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ORIGINAL PAPER

RELATIONSHIP OF MAGNESIUM LEVEL WITH GLYCEMIC CONTROL AND LIPID PROFILE IN ADULT PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

Type 1 diabetes mellitus (T1 DM) is a disease caused by the autoimmune destruction of pancreatic beta cells due to environmental factors in individuals with genetic predisposition. Magnesium (Mg) is one of the environmental factors suggested to be effective in the pathogenesis and progression of T1 DM. While studies link Mg deficiency with poor glycemic control and dyslipidemia, there are also findings suggesting no association. We aimed to assess the serum Mg levels in adults with T1 DM and evaluate its relationship with glycemic control and lipid profile. The study included 95 type 1 diabetic patients, who presented at the Endocrinology outpatient clinic, and 95 age- and gender-matched individuals without chronic disease. The comparison between the study groups was made using Student's *t*-test for qualitative data analysis and Mann-Whitney *U* test for quantitative data analysis without normal distribution. The Mg level of the diabetic patients was significantly lower than in the control group ($p<0.001$). In diabetic patients, the Mg level was significantly higher in the group with Hba1c <7% compared to the group with HbA1c ≥7%. The patients were divided into two groups according to the optimal Mg cut-off value (0.8 mmol L^{-1}) determined by ROC analysis. The median (interquartile range (IQR)) values of HbA1c were 8.9% (10) in patients with Mg levels <0.8 mmol L^{-1}; 7.6% (6) in patients with Mg levels ≥0.8 mmol L^{-1} ($p<0.001$). Although some studies have shown that Mg deficiency is associated with higher levels of LDL-cholesterol, triglyceride, and lower levels of HDL- cholesterol, there was no significant difference in the lipid profile parameters in our study. When the cut-off value of Mg level was taken as 0.8 mmol L^{-1}, we did not find a significant relationship between the Mg level and lipid profile parameters. We conclude that Mg levels were lower in patients with T1 DM, and it was associated with poor glycemic control. However, Mg levels were not associated with dyslipidemia. Maintaining the Mg level above 0.8 mmol L^{-1} should be a supportive approach for glycemic control; however, more prospective studies are needed on this topic.

Keywords: type 1 diabetes mellitus, adults, magnesium, lipid profile.

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INTRODUCTION

Type 1 diabetes mellitus (T1 DM) is a disorder resulting from chronic autoimmune destruction of insulin-producing pancreatic beta cells (Rodrigues et al. 2020). The autoimmune destruction of beta cells usually causes T1 DM, but the etiology is idiopathic in a small group of patients (Rodrigues et al. 2020). The process of autoimmune degradation occurs in genetically susceptible individuals, triggered by one or more environmental factors, including infections, vaccines and dietary factors (Paschou et al. 2018).

Some elements have been investigated as environmental T1 DM triggers. One of the essential elements examined in the pathogenesis of diabetes mellitus and the progression of its complications is magnesium, Mg (Shahbah et al. 2017). Studies suggest that diabetes mellitus is the most common metabolic disorder associated with Mg deficiency, having 25% to 39% prevalence (Rude 1992). Mg deficiency has been shown to be associated with an increased incidence of T1 DM and poor glycemic outcomes in several studies (Cutfield et al. 2011, Lin, Huang 2015, Ramadass et al. 2015, Shahbah et al. 2017). Despite the relationship between reduced Mg levels and increased incidence of T1 DM or poor glycemic control, the causality between these variables is not clear (Rodrigues et al. 2020). Mg is involved in the modulation of insulin synthesis, secretion and action (Fox et al. 2001, Kim et al. 2010). It sensitizes cells to insulin by increasing the affinity of insulin receptors for ATP, blocking the entry of Ca^{2+} into adipocytes (Guerrero-Romero, Rodriguez-Moran 2011, Gommers et al. 2016). Additionally, it is shown that Mg deficiency is associated with high levels of tumor necrosis factor-alpha (TNFα), which leads to peripheral insulin resistance (Dasgupta et al. 2012). It has been determined that Mg plays a role in insulin secretion, transport of glucose across membranes and in glucose oxidation (Ziegler et al. 1983, Saris et al. 2000). Besides, some studies have suggested that Mg supplementation may have positive effects on pancreatic beta cells (Gueux, Rayssiguier 1983). On the other hand, several causes are suggested to contribute to low Mg levels in diabetic individuals. Osmotic diuresis caused by hyperglycemia may lead to an increase in renal excretion of Mg (Shahbah et al. 2017). Also, insulin resistance may cause a decrease in the tubular reabsorption of Mg (Shahbah et al. 2017).

Mg deficiency has also been associated with low serum LDL-cholesterol, triglycerides, total cholesterol and with high HDL-cholesterol levels (Shahbah et al. 2016, Shahbah et al. 2017). Additionally, some interventional studies have found an association between Mg supplementation and a favorable lipid profile (Rasmussen et al. 1989, Singh et al. 1991). Effects of Mg on lipid profile have been attributed to its role in modifying enzymes related to lipid metabolism and degradation, such as lipoprotein lipase, HMG CoA reductase and lecithin acyltransferase (Lin et al. 2016). Additionally, it has been suggested that Mg is involved in regulating LDL-cholesterol uptake and oxidation (Bjelakovic et al. 2009).

Although there are studies showing that Mg deficiency is associated with poor glycemic control and elevated serum LDL-cholesterol, and with total cholesterol and triglycerides levels, there are also publications claiming the opposite (Shahbah et al. 2017).

Although it has been shown in many studies that there is a relationship between reduced serum Mg levels and poor glycemic control or the presence of dyslipidemia, the causality between these variables is not clear. In this study, we aimed to evaluate the relationship between serum HbA1c levels and lipid profile and serum Mg levels in patients with T1 DM.

MATERIAL AND METHODS

Patient population

This study was conducted as a retrospective, case-control study, carried out at the Trakya University Faculty of Medicine, using the data of patients who presented at the Endocrinology and Metabolic Diseases Outpatient Clinic between January 2015 and December 2019. The Ethics Committee of Trakya University Faculty of Medicine approval was granted before the study (TÜTF-BAEK-2020/452).

Patients with T1 DM over 18 years old and admitted to the outpatient clinic for any reason were included in the study. Age, gender, clinical follow-up characteristics and laboratory values of these patients were recorded from the file records and hospital information systems. People who applied to our clinic and had no chronic diseases were included in the control group. Ninety-five T1 DM patients (47 males and 48 females) and 95 control individuals (41 males, 54 females) were included in our study. Age and gender were used as demographic data; serum HbA1c, LDL-cholesterol, HDL-cholesterol, triglyceride, total cholesterol, Mg, phosphorus, creatinine, albumin, calcium levels were used as laboratory data (High-performance liquid chromatography method for HbA1c; spectrophotometry method for other laboratory parameters). Patients with diseases that could cause changes in Mg levels, such as parathyroid disease and metabolic syndrome, were not included in the study. Also, those who used drugs that contain Mg or may affect serum Mg levels were excluded from the study.

Magnesium analysis

The spectrophotometric method was used for the determination of Mg in a Beckman Coulter AU5800. The reference values of the normal range of Mg were 0.74–1.07 mmol L^{-1}.

Statistical analysis

The values were expressed as a mean (standard deviation) or median and range. The Shapiro-Wilk test was used to evaluate distribution for all variables. The comparison between study groups was evaluated using Student's *t*-test for qualitative data analysis and Mann-Whitney *U* test for quantitative data analysis without normal distribution. Correlation between variables was assessed using the Pearson correlation coefficient. When <7% was taken as the HbA1c target, a receiver operating characteristic (ROC) curve analysis was performed to determine the optimal Mg cut-off value, and the area under the curve (AUC) value with 95% CI was calculated. A Multivariate Logistic Regression analysis was performed to examine the effect of Mg level on HbA1c levels. *P* values of <0.05 were considered statistically significant.

RESULTS

The mean age in years of diabetic patients and the control group were 33.1±10.7 and 32.7±9.8, respectively. The Mg level of the patients with T1 DM was significantly lower than the control group (0.78±0.06 mmol L^{-1}) in the diabetic group versus 0.84±0.06 mmol L^{-1} in the control group, $p<0.001$). However, there was no significant difference in lipid profile parameters between the patient and control groups (Table 1).

Table 1

Laboratory evaluation results in type 1 diabetes mellitus and control group

Specification	Control group (*n*=95)	Diabetic patients (*n*=95)	*P*
Age	32.7±9.8	33.1±10.7	0.678[a]
Gender (female/male)	54(56.8%)/41(43.2%)	48(50.5%)/47(49.5%)	0.383[a]
Magnesium (mmol L^{-1}) Mean ± SD	0.84±0.06	0.78±0.06	**<0.001**[a]
Total cholesterol (mmol L^{-1}) Mean ± SD	4.95±0.98	5.12±1.17	0.289[a]
HDL-cholesterol (mmol L^{-1}) Mean ± SD	1.33±0.33	1.42±0.37	0.092[a]
LDL-cholesterol (mmol L^{-1}) Mean ± SD	3.33±0.78	3.33±0.89	0.656[a]
Triglyceride (mmol L^{-1}) Mean ± SD	1.33±0.81	1.30±0.77	0.844[a]

P<0.005 – significant, *a* – independent Student's *t* test, HDL-cholesterol – cholesterol- high density lipoprotein fractions, LDL-cholesterol – cholesterol- low density lipoprotein fractions, SD – standard deviation, *n* – number of individuals.

In diabetic patients, Mg level was significantly higher, and albumin was lower in the group with Hba1c <7% compared to the group with HbA1c ≥7%. (Table 2). However, no relationship was found between HbA1c levels and age, gender, creatinine, calcium, phosphorus levels. As a result of the multivariate analysis, it was found that only the Mg value was related to the HbA1c level, whereas albumin was not (Table 3). ROC analysis was performed to determine the optimal cut-off value of Mg levels with <7.0 % as the HbA1c target. The cut-off value for the Mg level was determined as 0.8 mmol L^{-1} with 77.3% sensitivity and 67.1% specificity when the likelihood ratio was calculated to be 2.3 in the analysis with the area under the curve of 0.790 and 95% confidence interval (Figure 1). Patients were divided into two groups; group 1: Mg level <0.8 mmol L^{-1} and group 2: ≥0.8 mmol L^{-1}. A statistically significant difference was found between 2 groups with a higher

Table 2

Analysis of parameters affecting the Hba1c levels

Specification	HbA1c <7.0% (*n*=22)	HbA1c ≥7.0% (*n*=73)	*P*
Age Mean±SD	32,4±9.2	33.2±11.1	0.763[a]
Gender (female/male)	13(59.1%) / (40.9%)	35(47.9%) / 38(52.1%)	0.501[b]
Magnesium (mmol L^{-1}) Mean±SD	0.85±0.08	0.75±0.09	**<0.001**[a]
Creatinine (umol L^{-1}) Mean±SD	61.01±15.03	69.85±53.05	0.447[a]
Albumin (g L^{-1}) Mean±SD	38±5	41±4	**0.012**[a]
Calcium (mmol L^{-1}) Mean±SD	2.3±0.12	2.35±0.10	0.076[a]
Phosphorus (mmol L^{-1}) Mean±SD	1.13±0.26	1.19±0.26	0.225[a]

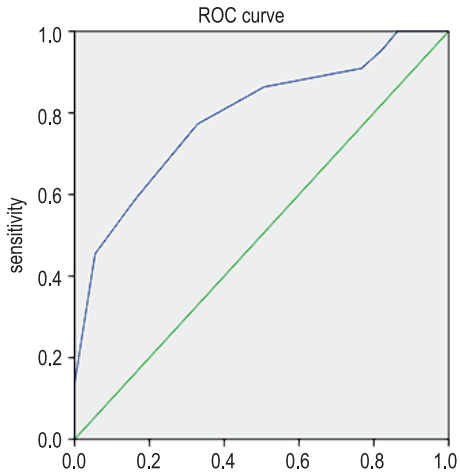
P<0.05 – significant, *a* – independent Student's *t* test, *b* – Yates's correction for continuity, HbA1c – glycated hemoglobin A1c, SD – standard deviation, *n* – number of patients

Table 3

Multivariate analysis showing the effect of some variables on HbA1c level

Variables	Regression coefficient	Standard error	*P*
Age	+0.017	0.028	0.549
Gender	-0.708	0.610	0.246
Magnesium (mmol L^{-1})	-6.264	1.824	**0.001**
Albumin (g L^{-1})	+0.710	0.627	0.258
Constant	+11.252	5.165	-

P<0.05 – significant



Area Under the Curve

Test Result Variable(s): mg

Area	Std. error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
			lower bound	upper bound
.790	.059	.000	.674	.906

Fig. 1. ROC curve analysis for magnesium cut-off value when Hba1c is <7% as the target

Table 4

The relationship of the magnesium level with metabolic parameters when the optimal Mg cut-off value is 0.8 mmol L^{-1}

Specification	Mg <0.8 mmol L^{-1} (n=54)	Mg ≥0.8 mmol L^{-1} (n=41)	P
HbA1c (%)	8.9(10)	7.6(6)	**<0.001**[b]
Total cholesterol (mmol L^{-1}) Median (IQR)	4.95(5.05)	5.02(6.32)	0.787[b]
HDL-cholesterol (mmol L^{-1}) Median (IQR)	1.3(1.61)	1.45(1.89)	0.116[b]
LDL-cholesterol (mmol L^{-1}) Median (IQR)	3.21(4.35)	3.16(4.58)	0.628[b]
Triglyceride (mmol L^{-1}) Median (IQR)	1.14(2.81)	0.96(4.75)	0.147[b]

P<0.005 – significant, b – Mann-Whitney U test, HDL-cholesterol – cholesterol- high density lipoprotein fractions, LDL-cholesterol – cholesterol- low density lipoprotein fractions QR: interquartile range, n – number of individuals.

value of HbA1c in group 1. The median (interquartile range (IQR)) values of HbA1c were 8.9% (10) in group 1; 7.6% (6) in group 2 (p<0.001) – Table 4.

DISCUSSION

The dietary factor is one of the environmental factors that play a role in the development of T1 DM. Some elements, mostly Mg, have been investigated in many studies regarding their relationship with T1 DM (Shahbah et al. 2017).

In our study, it was found that the Mg level in the patient group with T1 DM was statistically significantly lower than in the healthy control group (p<0.001). These results were consistent with the studies of Bjelakovic et al. (2009), Salmonowicz et al. (2014), Lin et al. (2016), Shahbah et al. (2017). Additionally, Wegner et al. (2010) and Xu et al. (2013) also found that serum Mg levels in young adults with Type 1 diabetes were lower than in the control group. In a study conducted with Danish children, no difference was found between the patients with T1 DM and the control group regarding serum ionized Mg levels (Matthiesen et al. 2004). Contrary to our study, in a study conducted on patients with type 2 diabetes mellitus (T2 DM), the serum ionized Mg level was lower in the healthy control group (Mikhail, Ehsanipoor 1999). However, these studies were conducted in different populations and ages from our study population.

Studies investigating the relationship between Mg and glycemic control generally focused on T2 DM. Studies on patients with a diagnosis of T1 DM have mostly been conducted on children and adolescents. Conflicting results were obtained in these studies. We found a negative correlation between serum HbA1c and Mg levels in adults with T1 DM. HbA1c levels were significantly higher in cases with Mg levels below 0.8 mmol L^{-1}. The results of a few studies on children and adolescents with T1 DM are consistent with our study (Rasmussen et al. 1989, Galli-Tsinopoulou et al. 2014). Similar results were observed in adult patients with T2 DM in studies conducted by Sinha, Sen (2014) and Ramadass et al. (2015). In four studies that are inconsistent with our study, Matthiesen et al. (2004), Wegner et al. (2010), Salmonowicz et al. (2014), and Lin et al. (2016) found no relationship between Mg levels and glycemic control in children and adolescents with T1 DM. In a study conducted on an adult age group, no significant relationship was observed between Mg levels and poor or good glycemic control in patients with T1 DM (Zargar et al. 2020).

Pathogenetic mechanisms that can explain the relationship of Mg with glycemic control have been stated in some studies found in the literature. It has been emphasized that Mg is the cofactor of many enzymes that are effective in the secretion, metabolism and activity of insulin (Fox et al. 2001, Kim et al. 2010). It has also been found that Mg deficiency increases insulin resistance through TNFα levels (Dasgupta et al. 2012). The intracellular Mg concentration within normal limits increases insulin sensitivity. Some studies have shown that Mg increases the affinity of insulin receptors for ATP. It is necessary for the auto-phosphorylation of these receptors and tyrosine kinase activity (Guerrero-Romero, Rodriguez-Moran 2011, Gommers et al. 2016). Also, Mg deficiency can increase the calcium level in adipocytes, which can cause insulin resistance, oxidative stress and inflammation (Nielsen et al. 2007, Gommers et al. 2016). Gueux, Rayssiguier (1983), and Ziegler et al. (1983) showed positive effects of Mg supplementation on pancreatic beta-cell functions in rat studies. This is another mechanism that may explain the

relationship between Mg and glycemic control. Furthermore, some studies have found that magnesium supplementation is associated with lower levels of Hba1c and also lower fasting and postprandial serum glucose levels (Rodríguez-Moran, Guerrero-Romero 2003, Shahbah et al. 2017). These studies suggest that Mg supplementation may contribute to maintaining normal serum glucose levels. Also, some studies in the literature have shown a correlation between hyperglycemia and magnesium excretion in type 1 DM (Djurhuus et al. 2000, Shahbah et al. 2017).

Our study did not show a significant difference in lipid parameters between diabetic patients and healthy controls. In addition, no statistically significant difference was found between diabetic patients with Mg <0.8 mmol L^{-1} and patients with ≥0.8 mmol L^{-1} in terms of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels. There are many studies investigating the relationship between the serum Mg level and lipid profile; however, different results were obtained regarding this effect in these studies. Wegner et al. (2010) did not observe a difference in lipid parameters between the hypomagnesemic and normomagnesemic groups in their study on children with T1 DM. Furthermore, Xu et al. (2013) could not show a positive or negative effect of Mg levels on the lipid profile in diabetic patients. These two studies are compatible with our results. However, there are also studies showing contrary results to our study. In the study conducted by Guerrero-Romero, Rodriguez-Moran (2000), hypomagnesemia was found to be associated with low serum HDL-cholesterol levels in patients with T2 DM. In another study conducted on adults with T2 DM, a positive correlation was observed between serum Mg levels and HDL-cholesterol and a negative correlation with triglycerides (Mishra et al. 2012). Also, oral Mg supplementation has been shown in interventional studies to increase HDL-cholesterol levels and lower serum triglycerides, LDL-cholesterol, total cholesterol and apolipoprotein B levels (Rasmussen et al. 1989, Singh et al. 1991).

CONCLUSIONS

As a result, Mg levels were lower in patients with T1 DM, and Mg deficiency was associated with poor glycemic control. We found a negative correlation between serum HbA1c and Mg levels in adults with T1 DM. HbA1c levels were significantly higher in cases with Mg levels below 0.8 mmol L^{-1}. However, Mg levels were not associated with dyslipidemia. Although the causality between reduced Mg levels and elevated HbA1c levels has not been clearly established, maintaining the Mg level above 0.8 mmol L^{-1} can be a supportive approach for glycemic control.

STUDY LIMITATIONS

We also need to mention a few limitations of our study. We did not assess the supply of Mg in the diet. Additionally the patients were not randomized. However, we think that this limitation did not affect our purpose and results, as we have a good number of patients with a gender and age matched control group.

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Contribution statement: BA, BYB , DMD and MC conceived the study design. BA, MC and DMD were involved in data collection. BA, MC and BYB performed the statistical analysis. BA, BYB, DMD and MC interpreted data and prepared the manuscript draft. All authors critically reviewed the final version of the manuscript. All authors approved the final version of the manuscript.

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