Original Article

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Low Serum Magnesium Level Can be a Risk Factor for Retinopathy in Diabetic Patients: A Cross-Sectional Controlled Study

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Abstract

Aim: Uncontrolled diabetes can lead to complications which are related to high blood sugar and insulin resistance (IR). A decrease in serum magnesium (Mg) levels can cause an increase in IR and a worsening of glycaemic control. In this study, we aimed to investigate the relationship between diabetic retinopathy (DR) and serum Mg levels.

Methods: The study was designed as a cross-sectional study in the internal medicine department of a tertiary referral center (Adana Numune Training and Research Hospital) in Turkey. A total of 554 subjects, including 176 patients with DR patients, 209 patients without DR, and 169 healthy individuals were included in this study. Serum fasting glucose levels, insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR), HbA1c percentages, and Mg levels were measured for all subjects.

Results: Serum Mg level was lower in patients with DR ($p<0.001$). Furthermore; HOMA-IR, HbA1c and fasting glucose levels were higher in patients with DR ($p<0.001$, respectively). Incidence of DR was associated with serum Mg levels (odds ratio: 2.1, confidence interval: 95% 1.2-3.6, $p=0.005$).

Conclusion: Low Mg level can lead to retinopathy by impairing glucose homeostasis. In patients with diabetes, Mg levels should be checked since Mg may be a supporting treatment.

Keywords: Diabetic retinopathy, hyperglycemia, insulin resistance, magnesium, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) has become an important disease for the reason that increasing prevalence and complications. Approximately, 347 million people have diabetes worldwide and a significant portion of them have an increased risk of cerebrovascular diseases, kidney failure, heart disease, non-traumatic lower-limb amputations, blindness, and premature death (1).

Diabetic retinopathy (DR) is a common microvascular complication of T2DM and a recent report on the prevalence of DR showed that it is one of the major causes of visual impairment in the adult population in industrialized countries (2,3). The pathogenesis of DR is still unknown. The decrease in retinal perfusion due to the endothelial dysfunction in diabetes leads to many biochemical and metabolic alterations. The retina is also disturbed by non-enzymatic glycosylation due to chronic high blood glucose. Ischemia, inflammation, and vitreoretinal traction are relationship with the evolution of DR (4,5).

Magnesium (Mg) has a role in many enzymatic reactions and affects glucose metabolism and insulin homeostasis (6). The Mg and T2DM relationship has been shown previously (7,8). In our study, we aimed to investigate the effects of low serum Mg levels on the development of retinopathy in patients with T2DM.

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Methods

This cross-sectional study was performed in the internal medicine department of a tertiary, training and research hospital in Turkey, from 11 July 2013, to 20 March 2015. The study was approved by the local ethics committee and informed consent was provided, and then received from all participants. Approval was obtained from Adana Numune Training and Research Hospital's non-invasive clinical research ethics committee (IRB approval number: ANEAH.EK.2015/126). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice standards and ethical standards of the Human Experiments Responsible Committee.

Study Population

A total of 554 subjects, including 176 patients with DR patients, 209 patients without DR, and 169 healthy participants were included in this study. The study group (patients with retinopathy) was divided into two subgroups according to the retinopathy type (proliferative and non-proliferative). The subgroups included 81 and 95 patients with proliferative retinopathy (PR) or non-proliferative retinopathy (NPR), respectively.

Patients with a history of smoking or alcohol intake, renal failure, hypertension, malignancies, acute or chronic diarrhea, sepsis, malabsorption, and who were lactating or pregnant were excluded from this study. Eighteen patients were excluded due to the incomplete data.

Body mass indexes (BMI) of all the subjects were calculated (weight in kg/height in m^2). Sphygmomanometers (Erka, Germany) were used to measure the blood pressures of the subjects. When the systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg was diagnosed as hypertension. Patients with hypertension were excluded from our study.

The diagnosis of DR was done by mydriatic fundus examination and fluorescence angiography. An experienced ophthalmologist classified the retinopathy status according to the internationally accepted classification (9).

Biochemical Parameters

Serum Mg level, fasting glucose, HbA1c percentage, insulin, creatinine, systolic and diastolic blood pressures, BMIs and duration of diabetes were measured. The calorimetric method was used to analyze the Mg levels with Roche C-501 (Japan) device (reference range: 1.8-2.6 mg/dL). Creatinine and serum fasting glucose levels were analyzed by commercially available kits with Beckman Coulter Synchron LX 20 (Massachusetts, USA). A high-performance liquid chromatography technique was used to analyze HbA1c percentages. Insulin levels were measured by Abbott Architect I 2000 SR analyzer system (Illinois, USA). IR [homeostasis model assessment of insulin resistance (HOMA-IR)] was calculated according to the fasting insulin x fasting glucose/405 formula.

Statistical Analysis

Statistical analyses were performed with the MedCalc software program (version 15.6.1; MedCalc, Belgium). The distribution of normality of numerical variables was evaluated using the Kolmogorov-Smirnov test. To compare the categorical measurements between the groups the chi-square test was used. The independent groups Mann-Whitney U tests or t-test were used for the comparison of the numerical variables between two groups, and the ANOVA (post-hoc: Scheffé's test) or Kruskal-Wallis tests (post-hoc: Dunn's test) were used between the groups more than two. Pearson and Spearman correlation analysis was used to evaluate the relationship between numerical variables. Odds ratio (OR) was used to evaluate the association between serum Mg levels and DR. A multiple linear regression model was used to identify independent predictors of HbA1c. A p-value of <0.05 was considered significant in all tests.

Table 1. Clinical and demographical data of the groups

	T2DM with retinopathy	T2DM without retinopathy	Healthy group	p
	N=176	N=209	N=169	
Age (years)	53.7±7.5	54.1±10.9	51.9±10.3	0.693
Female (N) (%)	100 (56.9%)	130 (62.3%)	95 (56.3%)	0.798
Magnesium (mg/dL)	1.88±0.25	1.94±0.19	2.10±0.26	<0.001[a]
HbA1c (%)	9.2±2.1	8.1±1.9	5.3±0.4	<0.001[b]
Fasting blood glucose (mg/dL)	221.7±115.2	181.2±85.7	92.1±11.5	<0.001[a]
Insulin (mcU/mL)	13.9±13.6	18.3±20.9	11.8±9.5	<0.001[a]
HOMA-IR	8.5±13.8	8.2±11.2	2.3±1.7	<0.001[a]
Creatinine (mg/dL)	0.78±0.18	0.77±0.59	0.74±0.17	0.304
Systolic blood pressure mmHg	125.0±13.0	123.7±11.5	110.4±13.5	<0.001[b]
Diastolic blood pressure mmHg	76.0±8.8	76.6±7.7	68.3±10.2	<0.001[b]
Duration of diabetes (years)	10.1±5.4	9.4±6.1	-	0.063

[a]: Kruskal-Wallis tests (post-hoc: Dunn's test), [b]: ANOVA (post-hoc: Scheffé's test) were used. T2DM: Type 2 diabetes mellitus, HOMA-IR: Homeostasis model assessment of insulin resistance

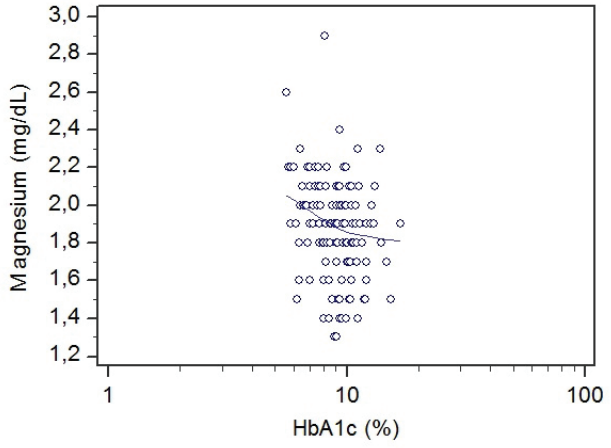

Figure 1. In a scatter diagram, the relation between magnesium and Hba1c is presented graphically

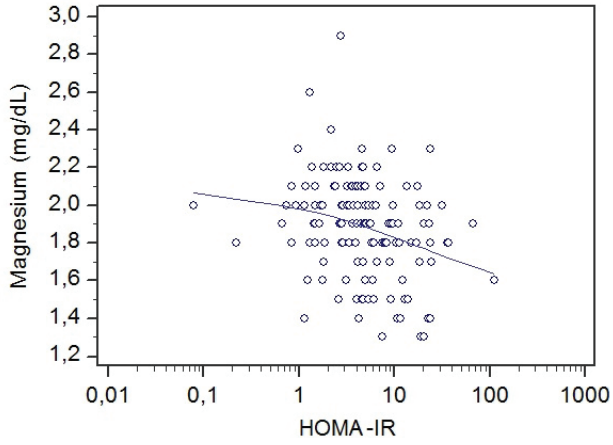

Figure 2. In a scatter diagram, the relation between magnesium and HOMA-IR is presented graphically
HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2. Correlation analyses between magnesium and fasting blood glucose, HbA1c, HOMA-IR

	Fasting blood glucose	HbA1c	HOMA-IR
Magnesium	r=-0.209 p=0.005	r=-0.205 p=0.006	r=-0.284 p=0.001*

*Pearson correlation analysis was used. HOMA-IR: Homeostasis model assessment of insulin resistance

Results

The clinical and demographical data's of the study groups were shown in Table 1. Gender and age distributions were similar between the groups (p=0.798 and 0.693, respectively; Table 1).

Mean Mg levels of patients with DR were significantly lower than in those patients without retinopathy and in the healthy participants (1.88±0.25 vs 1.94±0.19 vs 2.10±0.26; p<0.001, respectively). Mean HbA1c percentages, mean serum fasting glucose levels, mean insulin levels, mean HOMA-IRs and mean BMIs were statistically different (p<0.001, respectively). Other parameters did not differ between groups. Mean systolic and diastolic blood pressures of the patients with diabetes and with or without retinopathy were higher than in those healthy controls (p<0.001) (Table 1).

Table 3. Clinical and demographical data of the subgroups

	T2DM+PR (N=81)	T2DM+NPR (N=95)	p
Age (years)	54.7±7.7	52.8±6.8	0.096
Female N (%)	42 (51.9%)	61 (64.2%)	0.132
Magnesium mg/dL	1.84±0.25	1.91±0.24	0.069
HbA1c (%)	8.9±2.0	9.5±2.1	0.063
Fasting blood glucose (mg/dL)	213.2±121.1	229.8±109.9	0.154
Insulin mcU/mL	14.1±16.2	13.8±11.0	0.428
HOMA-IR (BMI kg/m²)	8.7±17.8 29.4±5.2	8.2±9.1 31.5±6.8	0.031[a] 0.024[b]
Creatinine mg/dL	0.79±0.18	0.77±0.17	0.435
Systolic blood pressure (mmHg)	123.9±13.5	125.9±12.6	0.296
Diastolic blood pressure (mmHg)	75.7±8.8	76.3±8.8	0.640
Duration of diabetes (years)	10.9±5.8	9.4±5.4	0.077

T2DM+PR: Type 2 diabetes mellitus+proliferative retinopathy
T2DM+NPR: Type 2 diabetes mellitus+non-proliferative retinopathy
[a]: Mann Whitney U tests, [b]: T-test were used. HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index

There was a negative correlation between Mg level and serum fasting glucose (r=-0.209, p=0.005), HbA1c (r=-0.205, p=0.006, Figure 1,) and HOMA-IR (r=-0.284, p=0.001, Figure 2) (Table 2). Mg levels were found to be strongly associated with DR (OR: 2.1; 95% confidence interval: 1.2-3.6; p=0.005).

There were 95 and 81 patients with NPR and PR, respectively. In Table 3, the comparisons of these subgroups were shown. BMIs of the patients with NPR were higher than in those in patients with PR (29.4±5.2 vs. 31.5±6.8, p=0.024). Mg levels did not differ significantly in NPR and PR groups (1.91±0.24 vs 1.84±0.25; p=0.069, respectively). HOMA-IR levels of the patients with PR were higher than in patients with NPR (8.7±17.8 vs. 8.2±9.1, p=0.031). Other parameters did not differ between NPR and PR groups (Table 3).

Factors affecting HbA1C levels were evaluated by multiple linear regression analysis. The model included Mg, fasting blood glucose, HOMA-IR, age and duration of diabetes. Decreased Mg levels (β±SE=-0.92±0.40; p=0.022) and increased fasting blood glucose levels (β±SE=-0.012±0.0009; p<0,001) were determined as independent risk factors increasing HgA1C level (Table 4).

Table 4. Multiple regression analyses (backward method) were performed with HbA1c as a dependent variable and with magnesium fasting glucose. HOMA-IR, age and duration of diabetes as independent variables

Independent variables	Coefficient	Std. error	$r_{partial}$	t	p
(Constant)	7.9838	-	-	-	-
Magnesium	-0.9203	0.4020	-0.1211	-2.289	0.022
Fasting glucose	0.01200	0.0009008	0.5790	13.323	<0.001

Std. error: Standard error, HOMA-IR: Homeostasis model assessment of insulin resistance

Discussion

We showed low levels of Mg in patients with DR compared to patients without retinopathy and the healthy subjects in our study. Additionally, we found an inverse relationship between Mg and HbA1c levels. Our findings are consistent with previous studies (10-12). However, our study is the first which investigates the Mg-DR association with the largest sample size. Moreover, we also investigated the patients according to the non-proliferative and proliferative retinopathy. Similarly, the relationship between serum Mg levels and HOMA-IR in DR was investigated firstly in the current study.

Many studies have been done to evaluate the relationship between Mg and T2DM. (7,13-15) . According to those studies; we have understood that not only low serum Mg level is a risk factor for hyperglycaemia but also T2DM is one of the causes of hypomagnesemia (13). hypomagnesemia may lead to disturbances in cellular glucose transport, pancreatic insulin secretion and insulin receptor sensitivity. Tyrosine kinase activity is also negatively affected by hypomagnesemia (8,14). Furthermore, long term Mg deficiency has also been associated with high TNF-alpha levels, which is associated with post-receptor IR (16). On the other hand, T2DM leads to hypomagnesemia due to the excess renal excretion, glycosuria and insulin resistance; additionally, reduced intestinal absorption of Mg due to autonomic nerve damage (14,17).

In our study, Hba1c levels were observed to be higher in patients with DR. This result may be strongly related to uncontrolled DM due to hypomagnesemia, or IR, or hyperglycemia. It supports this hypothesis; in our study, fasting blood glucose and IR levels were higher in patients with diabetes and retinopathy. Similarly, high levels of Hba1c were reported in Kundu et al. (12) Srinivasan et al. (18) and studies.

High levels of insulin and IR were found to be a relationship with obesity and hypertension in previous studies (19,20). In the present study, we have also reported high levels of systolic, diastolic blood pressures and BMI in the study group which is more associated with IR.

Mg levels have a negative correlation with HOMA-IRs, serum fasting glucose levels and Hba1c percentages. Similar results were reported in previous studies (12,18,21). Kundu et al. (12) reported an inverse correlation between Mg levels, fasting glucose levels, and Hba1c. Similar findings have been demonstrated in the Agrawal et al. (21) study. However, the sample size of the present study is larger than in previous studies. In addition, we also analysed HOMA-IR values and showed the correlation between Mg and HOMA-IR levels in patients with diabetes and retinopathy for the first time.

Mg values were lower in patients with diabetic PR patients compared to patients with diabetic NPR. However, this result did not reach statistical significance. On the other hand, we have calculated higher HOMA-IR levels in patients with PR. This result may be related to low serum Mg levels in these patients.

Hypomagnesaemia can increase IR and worsen glycaemic control. Most of the complications of diabetes are related to uncontrolled glycemia. Malabsorption due to diabetic autonomic neuropathy and reduced insulin requirement due to nephropathy may cause weight loss (8,10,11,22). In this study, patients in both of the subgroups were overweight. However, the BMIs of the patients with PR were lower than those in patients with NPR. The lower BMIs in patients with PR can be associated with hypomagnesemia and insulin resistance.

Study Limitations

The nutrition status of the subjects was not the same in the current study; so, it was impossible to know how much Mg each subjects received daily. This can be a limitation for this study.

Conclusion

Magnesium imbalance in patients with T2DM was shown in the literature and a low Mg level can lead to vascular complications by impairing glucose homeostasis and insulin sensitivity (7,10,12,13). In patients with diabetes, serum Mg levels should be checked and Mg supplementation can be considered. Magnesium replacement decreases the risk of diabetes by improvement of IR.

Acknowledgement

The authors have declared that no conflict of interest exists.

Authorship Contributions

Concept: M.B., T.S., S.O.K., Design: M.B., T.S., S.O.K., Data Collection or Processing: M.B., S.O.K., N.S.K., S.C., Analysis or Interpretation: M.B., T.S., S.O.K., Literature Search: M.B., T.S., S.O.K., N.S.K., Writing: M.B., T.S., S.O.K.,

Conflict of Interest: No conflict of interest was declared by the authors.

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