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Research Article

Magnesium in type 2 diabetes mellitus and its correlation with glycemic control

Nehal Hamdy El-said[1], Noha Adly Sadik[1]*, Nagwa Abd EL-Ghaffar Mohammed[2]

[1]Department of Internal Medicine, Kasr Al Ainy hospital, Faculty of Medicine, Cairo University, Egypt
[2]Clinical and Chemical Pathology Department, National Research Center, Cairo, Egypt

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***Correspondence:**
Dr. Noha Adly Sadik,
E-mail: noha_adly@yahoo.com

ABSTRACT

Background: Hypomagnesaemia may have negative impact on glucose homeostasis and insulin sensitivity. This study was done to compare serum Mg levels in type 2 diabetic patients with non diabetic healthy control subjects and to assess the correlation between serum Mg levels and glycemic control in Egyptian patients.
Methods: 60 type 2 diabetic patients attending the outpatient clinic of diabetes at Kasr Al Aini hospital faculty of medicine Cairo University and 30 healthy age matched control subjects were enrolled. Fasting blood sugar, fasting insulin, fasting lipids, Hb A1C and serum Mg were measured. Weight, height and blood pressure were recorded. BMI, IR (HOMA), were calculated. The data was analyzed and expressed in terms of mean ± SD. Pearson correlation was performed to establish the relationship between Mg and metabolic variables in type 2 diabetic patients.
Results: serum Mg levels were significantly reduced in type 2 diabetic patients compared to the control group with mean ±SD (1.29 ± 0.31 mg/dl) versus (2.41 ± 0.13 mg/dl) with P value < 0.001. There were highly significantly negative correlations between serum Mg levels and HbA1c, fasting glucose and insulin resistance with (r = -0.969, -0.894, -0.653) respectively, P value < 0.001. The best cut off point of Mg was ≤ 2.0 mg/dl in differentiating cases from controls using ROC curve analysis.
Conclusion: hypomagnesaemia is closely linked to type 2 diabetes mellitus and it is strongly correlated to glycemic control. We recommend to measure serum Mg in type 2 diabetes and patients who need supplementation should be considered.

Keywords: Hypomagnesaemia, Type 2 diabetes mellitus, Glycemic control

INTRODUCTION

Magnesium (Mg) is an essential intracellular cation which plays a fundamental role in many physiological[1] and biological process in the human body.[2] It is an enzyme activator for neuromuscular excitability, cell permeability and serves as regulator for ion channels and mitochondrial functions which is important for cell proliferation and apoptosis.[3]

Magnesium is involved in many enzymatic reactions that need ATP and in protein synthesis.[4] It is an essential factor in the reactions that need kinases. [5] Magnesium has an essential role in glucose homeostasis.[6] It acts as a co factor in glucose transportation across the cell membrane and for various enzymes in carbohydrate oxidation.[7] It plays an important role in the regulation of blood glucose levels[4] as it is essential for insulin secretion; binding to its receptor and activity[7] also it has antioxidant properties by scavenging the oxygen radicals through regulating the rate of spontaneous dismutation of super oxide anions.[8]

Type 2 diabetes is a chronic metabolic disease characterized by insulin resistance (IR) and relative insulin deficiency[4] which needs a multidisciplinary approach to detect and treat every potential complicating

factor.[3] Hypomagnesaemia has been documented to be frequently associated with diabetes mellitus with prevalence 25-39%.[9] Hypomagnesaemia may be a cause or a consequence of diabetic complications.[10] It has been documented to have negative effect on glucose homeostasis [11] and insulin resistance (IR).[12]

Low magnesium levels result in defective tyrosine kinase activity at the insulin receptor level[13] which lead to impairment in insulin action and worsening IR in type 2 diabetes.[14] It has been associated with increased levels of TNF-α which lead to post receptor IR.[15] Hypomagnesaemia leads to increase in the free oxygen radical formation and decrease in the antioxidant properties contributing to the oxidative stress in type 2 diabetes.[8] Insulin regulates the intracellular Mg levels where it activate the Na^+, Mg^+ exchange at the plasma membrane and this may explain the occurrence of low cellular Mg levels as a result of insulin resistance.[10]

For these our study was done to assess the serum Mg levels in type 2 diabetic patients and compare it with non diabetic healthy control subjects and to detect the association between serum Mg levels with glycemic control and the metabolic disorders in Egyptian type 2 diabetic patients.

METHODS

Subjects

The study was conducted on 60 female patients with type 2 diabetes mellitus who had attended the diabetes and endocrine clinic at Kasr Al Ainy Hospital, Cairo University and 30 female healthy age matched control subjects. The study was performed from March 2014 to November 2014. Type 2 diabetes was defined according to American Diabetes Association 2012.[16] All patients were diagnosed to have diabetes mellitus for at least 5 years. All subjects were subjected to history taking and clinical examination. Fasting blood sugar (FBS), fasting lipids (total cholesterol (TC), triglycerides (TAG), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), glycosylated hemoglobin (Hb A1C) , fasting insulin, and serum magnesium (Mg) were measured. Weight, height and blood pressure were recorded. Body mass index (BMI) and homeostasis model assessment insulin resistance (HOMA-IR) were calculated.

Exclusion Criteria

Patients taking magnesium supplementation, loop diuretics and those with liver disease, congestive heart failure and cerebrovascular disorders were excluded.

Ethical aspects

Research protocols were approved by the medical ethics committee of Kasr Al Ainy Medical School, Cairo University. All participants provided a written informed consent after the research protocols were carefully explained to them. Informed consent was obtained from all the study participants and their approval taken by signature.

Weight and height were measured while the subjects wearing light clothes and no shoes, the body mass index (BMI) was calculated as (kg/m^2).

Five ml of fasting (12-14 hours) venous blood samples were taken from each subject in the study and divided into parts: The first part was 2 ml and added to a tube containing EDTA for determination of HbA1C by cation exchange resin. [17] The rest of the blood (3 ml) was left to clot and the serum was separated by centrifugation for 15 minutes at 3000 x g and fasting blood glucose was determined immediately on Hitachi auto analyzer (Hitachi 736, Japan) by glucose oxidase method. The rest of the serum was stored at -20°C for determination of the followings: serum cholesterol, serum triglyceride, LDLC, HDLC, serum insulin and serum magnesium.

The determination of serum cholesterol and serum triglyceride were carried out on Hitachi 912 (Roche Diagnostics GmbH, D-68298 Mannheim, USA) by colorimetric techniques. For determination of HDL-cholesterol, phosphotungestic acid and magnesium ions were used for precipitating all lipoproteins except HDL fraction that was present in the supernatant and measured by auto analyzer. LDL cholesterol was measured by Friedwald formula.[18]

Fasting serum insulin was determined using radio immuno assay.[19] Insulin resistance was calculated according to the homeostasis model assessment (HOMA-IR) using the following equation: HOMA-IR=fasting blood glucose (mg/dl) x fasting serum insulin (μIU/ml)/405.[20] HOMA-IR cut-off value used was 2.7 (>2.7 was considered insulin resistant and <2.7 was considered insulin sensitive).[20]

Serum magnesium was determined using flame atomic absorption spectrophotometer; (AA-630-12) (Schimadzu Europe, GmbH, Albert-Hahn-Strasse 6-10, Germany.[21]The reference range of Mg was 1.6-2.6 mg/dl.

Statistical analysis

Pre-coded data was entered on the computer using "Microsoft Office Excel Software" program (2010) for windows. Data was then transferred to the Statistical Package of Social Science Software program, version 21 (SPSS) (SPSS, Inc., Chicago, IL) to be statistically analyzed. Data was summarized using mean, and standard deviation for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample t-test for quantitative variables and Chi square or Fisher's exact test for qualitative ones. Pearson correlation coefficients were calculated to signify the association between different

quantitative variables. Receiver Operating Characteristics (ROC) analysis was conducted to explore the discriminant ability of magnesium in differentiating cases from controls. P values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

RESULTS

Our demographic and laboratory data of the studied groups are shown in table (1). Using students t-test serum magnesium levels were significantly lower in type 2 diabetic patients compared to the control group, P< 0.001 (Table 1, Figure 1). SBP was significantly higher in diabetic subjects than control group, P<0.01. BMI, fasting lipids, fasting glucose, HbA1c and calculated HOMA-IR were significantly higher in diabetic subjects than control group, P<0.001 (Table 1). Using ROC curve analysis the value ≤ 2.0 mg/dl was the cut-off point level of serum magnesium to discriminate between diabetic patients and non-diabetic controls with 100% sensitivity and specificity, P<0.001 (Table 3, Figure 2). Serum magnesium levels were strongly negatively correlated with fasting glucose, HbA1c and HOMA-IR, P<0.001 (Table 2, Figure 3, 4 & 5). There were not any significant correlations between serum magnesium and fasting lipids.

Table 1: Demographic and laboratory data of the studied groups.

	Cases (n=60)	Controls (n=30)	P value
Age (years)	49.5±6.0	43.7±7.4	<0.001
SBP (mmHg)	129.4±19.6	121.0±12.1	0.01*
DBP(mmHg)	72.4±18.1	73.3±10.6	0.8
Weight (kg)	97.6±19.3	57.3±4.6	<0.001*
Height (cm)	157.3±5.4	163.3±4.4	<0.001*
BMI (kg/m^2)	39.4±7.0	21.5±2.1	<0.001*
TAGs (mg/dl)	144.0±38.7	102.1±14.9	<0.001*
Total cholesterol (mg/dl)	197.8±39.8	153.8±19.8	<0.001*
HDL-C (mg/dl)	33.5±7.2	44.4±5.6	<0.001*
LDL-C (mg/dl)	134.2±41.8	87.0±24.4	<0.001*
Fasting glucose (mg/dl)	230.0±82.1	91.7±5.8	<0.001*
HbA1c	9.0±2.0	5.3±0.5	<0.001*
Insulin (mU/L)	28.0±7.2	10.2±2.7	<0.001*
HOMA-IR	15.8±7.1	2.3±0.6	<0.001*
Magnesium (mg/dl)	1.29±0.31	2.41±0.13	<0.001*

Values are expressed as means ± SD, *P < 0.05 is significant, SBP, systolic blood pressure, DBP, diastolic blood pressure, FBS, fasting blood sugar, TAG, triglycerides, HDLC, high-density lipoprotein cholesterol, LDLC, low-density lipoprotein cholesterol, HOMA-IR, homeostasis model assessment insulin resistance

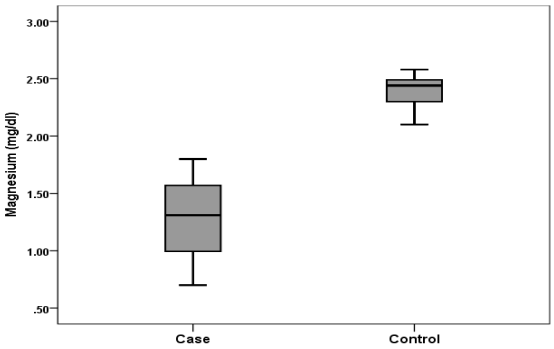

Figure 1: Box plot showing the distribution of magnesium among the studied groups.

Table 2: Correlation of magnesium with different parameters within the diabetic patients.

	r	P Value
Weight	0.082	0.534
Height	0.036	0.787
BMI	0.061	0.644
Age	0.019	0.888
HbA1c	-0.969	<0.001*
TG	-0.029	0.824
Total cholesterol	-0.208	0.111
HDL-C	0.135	0.303
LDL-C	-0.087	0.507
Fasting glucose	-0.894	<0.001*
Fasting insulin	0.018	0.894
SBP	0.181	0.167
DBP	-0.045	0.732
HOMA-IR	-0.653	<0.001*

r= Pearson correlation coefficient.* P< 0.05 is significant

Table 3: ROC curve analysis.

Tested variable	AUC	95% CI	P value	Cut-off point	Sensitivity	Specificity
Mg	1.0	1.0 – 1.0	<0.001	≤ 2.0	100.0%	100.0%

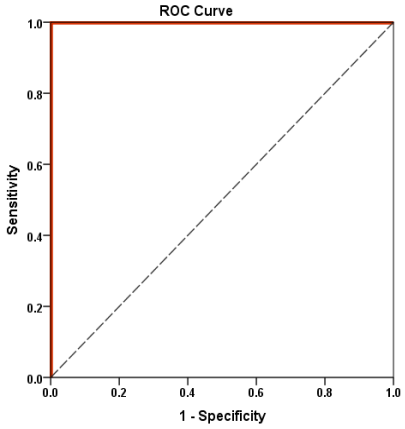

Figure 2: ROC curve analysis to explore the discriminated ability of serum magnesium to differentiate between cases & controls.

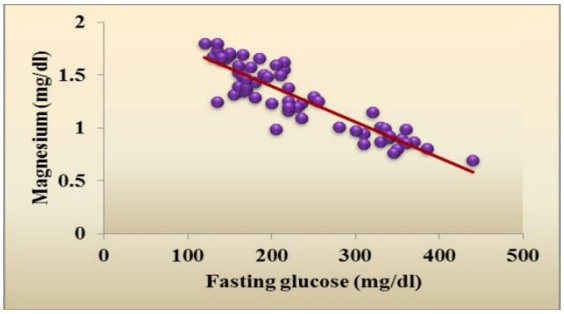

Figure 3: Scatter plot graph showing the negative correlation between fasting glucose and serum magnesium in type 2 diabetic patients.

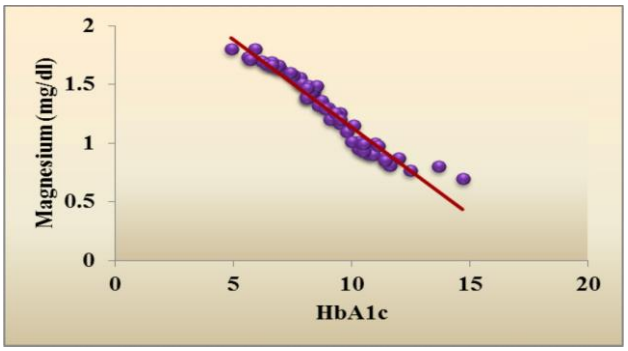

Figure 4: Scatter plot graph showing the negative correlation between HbA1c and serum magnesium in type 2 diabetic patients.

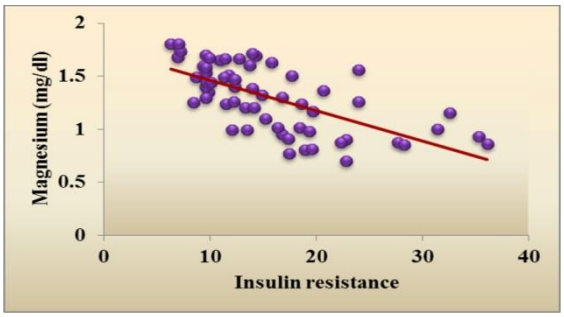

Figure 5: Scatter plot graph showing the negative correlation between Insulin resistance & serum magnesium in type 2 diabetic patients.

DISCUSSION

In our study we found the serum magnesium levels of type 2 diabetic patients were significantly lower than in healthy control subjects, P <0.001 and the value ≤ 2.0 mg/dl was the cut-off point level of serum magnesium to discriminate diabetic patients from non-diabetic controls using ROC curve analysis. These results were in agreement with previous studies which reported low serum magnesium levels in type 2 diabetes.[6,14,22]

In contrast to these results Naila M et al.[23] and Zargar AH et al.[24] did not report any significant difference in serum magnesium level in type 2 diabetic patients when compared to healthy controls.

There are several explanations for hypomagnesaemia in type 2 diabetes. This may be related to gastro paresis and diarrhea due to autonomic neuropathies that occur in diabetes[25] or may be related to glomerular hyperfilteration, increased filtered load, hyperglycemia and osmotic diuresis in diabetic patients.[26] Other factors related to metabolic disturbances that occur in diabetes as hypokalemia,[27] metabolic acidosis[28] and the use of diuretics[29] which lead to increased magnesium excretion and hypomagnesaemia.

In our study we found negative correlation between serum magnesium levels with fasting blood sugar, P<0.001. This was in agreement with Karim et al.[30] and Mishra S et al.[4] who found significant negative correlation between serum magnesium levels and fasting blood sugar in type 2 diabetes.

We found statistically significant negative correlation between serum magnesium levels and HbA1c, P<0.001 this finding was reported by previous studies.[6,8,31,32] In contrast Wälti MK et al.[22] and other studies[33,34] did not find such correlation between serum magnesium levels and HbA1c.

Usually we measure HbA1c levels in diabetic patients for monitoring glycemic control but it also can be used to predict the risk of development diabetic complications.[35] Therefore, the association between low serum magnesium levels and increased HbA1c levels suggests its role in progression and development of diabetic complications and the associated risk of hypomagnesaemia with uncontrolled diabetes.

In our study serum magnesium levels negatively correlated with HOMA-IR in type 2 diabetic patients, P<0.001 this was in agreement with Rasic et al.[14] who documented negative correlation between serum magnesium levels and HOMA-IR in type 2 diabetic patients, P=0.04.

In our study we did not find any correlations between serum magnesium levels and fasting lipids and this in contrast with Mishra S et al.[4] who found negative correlation between serum magnesium with triglycerides and positive correlation with HDL. Also Hamid et al.[36] reported negative correlations between serum magnesium with total cholesterol and LDL and didn't find any correlations between TG and HDL. The association between hypomagnesaemia and lipid abnormalities needs further investigation especially previous studies were mainly done to detect the effect of magnesium supplementation on the lipid profile of diabetic patients.[37]

Previous studies reported improvement in insulin sensitivity and metabolic control in type 2 diabetic patients who received magnesium supplementation.[38,39] Contradictory results about the correlation between serum Mg and glycemic control and the effect of oral magnesium supplementation on the metabolic parameters

of type 2 diabetic patients may be related to different study designs and different populations which need further large scale studies.

CONCLUSION

We have documented hypomagnesaemia in type 2 diabetes and it was strongly correlated with glycemic control and insulin resistance which may be an additional risk factor for uncontrolled diabetes and diabetic complications. Therefore we recommend to measure serum Mg routinely in type 2 diabetes and patients who need supplementation should be considered.

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Conflict of interest: None declared

Ethical approval: the study was approved by the medical ethics committee of Kasr Al Ainy Medical School, Cairo University.

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