with nondiabetic controls. Increased urinary excretion of Mg in poor glycemic control has also been attributed to hyperglycemia, glucosuria, and osmotic diuresis (38,46). Serum Mg correlated negatively with urine Mg in the diabetic population of this study. The status of body Mg balance is determined by the renal excretion. Thus, when the Mg status is suboptimal, Mg receptors on the thick ascending limb of the loop of Henle sense the need for Mg retention and cause more reabsorption (38). Hence, the lower the urine excretion of Mg, the higher the serum Mg concentration and vice versa. Therefore, it is concluded that DM and poor glycemic control alter the metabolism of Mg by causing hypermagnesuria and hypomagnesemia.

Deficiencies of Mg in diet and serum have been associated with an increased risk of developing glucose intolerance and DM. However, increased Mg intake is associated with a significant decline in the incidence of T2 DM (28,32,39,47,48). Thus, foods rich in Mg (such as nuts, green vegetables, soybeans, and whole grains) may provide protection against this chronic disease. It is suggested that patients with DM should take Mg-rich foods every day, which provides recommended intakes of Mg and maintains normal storage levels of this mineral. Dietary intake of Mg can often restore mildly depleted Mg levels, but Mg supplementation is required to restore very low Mg levels to normal.

Mg is involved in nearly every physiological system. Although Mg supplementation is used for treating some cardiovascular disorders, the beneficial effects of Mg replacement in preventing DM-related complications have not yet been proven in long-term studies. Some observations have suggested that chronic Mg supplementation may be useful in treating patients with DM, improving the glycemic control and preventing the development of chronic complications (49,50). Further studies are needed to define the clinical scope of therapy with Mg.

CONCLUSIONS

The present study demonstrated a significant correlation of HbA1c with the FSG levels. HbA1c can be used as a reliable, feasible, and fairly accurate tool for screening DM. The findings of this study indicated that diabetic subjects are Mg deficient and the diabetic state enhances the urinary loss of this element. It also found that hypomagnesemia was associated with increased levels of FSG and HbA1c. In diabetic subjects, aging and increasing duration of DM enhance the urinary loss of Mg. Therefore, it is concluded that DM and poor glycemic control alter the metabolism of Mg by causing hypermagnesuria and hypomagnesemia. It is prudent to monitor Mg levels in all patients with T2 DM regularly and treat the condition whenever possible. All persons with T2 DM must be started on primary prevention by encouraging healthy lifestyle diets so as to reduce the risk of coronary heart disease and atherosclerosis. It is also suggested that patients with DM should take Mg-rich foods such as whole grains, legumes, fruits, and vegetables (especially dark green, leafy vegetables) every day, which provide recommended intakes of Mg and maintain storage levels of this mineral. Dietary intake of Mg can often restore mildly depleted Mg levels, but Mg supplementation is required to restore very low magnesium levels to normal. Thus, studies on the role of Mg supplementation in T2 DM in the Saudi population are recommended. Health care providers should invest more effort in diet changes rather than focusing on micronutrient supplementation to achieve metabolic control in their patients.

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