Journal of Elementology ISSN 1644-2296

Akyüz O., Ardahanlı I., Aslan R. 2020.
Relationship between chronic complications of type 2 diabetes mellitus and hypomagnesemia.
J. Elem., 25(2): 565-579. DOI: 10.5601/jelem.2020.25.1.1951

RECEIVED: 31 December 2019
ACCEPTED: 9 February 2020

ORIGINAL PAPER

RELATIONSHIP BETWEEN CHRONIC COMPLICATIONS OF TYPE 2 DIABETES MELLITUS AND HYPOMAGNESEMIA

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Abstract

Chronic complications of diabetes are an important cause of morbidity, mortality and health costs worldwide. Magnesium is involved in many important physiological processes in the body. We aimed to investigate the relationship between hypomagnesemia levels and metabolic values and chronic complications of diabetes in type 2 diabetes mellitus in patients. 103 patients with type 2 diabetes mellitus but without any conditions affecting serum magnesium levels were included in the study. Patients were divided into two groups (normal and low blood magnesium levels). Chronic complications of type 2 diabetes mellitus were evaluated by measuring HbA1C, HDL-cholesterol, LDL-cholesterol, triglyceride and magnesium levels. Magnesium was found to be significantly lower in patients with type 2 diabetes mellitus and neuropathy (n=10, p=0.040). There was an inverse correlation between HbA1c and magnesium. However, there is no significant relationship between magnesium levels and HDL-cholesterol, LDL-cholesterol, triglyceride. Hypomagnesemia was associated with poor glycemic control. Hypomagnesemia seen in diabetic patients should be kept in mind as it may be related to neuropathy and hypertension itself or its course. In the course of diabetes mellitus, we recommend that serum magnesium levels be monitored at regular intervals and magnesium replacement be administered in patients who develop complications.

Keywords: type 2 diabetes mellitus, hypomagnesemia, chronic complications of diabetes.

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INTRODUCTION

Diabetes Mellitus (DM) is an epidemic disease that grows in importance every day due to its increasing prevalence all over the world. DM is an important health problem due to the increase in incidence and the morbidity caused by its complications (Malhan et al. 2014, Ogurtsova et al. 2017). The global prevalence of diabetes is estimated to be 415 million cases (8.8%) and will increase to 642 million over the next 25 years (Ogurtsova et al. 2017). Type 2 DM frequently occurs in middle and advanced ages (Liamis et al. 2013). DM is one of the most common causes of hypomagnesemia, and in many studies between 13.5% and 47.7% of patients have been diagnosed with hypomagnesemia (Dasgupta et al. 2012). Many studies have shown that hypomagnesemia is more frequent in type 1 and type 2 DM patients than in control groups, and there is a negative correlation between magnesium and fasting glucose, HbA1c, Homeostatic Model of Assessment-Insulin Resistance (HOMA-IR) (Sales et al. 2006, Kim et al. 2010).

This study aimed to investigate the relationship between hypomagnesemia and chronic complications of type 2 DM in patients with type 2 DM who were not taking medications affecting magnesium levels.

MATERIALS AND METHODS

One hundred and three patients with type 2 DM who were admitted to internal medicine outpatient clinics of Haydarpasa Numune Training and Research Hospital in Turkey between 01.01.2013 and 30.01.2014 were included in this study. There was no drug use (for example: loop diuretics, digoxin, cefuximab, loop diuretics, thiazides and osmotic diuretics) affecting the magnesium level in the patients. The patients were divided into two groups: with normal blood magnesium ($\geq$1.6 mg dm^{-3}) levels and with low blood magnesium ($\leq$1.5 mg dm^{-3}) levels. Blood samples were taken after 12 h of fasting. HbA1C, HDL-cholesterol, LDL-cholesterol, triglyceride, magnesium levels were analyzed. HbA1c, magnesium and lipid parameters were determined with an ARCHITECT c16000 model device. Serum magnesium levels were studied by the ion-selective electrode method. HbA1c was assessed by immunoturbidimetric methods. Lipid levels were examined by the colorimetric enzyme test method. Protein turbidimetric method was determined in 24-hours urine. The demographic information, drug use information and metabolic data of the individuals included in the study were obtained retrospectively from the information system of our hospital. Patients who were newly diagnosed with hypertension (arterial blood pressure>140/90) and were receiving antihypertensive medication were considered to be hypertensive. Among these patients, those who did not use diuretics in their treat-

ment were included in the study. The patients who were treated for urinary albumin excretion in urine for 24 h were enrolled in the study. Urinary albumin excretion (UAE) was considered normoalbuminuria in those under 30 mg/day, microalbuminuria in those over 30-300 mg/day, and macroalbuminuria in those over 300 mg/day. Results of ophthalmoscopic eye and fundus examination performed by an ophthalmologist were included in the study with or without retinopathy. Physical examination findings of the patients with or without the diabetic foot were added to the study. The presence of diabetic neuropathy was determined in the form of diabetic neuropathy present or absent in the examination conducted by a neurologist. The known history of coronary artery disease (CAD) and cerebrovascular events (SVE) was obtained from all patients and included in the study.

The following were exclusion criteria:

– under the age of 18;
– the use of drugs affecting serum magnesium levels (aminoglycosides, amphotericin-B, cyclosporine, digoxin, cefuximab, loop diuretics, thiazides and osmotic diuretics);
– patients with reduced renal function (creatinine $\geq$ 1.5 mg dm^{-3});
– patients with a chronic liver disease;
– patients with acute or chronic diarrhoea and malabsorption;
– use of medicines containing magnesium;
– patients with metabolic acidosis;
– patients with a chronic pulmonary disease;
– presence of active infection;
– pregnancy and lactation;
– alcohol use (alcohol intake of more than 30 g per week);
– a history of acute inflammatory disease and malignancy.

A software package SPSS version 23.0 (Statistical Package for Social Sciences Inc.) was used to analyze the data. Descriptive statistical methods (mean, standard deviation, median, frequency, rate), as well as the normal distribution of parameters, were compared using the Student *t*-test. The Mann Whitney *U* test was used for comparisons between the groups that did not show normal distribution. For comparison of qualitative data, the Yates Continuity Correction test and Fisher's Exact test were employed. The Pearson Correlation Analysis and Enter Logistic Regression Analysis were applied to evaluate relationships between the parameters. The results were assessed at a 95% confidence interval and $p<0.05$ significance level.

RESULTS AND DISCUSSION

The study was conducted on 103 type 2 DM patients who met the criteria. The age of the patients in the study ranged from 28 to 82 years. The mean age was 55.37 ± 11.31 years. 56.3% (*n*=58) of the patients were female and 43.7% (*n*=45) were male. The BMI of the participants ranged from 14.3 kg m^{-2} to 41.9 kg m^{-2} with an average of 28.62 ± 4.99 kg m^{-2} (Table 1).

Table 1

Distribution of demographic characteristics of patients

		Min-Max	Mean±SD
Age (years)		28-82	55.37±11.31
BMI (kg m^{-2})		14.3-41.9	28.62±4.99
		n	(%)
Gender	Female	58	56.3
	Male	45	43.7

SD – Standard Deviation, BMI – Body Mass İndex

The duration of diabetes was 11.14 ± 4.06 years in the hypomagnesemia group and 11.40 ± 4.28 years in the normal serum magnesium group. There was no significant difference between the duration of diabetes and serum magnesium levels (*p*=0.766) – Table 2.

Table 2

Distribution of ciabetes duration of cases

Duration of diabetes (years)	Hypomagnesemia (≤1.5 mg dm^{-3}) *n*=17	Normal magnesium (≥1.6 mg dm^{-3}) *n*=86
	mean±SD	mean±SD
	11.14±4.06	11.40±4.28

Mean HbA1c measurements were 9.53 ± 2.83%, LDL-C values were 116.99 ± 32.44 mg dm^{-3}, triglyceride values were 214.47 ± 165.43 mg dm^{-3} and HDL-C values were 37.91 ± 9.86 mg dm^{-3}. Magnesium measurements ranged from 1.31 mg dm^{-3} to 2.23 mg dm^{-3} with an average of 1.80 ± 0.18 mg dm^{-3} (Table 3).

Table 3

Distribution of biochemical measurements of cases

Specification	Min-Max	Mean±SD
HbA1c (%)	5.3-17.4	9.53±2.83
LDL-C (mg dm^{-3})	57-217	116.99±32.44
Triglyceride (mg dm^{-3})	55-1316	214.47±165.43
HDL-C (mg dm^{-3})	16-68	37.91±9.86
Magnesium (mg dm^{-3})	1.31-2.23	1.80±0.18

17.5% (*n*=18) of the participants did not use any medication for DM. 18.4% (*n*=19) were using insulin, 46.6% (*n*=48) were using oral antidiabetics (OAD) and 17.5% (*n*=18) were using both insulin and OAD (Table 4) – Figure 1.

Table 4

Distribution of patients by treatment

Treatment	(*n*)	(%)
No drugs	18	17.5
Insulin	19	18.4
Oral antidiabetic (OAD)	48	46.6
Insulin ve OAD	18	17.5

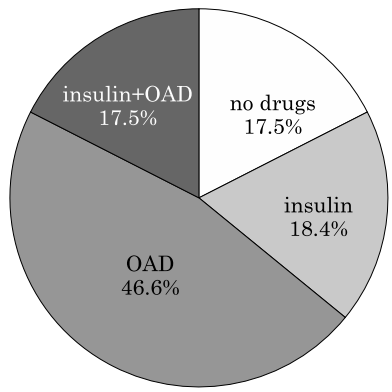

Fig. 1. Distribution of cases according to the treatments used

Among the study participants, 33% (*n*=34) were microalbuminuric, 60.2% (*n*=62) were normoalbuminuric, and 6.8% (*n*=7) were macroalbuminuric. 35% of patients had hypertension (*n*=36), % 18.4% (*n*=19) retinopathy, 36.9% (*n*=38) neuropathy, 3.9% (*n*=4) diabetic foot, 14.6% (*n*=15) developed coronary artery disease, 1.9% (*n*=2) had a history of cerebrovascular accident (Table 5) – Figure 2.

Table 5

Distribution of chronic complications of type 2 diabetes

Specification		*n*	(%)
Proteinuria	microalbuminuria	34	33.0
	normoalbuminuria	62	60.2
	macroalbuminuria	7	6.8
Retinopathy		19	18.4
Neuropathy		38	36.9
Diabetic foot		4	3.9
Coronary artery disease		15	14.6
Cerebrovascular event		2	1.9
Hypertension		36	35.0

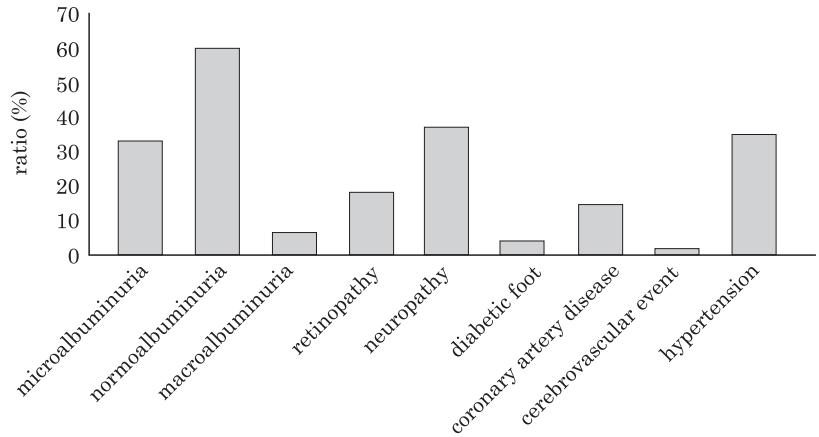

Fig. 2. Distribution of chronic complications in patients

There was no statistically significant difference between the mean age of the patients according to magnesium levels (p=0.775). There were no statistically significant differences between BMI measurements of the patients according to magnesium levels (p=0.894). There were no statistically significant differences between the gender distributions of the cases according to magnesium levels (p=0.566) – Table 6.

Table 6

Magnesium levels according to demographics

Specification		Magnesium		p
		hypomagnesemia (≤1.5 mg dm^{-3}) n=17	normal magnesiu (≤1.6 mg dm^{-3}) n=86	
		mean±SD	mean±SD	
Age (years)		54.65±11.54	55.51±11.32	0.775$^{\#}$
BMI (kg m^{-2})		28.47±5.65	28.65±4.89	0.894$^{\#}$
		n (%)	n (%)	
Gender	female	8 (47.1)	50 (58.1)	0.566^{+}
	male	9 (52.9)	36 (41.9)	

$^{\#}$ Student-t Test, $^{+}$ Continuity Correction Test

There was no statistically significant difference between HbA1c measurements and lipid profiles according to magnesium levels (Table 7).

No statistically significant difference was found between the distributions of patients who did not receive medication according to magnesium levels (p=0.730). No statistically significant difference was found between the distributions of patients who used insulin as a medication (p=0.301). No statistically significant difference was found between the distributions

Table 7

Comparison of HbA1c, LDL-C, HDL and TG parameters according to magnesium levels

Specification	Magnesium		*p*
	hypomagnesemia (≤1.5 mg dm^{-3}) *n*=17	normal magnesium (≥1.6 mg dm^{-3}) *n*=86	
	mean±SD	mean±SD	
HbA1c (%)	10.51±3.26	9.34±2.72	0.122#
LDL-C (mg dm^{-3})	118.18±37.42	116.76±31.61	0.870#
HDL-C (mg dm^{-3})	36.53±8.77	38.19±10.08	0.529#
Triglyceride (mg dm^{-3}) (median)	242.53±163.68 (200.0)	209.92±166.16 (167.5)	0.335+

Student-*t* Test, + Mann Whitney *U* Test

of OAD as drug treatment (p=0.449). No statistically significant difference was found between the distributions of patients using insulin and OAD as a medication (p=0.491) – Table 8.

Table 8

Evaluation of treatment according to magnesium levels

Treatment	Magnesium		*p*
	hypomagnesemia (≤1.5 mg dm^{-3}) *n*=17 (%)	normal magnesium (≥1.6 mg dm^{-3}) *n*=86 (%)	
No drugs	2 (11.8)	16 (18.6)	0.730+
Insulin	5 (29.4)	14 (16.3)	0.301+
OAD	6 (35.3)	42 (48.8)	0.449#
Insulin+OAD	4 (23.5)	14 (16.3)	0.491+

Continuity Correction Test, + Fisher's Exact Test

There was no statistically significant difference between the distribution of albuminuria according to magnesium levels. The prevalence of hypertension in patients with low magnesium levels was significantly higher than those with normal magnesium levels (p=0.011) – Figure 3. There was no statistically significant difference between the distribution of cases with retinopathy according to magnesium levels (p= 0.301). The incidence of neuropathy was significantly higher in the hypomagnesemic group (p=0.040) – Figure 4. The incidence of the diabetic foot, coronary artery disease and cerebrovascular events was similar in both groups (p=0.520, p=0.710 and p=1.000, respectively) – Table 9.

The negative correlation between magnesium levels and HbA1c measurements (as magnesium value increases, HbA1c value decreases) at 24.7% level was found to be statistically significant (r=-0.247; p=0.012; p<0.05 – Figure 5. There was no statistically significant relationship between magne-

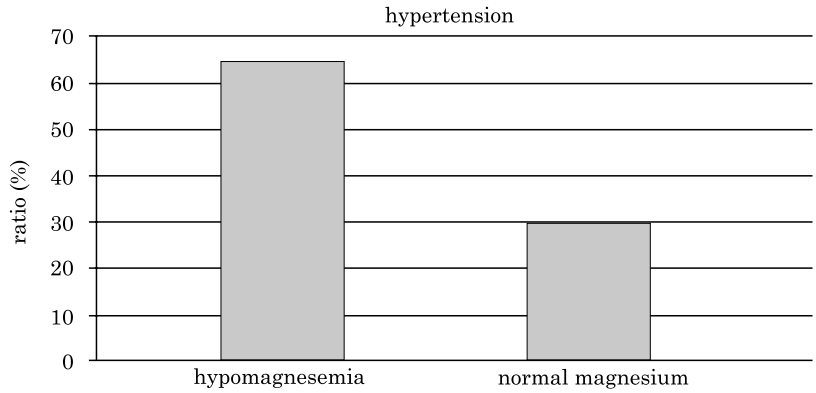

Fig. 3. Rates of hypertension according to magnesium levels

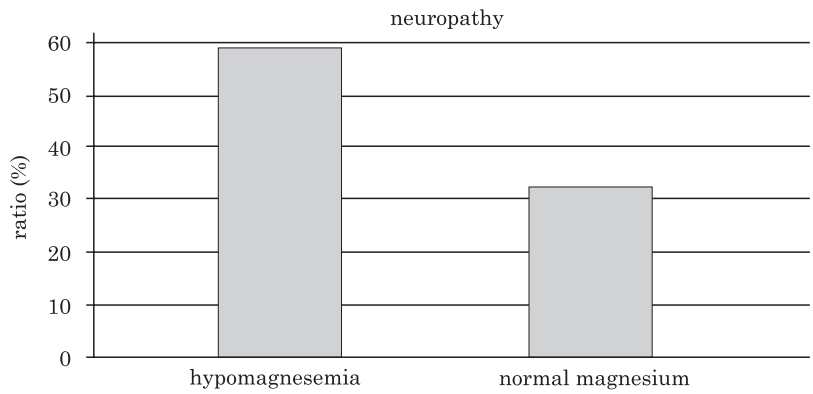

Fig.4. Rates of neuropathy according to magnesium levels

Table 9

Evaluation of parameters according to magnesium levels

Specification		Magnesium		*p*
		hypomagnesemia ($\leq$1.5 mg dm^{-3}) *n*=17 (%)	normal magnesium ($\geq$1.6 mg dm^{-3}) *n*=86 (%)	
Proteinuria	microalbuminuria	6 (35.3)	28 (32.6)	1.000$^{\#}$
	normoalbuminuria	9 (52.9)	53 (61.6)	0.691$^{\#}$
	macroalbuminuria	2 (11.8)	5 (5.8)	0.325^{+}
Hypertension		11 (64.7)	25 (29.1)	0.011*$^{\#}$
Retinopathy		5 (29.4)	14 (16.3)	0.301^{+}
Neuropathy		10 (58.8)	28 (32.6)	0.040*$^{\#}$
Diabetic foot		1 (5.9)	3 (3.5)	0.520^{+}
Coronary artery disease		3 (17.6)	12 (14.0)	0.710^{+}
Cerebrovascular event		0 (0.00)	2 (2.3)	1.000^{+}

$^{\#}$ Continuity Correction Test, $^{+}$ Fisher's Exact Test, * p<0.05

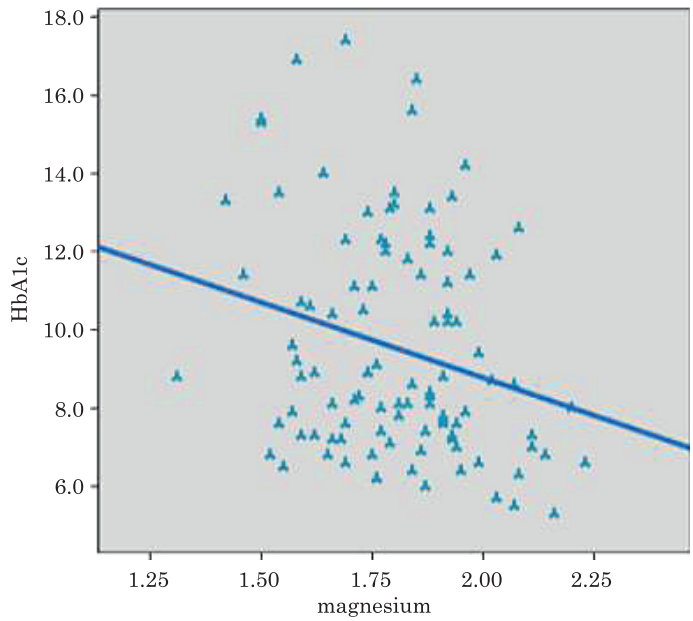

Fig. 5. Relationship between magnesium and HbA1c measurements

Table 10

Correlation analysis of magnesium levels and biochemical parameters

Specification	*r*	*P*
Magnesium – HbA1c	-0.247	0.012*
Magnesium – LDL-C	0.059	0.551
Magnesium – TG	-0.076	0.444
Magnesium – HDL-C	0.042	0.675
Magnesium – age	0.022	0.825
Magnesium – diabetes duration	-0.053	0.595
Magnesium – BMI	0.063	0.525

r = Pearson Correlation Coefficient, * $p<0.05$

sium levels and LDL-C, TG, HDL-C, age, duration of diabetes and BMI ($p>0.05$) – Table 10.

Logistic regression analysis was used to evaluate age, gender, BMI, treatment modality, HbA1c and duration of diabetes among the factors that may affect magnesium deficiency. When the expected magnesium value is formulated according to HbA1c by logistic regression analysis; magnesium = 1.955 - (0.16xHbA1c). When we evaluated the effects of age, gender, BMI, treatment, HbA1c and diabetes duration on magnesium with enter logistic regression analysis, it was observed that the model was not significant ($p=0.492$; $p>0.05$) – Table 11.

Table 11

Multivariate analysis of factors affecting magnesium deficiency

Specification	*P*	ODDS	%95 CI	
			lower	upper
Age	0.226	0.954	0.883	1.030
Gender (E)	0.838	1.129	0.354	3.600
BMI	0.936	0.995	0.886	1.118
Treatment: insulin + OAD	0.281	2.902	0.418	20.149
Treatment: insulin	0.262	2.939	0.447	19.300
Treatment OAD	0.535	1.852	0.264	12.977
HbA1c	0.135	1.192	0.947	1.500
Diabetes duration	0.086	1.151	0.980	1.351

Intracellular magnesium has an important role in the movement of insulin, insulin-mediated glucose uptake and vascular tone. Low magnesium in diabetic diets, increased renal excretion due to osmotic diuresis, and the effect of intracellular magnesium transport due to insulin insensitivity lead to loss of extracellular magnesium (Schulze et al. 2007, Long, Romani 2014). Diabetic autonomic neuropathy due to insulin resistance and decreased tubular reabsorption, common use of loop and thiazide diuretics cause magnesium loss (Grober et al. 2015). Cellular magnesium is a critical cofactor for glucose transport, glucose oxidation, insulin secretion, and ATPase and adenylate cyclase enzymes (Durruty et al. 2019). In diabetic patients, decreased intracellular magnesium causes faulty tyrosine kinase activity, deterioration of post-receptor insulin effect and worsening of insulin resistance (Chhabra et al. 2013, Grober et al. 2015).

The Health Professionals Follow-Up Study and The Nurse's Health Study showed 33% lower risk of type 2 DM in the high magnesium group than in the low magnesium group (Ardisson Korat et al. 2014). Low serum magnesium levels in obese children have been associated with diet, and magnesium supplements have been recommended to obese patients to prevent the development of type 2 DM (Ramadass et al. 2015). In our study, there was no statistically significant difference between BMI measurements (p=0.894). Possible reasons for this are that we did not know the dietary habits of the participants, the number of cases was low and the study was retrospective.

Low magnesium levels accelerate calcium flow into the cell by activating calcium channels. As a result, vasoconstriction develops in the vascular system. Recently, studies reporting an inverse correlation between serum magnesium level and the frequency of hypertension have been published (Cunha et al. 2012, Kostov, Halacheva 2018). Hypertension is an important risk factor among the preventable causes of death in the world, and its prevalence was found to be around 31% in the adult population (Mills et al. 2016).

In our study, the prevalence of hypertension was 35%. This result was similar to the ones reported in studies conducted in many countries around the world, including Turkey. In the HDS (Hypertension in Diabetes Study) study, the prevalence of hypertension in newly diagnosed type 2 DM patients was found to be 39% (Horr, Nissen 2016). The prevalence of high hypertension in diabetic and hypomagnesemic patients may be due to the effect of diabetes and indirect hypomagnesemia. In our study, serum magnesium levels in patients with hypertension were significantly lower than those without hypertension (p=0.011). Our findings support these studies.

The most common dyslipidemia in diabetic patients is high TG and low HDL. In patients with type 2 DM, an increase in TG levels is observed as blood glucose regulation is impaired (Nelson 2013). Similarly, in our study, TG values were lower in patients with normal serum magnesium and higher in patients with hypomagnesemia. However, there was no statistically significant difference. We thought that this was due to the fact that most of the patients included in the study were receiving antihyperlipidemic treatment and the number of cases was relatively low. HDL-cholesterol levels were similar between patients with hypomagnesemia and normal serum magnesium levels.

If diabetes regulation is performed well, Haquea et al. reported that serum magnesium level and duration of diabetes were not directly related (Keskek et al. 2013). In our study, the mean duration of diabetes was not significantly different in both groups (p=0.766).

Many studies suggest that hypomagnesemia is more common in diabetic patients, and this increases the insulin resistance, thus making it difficult to control diabetes (Barbagallo, Dominguez 2015, Gommers et al. 2016, Velayutharaj et al. 2016). Especially in diabetic patients, hypomagnesemia is more common due to dietary intake, glomerular hyperfiltration, osmotic diuresis and recurrent metabolic acidosis (Barbagallo, Dominguez 2015). The mean HbA1c level of patients with hypomagnesemia was significantly higher in our study (p=0.012). In the correlation analysis between magnesium and HbA1c, we confirmed a statistically significant difference (r=-0.247; p=0.012; p<0.05). Although the HbA1c level does not provide an idea for blood sugar regulation for more than three months, it can be said that patients with hypomagnesemia have worse diabetic control when the mean HbA1c levels are compared. Peripheral neuropathy is a very common complication in diabetic patients. Studies show that hypomagnesemia causes endothelial dysfunction, forms atheroma plaque and increases LDL-cholesterol level (Tin et al. 2015, Lin, Lin 2016). The formation of atheroma plaque and the increase in LDL-cholesterol levels can accelerate atherosclerosis. Atherosclerosis, which develops in the lower limb veins, facilitates the development of diabetic foot ulcers and neuropathy. The increase in the frequency of neuropathy in hypomagnesemic patients may be related to this condition.

Altura et al. found that the lumen narrowed in the terminal arteriole,

capillary and post-capillary vessels when the magnesium level in diet was decreased (Altura et al. 2016). In patients with diabetic neuropathy and diabetic foot ulcers, local or systemic magnesium replacement therapy can enhance recovery by improving the circulatory system. Further studies are needed on this subject.

Intracellular magnesium levels in patients with peripheral neuropathy were found to be lower than those without neuropathy (De Lourdes Lima et al. 1998). Peripheral neuropathy is one of the well-known risk factors in the development of diabetic foot ulcers. Magnesium plays an important role in nerve conduction (Panahi et al. 2017). In a study performed by Mak et al. on mice, it was shown that chronic hypomagnesemia causes substance P increase and inflammation in nerves (Mak et al.2011). Hypomagnesemia may facilitate the development of neuropathy in patients. Axonal dysfunction due to metabolic factors is attributed to causes such as increased Na / K ATPase activity, decreased anaerobic glycolysis, deposition of polyols, decreased protein glycosylation, increased amount of myoinositol, and nerve ischemia due to microangiopathy (Kelsey, Gordon 2016). Prevalence of distal symmetric sensorimotor polyneuropathy is approximately 30% in hospitalized diabetes patients and 20-30% in community-based patients (Ziegler et al. 2014). In our study, the rate of neuropathy in the group with low serum magnesium was statistically significant (p=0.040).

Atherosclerosis and microangiopathy are common complications of diabetes. DM is one of the most common risk factors after hypertension responsible for cerebrovascular diseases (Chawla et al. 2016). Depending on the severity and type of diabetes, the risk of stroke increases in patients with diabetes (Lindsberg et al. 2011, Ergul et al. 2016). In our study, there was no statistically significant difference in the development of cerebrovascular events between the groups (p=1.000).

Many studies have shown that magnesium deficiency is associated with endothelial dysfunction, atherosclerosis and vascular calcifications. Low magnesium levels showed pro-atherosclerotic and pro-thrombotic properties in studies related to endothelial cells. It has also been shown to play a role at the beginning and subsequent processes of the plaque formation or in complications due to a plaque (Abbott et al. 2003, Fang et al. 2016). Similar results were found in a cohort study called the Framingham Heart Study (Khan et al. 2010). In our study, no significant relationship was found between coronary arterial disease and hypomagnesemia (p=0.710). It is clear that more work is needed on this issue. In previous study, some drugs (cisplatin, amphotericin B, cyclosporine, amikacin, gentamicin, tobramycin, laxatives, pentamidine, tacrolimus and carboplatin) had been shown to reduce magnesium levels. Magnesium replacement was demonstrated in this group of patients without clinical findings and laboratory results (Majewski et al. 2017). Many diabetic patients use multiple drugs. Therefore, magnesium replacement can be started without decreasing magnesium levels

and clinical signs. We think that education and awareness of one's diet are as important as medical treatment in diabetic patients. In a study with oncology patients, dietary education has been shown to support adequate magnesium intake (Majewski, Kucharczyk 2018). Special emphasis can be placed on magnesium-rich foods when providing nutritional education to diabetic patients.

CONCLUSION

A cause-effect relationship between hypomagnesemia and chronic complications of type 2 DM has not been fully elucidated. It should be kept in mind that hypomagnesemia, neuropathy and hypertension in diabetic patients may be related to itself or its course. It shows that until recently HbA1c has only been used in follow-up, nowadays it is a parameter that needs to be applied as a diagnostic criterion and should be studied further. Magnesium replacement therapy can improve vascular endothelial function, increase local blood flow, and accelerate wound healing. More comprehensive studies are needed on this subject.

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