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Hypomagnesemia As A Marker Of Diabetic Nephropathy

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Abstract

Magnesium is an essential element and has a fundamental role in carbohydrate metabolism in general and in the insulin action in particular. Magnesium is involved in multiple levels in insulin secretion, binding and activity. Cellular magnesium deficiency can alter the activity of the membrane bound Na+K+ ATPase, which is involved in the maintenance of gradients of sodium and potassium and in glucose transport (1).

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes as well as on the evolution of complications such as retinopathy, arterial atherosclerosis and nephropathy. Moreover, low serum magnesium is a strong, independent predictor of development of type 2 diabetes (2).

A cross sectional study included 105 type 2 diabetic patients. Twenty nine were males (27.6%) and seventy six were females (72.4%).Their ages ranged from 30-77 with a mean of 49.7± 10.6. All patients were subjected to full clinical examination, and investigations which included: serum creatinine, HbA1c, albumin creatinine ratio and serum magnesium.

Their mean BMI was 23 kg/m^2 and mean waist/hip ratio was 0.9.Their mean HbA1c was 8.55 %. Of all patients, 13 of them had normal level of A/C ratio (control group) and 92

were albuminuric with a mean A/C ratio 238.26 ± 727.9 with a range of 33.7 (0.09-4700), mean s.creatinine was 1.29 ± 1.16 and their mean s.magnesium level was 2.04 ± 0.49 with a range of 1.9 (0.8-3.9).

We observed significant negative correlation between A/C ratio and serum creatinine with a p-value of <0.0001.

The study shows negative correlation between serum magnesium and A/C ratio(r=-0.202, p=0.039).

Keywords: Type 2 diabetes, diabetic nephropathy, albuminura, hypomagnesemia.

Introduction:

Magnesium is the fourth most plentiful mineral and encountered as the second most abundant intracellular divalent cation and has been accepted as a cofactor for >300 metabolic reactions in in humans (3)**.**

The interrelationships between magnesium and carbohydrate metabolism have regained considerable interest over the last few years. Magnesium is a significant cofactor in a number of key enzymatic reactions and seems to play a vital role in glucose metabolism and insulin homeostasis (4)**.**

The release of insulin caused by a glucose challenge is partly dependent on adequate magnesium. Insulin, via its interaction with ligand activated tyrosine protein kinase associated receptors, initiates a cascade of biochemical interactions that result in several physiological, biochemical and molecular events that are involved in carbohydrate, lipid and protein metabolism (5). Although the binding of insulin to its receptor does not appear to be altered by magnesium status, the ability of insulin once bound to receptor to activate tyrosine kinase is reduced in hypomagnesaemia states (6). As a result reduced peripheral glucose uptake and oxidation are often noted in subjects

with hypomagnesaemia. Decrements in the enzymatic activities of several metabolic pathways are seen in DM patients as a result of the relative magnesium deficiency (7).

Various evidences suggesting a relationship of Mg deficiency and type 2 diabetes mellitus (T2DM), T2DM is a main global public health problem in the world and is rising in aging populations (4). In the study conducted by Dasgupta et al on 150 T2DM patients, low Mg level was documented in 11.33% of patients. They interpreted that hypomagnesaemia in diabetes mellitus was correlated with poorer diabetic control, nephropathy, retinopathy and foot ulcers (8).

The mechanism behind the role of magnesium deficiency in the development of diabetic microvascular complications has not been well investigated. However, significant clues can be extrapolated from previous studies. Serum magnesium levels are associated with insulin resistance and β cell function in patients with diabetes. Furthermore, magnesium deficiency is associated with decreased β cell function and increased insulin resistance, leading to elevated plasma glucose levels (9).

Aim of work:

To study serum magnesium level as a marker for development of diabetic nephropathy.

Subjects and methods:

This study included 105 adult patients from outpatient clinic of Internal medicine department in Fayoum University Hospital from December, 2016 to May, 2017.

All patients were diagnosed as having type 2 diabetes mellitus (T2DM).The diagnosis of T2DM was made on the usual criteria(fasting blood sugar and 2 hours post prandial glucose measurement in blood)earlier during their follow up outpatient. Informed consent was obtained from the patients.

All patients were subjected to:

Full clinical examination.

Measurement of weight, height, waist, hip and calculation of BMI and waist hip ratio.

The height and weight were measured and obesity was defined as body mass index (BMI) of ≥30 kg/m2 , where BMI was calculated by dividing the weight in kilograms on height in meters squared.

3)Laboratory investigations:

- Serum cratinine.
- HbA1c.
- Albumin / creatinine ratio.
- Serum magnesium.

Serum sample preparation:

Laboratory data including serum cratinine, HbA1c, albumin creatinine ratio and serum magnesium levels were measured using standard methodology in the clinical chemistry laboratory of Fayoum university hospital. Blood for determination of Mg was sampled into plain evacuated glass tubes with glycerine caps, while Vacutainer tubes were used for the other analytes. The samples were allowed to coagulate for at least 30 min at room temperature and were then centrifuged for 3 min at 2,000 rpm and stored in plastic vials at −25°C until analysis.

Reference values of measured investigation:

Microalbuminuria, which is defined as 30-300 mg/g creatinine, is a sign of progression towards nephropathy in patients with diabetes (10).Albuminuria is a sensitive marker of renal dysfunction, and the American Diabetes Association has recommended annual testing for albuminuria in 12- or 24-hr urine samples to predict the risk of cardiovascular disease and renal dysfunction in cases of diabetes mellitus (11). Samples with ACR values of 30-300 or >300 mg/g were considered "positive," while those with values of <30 mg/g were considered "negative (12).

Serum creatinine is primarily a metabolite of creatine, almost all of which is located in skeletal muscle. The normal level of creatinine is 0.8 to 1.4 mg/dL. Females usually have a lower creatinine (0.6 to 1.2 mg/dL) than males, because they usually have less muscle mass (13).

Reference range of serum creatinine used in this study was (0.6-1.2 mg/dl), serum magnesium (1.6-2.6 mg/dl).

Statistical analysis

The collected data were coded, tabulated, revised and statistical analyzed using SPSS program (statistical program for social science) (version 16).

Simple descriptive statistics in the form of numbers and percentages were done using mean and standard deviation for numerical parametric data and by number and percentage for categorical data. Statistical analysis was done for quantitative variables by using independent t-test in case of two independent groups, paired t-test in related samples with parametric data. Stepwise linear regression analysis used for significant clinical variables. The level of significance was taken at P value < 0.05.

Results

The mean BMI of all patients was 23 kg/m^2, the mean waist/hip ratio was 0.97. The mean HbA1c was 8.5%, the mean A/C ratio was 238.2 mg/dl, the mean serum creatinine was 1.29 mg/dl and the mean serum magnesium was 2 mg/dl. 13 patients were found to be with no albuminuria and 92 patients were found to be albuminuric 87.6%.

Table (1): comparison of anthrpometric measurements between the group with no albuminuria (N=13) (12.3%) and the group with albuminuria (N=92) (87.6%)

Variable	Normal (N=13)	Albuminuria (N=92)	P-value
	Mean ± SD		
Weight (KG)	62.69 ± 16.52	82.05 ± 15.29	0.428
Height (cm)	161.54 ± 7.44	161.59 ± 11.78	0.563
BMI	23± 5.51	50.97 ± 9.92	0.594
Waist (cm)	112.54 ± 16.43	109.04 ± 12.61	0.364
Hip	117.46 ± 14.81	113.57 ± 14.57	0.370
Waist/Hip ratio	0.96 ± 0.09	0.97 ± 0.12	0.798

Table (2): Serum creatinine in the 2 groups (N=105)

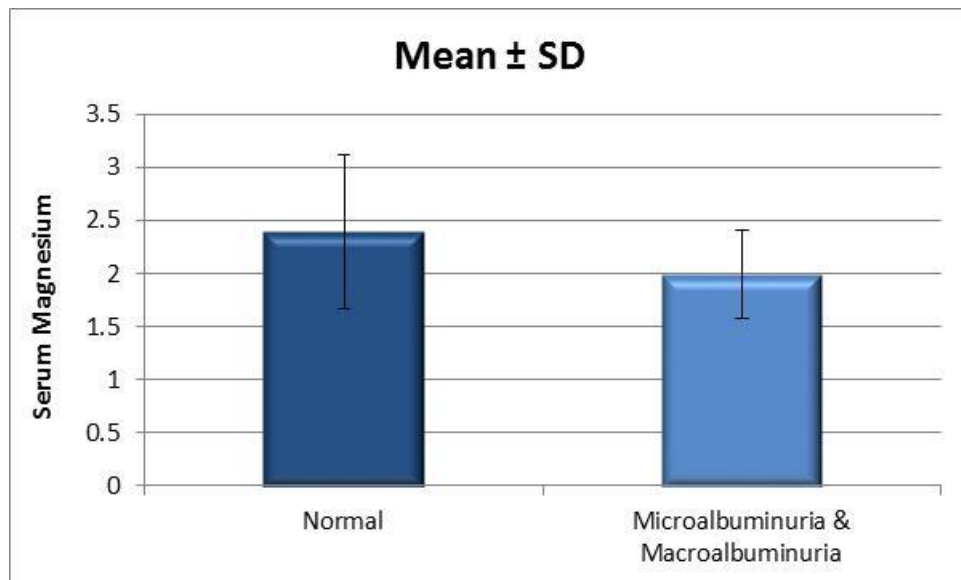| Variable	Normal (N=13)	Albuminuria (N=92)	P-value
	Mean ± SD	Mean ± SD	
Serum creatinine	0.96 ± 0.63	1.96n ± 1.48	**<0.0001***

Figure (1): Comparison between means of serum magnesium in normo- albuminuric and micro/macroalbuminuric patients,P value:0.006.

Table (3): Showing correlation of serum magnesium with different clinical and lab data,with a significant negative corrleation between ACR and serum Mg.

	Serum Mg	
	R	P-value
Age	-0.049	0.617
BMI	0.040	0.685
Waist/hip ratio	0.089	0.369
A/C ratio	-0.202	0.039*
Serum creatinine	-.014	0.888

Discussion:

Mg depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes (14). Mg deficiency is associated with poor glycemic control, and Mg supplementation improves insulin sensitivity (15). Moreover, there is substantial evidence of associations between hypomagnesemia and various complications of type 2 diabetes, including neuropathy, retinopathy, foot ulcers, and albuminuria (16). Preventing low Mg status in diabetics may therefore be beneficial in the management of the disease (17). Furthermore, a lower Mg level is directly associated with a faster deterioration of renal function in T2DM patients (18). Moreover, hypomagnesemia is associated with the long-term micro- and macrovascular complications of T2DM (19).

This work showed that lower magnesium level was detected in patients with diabetic nephropathy (as marked by albuminuria >30 mg/dl) more than diabetic patients without nephropathy (p-value:0.006). In a study conducted by Jayaraman et al., the level of magnesium decreases with increasing glucose levels, much more before the onset of diabetic micro and macro vascular complications. This can be used as a marker to assess the risk of complication even at the first encounter with diabetic patients (20).The work of Yossef et al conducted on 90 patients, serum Mg was significantly lower in diabetic patients than in control (*P*=0.007). Mg was lower in patients with complications than in patients without (21).,in addition to that the study conducted by Corsenello et al involved 30 patients who had type 2 diabetes without microalbuminuria, 30 with microalbuminuria, and 30 with overt proteinuria, Corsonello et al. observed a significant decrease in serum ionized Mg in both the microalbuminuria and overt proteinuria groups compared with the nonmicroalbuminuric group(22).A possible mechanisms explaining the relation between microalbuminuria 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(23). 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 (24). Another hypothesis is that by influencing the activity of Na^+/K^+-ATPase reduction of Mg favors the onset and the progression of diabetic microangiopathy (25).In this study there was no positive correlation between serum magnesium and serum creatinine. This was found by chu et al in2016 who performed a study on 978 patients with T2DM, (26).This may be explained by that insulin enhances Mg reabsorption at the thick ascending limb of the loop of Henle, where; 55% of the filtered Mg is reabsorbed (27).Therefore, in patients with type 2 diabetes, insulin resistance or deficiency can promote Mg loss at the thick ascending limb , which might compensate for the reduced glomerular filtration ((28).

In present study, there is no significant correlation was found between body mass index and albuminuria,also there was no correlation between waist hip ratio and albuminuria.this may be explained by the fact that Body mass index does not account for the wide variations in body fat distribution as a high BMI may be due to increased muscle bulk(29).while an increased waist hip ratio may be due an in increase in the subcutaneous fat and not the visceral fat and visceral is the responsible for diabetic complications(30).

Recommendations

Routine surveillance for hypomagnesemia should be done and the condition to be treated whenever possible.When hypomagnesemia is found, patients should be further investigated for complications of diabetes.

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