RESEARCH ARTICLE

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Low Magnesium Levels May Arise as a Risk Factor for the Development of Polyneuropathy in Patients with Type 2 Diabetes

ABSTRACT

Objective: Changes in magnesium metabolism have a different effect on the metabolic and signaling pathways in the development and progression of diabetes. This study aimed to determine the relationship between the serum magnesium level and polyneuropathy in patients with type 2 diabetes mellitus (DM).

Methods: The study included type 2 DM patients who presented to the neurology outpatient clinic of Ankara City Hospital with the complaint of pain and burning sensation in the hands and feet and received a pre-diagnosis of polyneuropathy based on electroneuromyography. Biochemistry and hormone parameters of patients were scanned retrospectively.

Results: A total of 116 patients, 49 (42.2%) female and 67 (57.8%) male, were included in the study. The frequency of polyneuropathy was significantly higher in the group with high HbA1C (>10.1%) compared to the group with low HbA1C (<7.1%) (P=0.004). Mg levels were significantly lower in patients with polyneuropathy (1.8±0.2 mg/dl) compared to those without polyneuropathy (2.0±0.4 mg/dl) (P=0.013). Patients with additional complications other than polyneuropathy had significantly lower magnesium levels than those without such complications(P=0.021). The mean Mg level was 1.82±0.50 mg/dl for the patients with complications while it was 1.88±0.18 mg/dl for those without complications.

Conclusions: This study showed that the magnesium levels were significantly associated with the development of polyneuropathy in patients with type 2 DM. It was concluded that an adequate magnesium level in patients with glycemic control can prevent the development of diabetic polyneuropathy.

Keywords: Diabetes mellitus, Type 2, Diabetic Polyneuropathy, Serum Albumin, Magnesium.

Düşük Magnezyum Seviyeleri Tip 2 Diyabetli Hastalarda Polinöropati Gelişimi İçin Bir Risk Faktörü Olarak Ortaya Çıkabilir

ÖZET

Amaç: Magnezyum metabolizmasındaki değişiklik, diyabetin gelişimi ve ilerlemesi üzerine metabolik ve sinyal yollarında farklı bir etkiye sahiptir. Bu çalışmanın amacı tip 2 Diabetes Mellitusu (DM) olan hastalarda serum magnezyum düzeyinin polinöropati üzerine ilişkisini belirlemektir.

Gereç ve Yöntem: Bu çalışmaya Ankara Şehir Hastanesi nöroloji polikliniğine el ve ayaklarda ağrı ve yanma şikayeti ile başvurup polinöropati ön tanısıyla elektronöromiyografisi yapılan Tip 2 DM tanılı hastalar dahil edildi. Hastaların biyokimya ve hormon parametreleri retrospektif olarak tarandı.

Bulgular: Çalışmaya 49 (%42,2)'u kadın, 67 (%57,8)'i erkek toplam 116 hasta dahil edildi. HbA1C değeri yüksek grupta (>%10,1) polinöropati görülme sıklığı HbA1C düşük gruba (<%7,1) göre anlamlı olarak daha fazlaydı (P=0,004). Mg seviyesi polinöropatisi olan hastalarda (1.8±0.2), Polinöropati saptanmayanlara (2.0±0.4) göre anlamlı derecede düşüktü(P=0,013). Polinöropati dışında ek komplikasyonu olan hastaların magnezyum seviyeleri olmayanlara göre anlamlı derecede daha düşüktü (P=0,021). Ortalama Mg düzeyi komplikasyonlu hastalarda 1,82±0,50 mg/dl iken komplikasyonsuzlarda 1,88±0,18 mg/dl'ydi.

Sonuç: Bu çalışmada Tip 2 DM tanılı hastalarında polinöropati gelişimiyle magnezyum düzeylerinin anlamlı derecede ilişkili olduğunu göstermiştir. Glisemik kontrolü sağlanan hastalarda yeteli magnezyum seviyesinin diyabetik polinöropati gelişimini önleyebileceği sonucuna ulaşılmıştır.

Anahtar Kelimeler: Diabetes mellitus, Tip 2, Diyabetik Polinöropati, Serum Albümini, Magnezyum.

INTRODUCTION

Diabetic polyneuropathy is the most common neurological complication of diabetes and an important cause of morbidity. Diabetic polyneuropathy begins distally and symmetrically in the feet, leading to a gradual loss of integrity of long nerve fibers. In addition to the risks of sensory loss, foot ulcer, and amputation involved in polyneuropathy, approximately 15-20% of patients experience painful symptoms, which are signs of small myelinated fiber involvement that can limit functionality and reduce quality of life (1,2). In nearly half of the cases, pain can be self-limited and resolve spontaneously within a year, while other patients may have permanent symptoms related to pain and loss of functionality (3).

Microelements play a great role in the improving and complications of diabetes (4). An important cation Magnesium (Mg), takes part in cellular mechanisms. These mechanisms are protein synthesis, energy homeostasis, and DNA stability. Hypomagnesemia is the most common micronutrient deficiency detected in diabetic patients. Among type 2 Diabetes mellitus (DM) patients, the prevalence of hypomagnesemia varies between 14 and 48% (5). The main factors under this condition are thought to be inadequate dietary intake, changed insulin metabolism, increased renal excretion, and gastrointestinal malabsorption (6). Serum Mg levels have been found to be associated with diabetic complications. These complications are coronary artery diseases, diabetic retinopathy, nephropathy and polyneuropathy (7-11). In the literature, there are data showing a negative correlation between serum Mg levels and fasting plasma glucose and glycated hemoglobin (HbA_{1C}) levels, as well as a significant decrease in the Mg values of patients with macrovascular complications (8).

It is known that serum albumin has powerful antioxidant properties that prevent the production of free hydroxyl radicals and can scavenge peroxy radicals (9, 10). It has also been suggested that albumin is the main ingredient in extracellular fluids with an antioxidant role (11). Many studies have shown that the excessive production of reactive oxygen species that cause oxidative and nitrosative stress plays a determinant role in the inflammatory pathogenesis and autoimmune diseases of the nervous system, such as neuromyelitisoptica (12), multiple sclerosis (13), and myasthenia gravis (14). Accordingly, a low albumin level can cause polyneuropathy by contributing to inflammation, as in Guillain-Barré syndrome (GBS) (15).

This study aimed to determine the relation of the serum Mg with polyneuropathy in type 2 DM patients with neuropathic pain complaints and to determine the relationship of polyneuropathy with the levels of serum albumin, HbA_{1C}, uric acid, calcium (Ca), sodium, potassium, phosphorus, vitamin B12, vitamin D, thyroid-stimulating hormone (TSH), folate, hemoglobin, ferritin, low-density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG) in these patients.

MATERIAL AND METHODS

Study Design: This study had a retrospective descriptive design.

Study Population and Design: Type 2 DM patients, presented to the neurology outpatient clinic of Ankara City Hospital between March 1, 2019 and October 1, 2019 with the complaint of pain and burning sensation in the hands and feet and received a pre-diagnosis of polyneuropathy based on electroneuromyography (ENMG) were included in the study. The information of the patients was retrospectively analyzed from their files. The recorded data on HbA_{1C}, uric acid, albumin, urine albumin to creatinine ratio, Mg, blood urea nitrogen (BUN), creatinine, glomerular filtration rate (GFR), alanine transaminase, aspartate transaminase, Ca, sodium, potassium, phosphorus, lipid profile tests (LDL, HDL, TG), TSH, vitamin B12, vitamin D, folate, hemoglobin and ferritin levels and ENMG reports, which had been originally obtained due to medical necessity or for routine control purposes, were screened from the hospital information system. In addition, the patients' files were reviewed to record age, gender, medications used, comorbidities, and DM-related complications. The type 2 DM diagnoses of the patients were not made by our clinic and they were based on the information included in the hospital system. Patients using any medication that could affect the electrolyte balance, such as diuretics and Ca, Mg, vitamin B12 and vitamin D supplements, those with advanced heart failure, liver cirrhosis, active malignancy, or thyroid dysfunction, and those with type 1 DM were excluded from the study. The GFR values of the patients were calculated using the simplified formula of Modification of Diet in Renal Disease (MDRD) (16), and those with a GFR below 60 mL/min were also excluded from the study. In repeated presentations, the initial reference values were taken into consideration. Normal Mg values in our laboratory are between 1.3 - 2.7 mg/dl.

ENMG tests were performed in the neurology clinic of Ankara City Hospital using the Nihon Kohden Neuropack S1 MEB-9400K device. During the test, the skin temperature of the patients was kept at 32-33 °C. Conduction velocity, compound muscle action potential amplitude, and distal latencies were measured as part of motor nerve studies on the median and tibial nerves. In sensory nerve studies, the action potential amplitude and conduction velocities of the medial, ulnar and sural sensory nerves were measured. A diagnosis of sensory polyneuropathy was made only in those with impaired sensory nerve conduction while those accompanied by motor

nerve conduction damage were grouped as sensorimotor polyneuropathy.

Statistical Analysis: The data were analyzed using a statistical package program (Statistical Package for the Social Sciences-SPSS for Windows, Version 25). The normality analysis of numerical values was performed using the Shapiro-Wilk test. Descriptive statistics were obtained. The frequencies of the data were expressed as percentage (%) and n values. The Mann-Whitney U test was used to compare numerical data that did not show normal distribution between two independent groups, and the Kruskal-Wallis H test was used for the comparison of more than two independent groups. The chi-square test was conducted to investigate the statistical difference between two variables with nominal dichotomous distribution. The results were evaluated at the 95% confidence interval and a. significance level of $P<0.05$

Ethical Approval: Prior to the commencement of the study, approval was obtained from the ethics committee of Ankara City Hospital (date and number: 30.01.2020-E1-19-228).

RESULTS

A total of 116 patients were included in the study. Patients' 49 (42.2%) were female and 67 (57.8%) were male. The mean age of the patients was 60.6 ± 10.4 (min: 31-max: 94) years.

According to the tertiles of HbA_{1C}, the patients were divided into three groups (<33 percentile, 33-67 percentile, and >67 percentile). The patients with high mean HbA_{1C} (>10.1%) values had a statistically significantly higher rate of polyneuropathy compared to the group with a low HbA_{1C} (<7.1%) value (P = 0.004). Various parameters compared between the groups are shown in Table 1.

Table 1. Comparison of various parameters between the groups according to the tertiles of HbA_{1C}

	HbA_{1C} (%)			
	Tertile 1 (n=34) <7.1	Tertile2 (n=44) 7.1-10.2	Tertile3 (n=30) >10.2	*P*
Polyneuropathy				
Present	22 (28.9%)	27 (35.5%)	27 (35.5%)	0.004*
Absent	12 (40%)	16 (53.3%)	2 (6.7%)	
Type of polyneuropathy				
Neural	12 (60%)	5 (25%)	3 (15%)	0.001*
Sensorimotor	10 (17.9%)	22 (39.3%)	24 (42.9%)	
Complications				
Present	7 (19.4%)	14 (38.9%)	15 (41.7%)	0.010*
Absent	27 (39.1%)	28 (40.6%)	14 (20.3%)	
Albumin (g/L)	45.9 ± 2.5	44.3 ± 2.2	43.8 ± 4.4	0.155
Magnesium(mg/dl)	1.8 ± 0.2	1.9 ± 0.4	1.8 ± 0.2	0.745
Calcium (mg/dl)	9.5 ± 0.3	9.3 ± 0.4	9.5 ± 0.5	0.439
LDL (mg/dl)	103.5 ± 33.4	115.0 ± 38.9	122.0 ± 44.3	0.183
HDL (mg/dl)	47.3 ± 13.5	43.2 ± 12.5	44.2 ± 9.5	0.347
TG (mg/dl)	153.4 ± 79.4	184.4 ± 75.0	194.6 ± 96.9	0.081
GFR (mg/dl)	92.1 ± 13.1	90.5 ± 14.3	85.1 ± 13.3	0.131

HDL; high-density lipoprotein, LDL; low-density lipoprotein, TG; triglyceride
GFR; glomerular filtration rate, *$P<0.005$

Thirty-three percent (n = 37) of the patients had complications associated with type 2 DM. Patients' 22.4% (n = 26) had coronary artery disease, 8.6% (n = 10) had retinopathy, 6.9% (n = 8) had nephropathy and 0.9% (n = 1) had peripheral artery disease. Of the evaluated ENMG reports, 28.9% (n=33) were normal while 17.5 (n=20) were consistent with sensory polyneuropathy and 53.5% (n = 61) with sensorimotor polyneuropathy. There was no significant difference between the genders in terms of the presence of polyneuropathy (P = 0.291). The mean age of the patients with polyneuropathy was 63.1 ± 9.7 years, while that of the patients without polyneuropathy was 54.9 ± 9.8 years, indicating a significant difference (P < 0.001). However, there was no significant relationship between the type of polyneuropathy detected (sensory/sensorimotor) and gender (P = 0.576). The comparison of various parameters according to the presence of polyneuropathy is presented in Table 2.

When the Mg levels were compared between the patients with different polyneuropathy types, there was no significant difference between those with sensory polyneuropathy and those with sensorimotor polyneuropathy (P = 1.000). The mean Mg level was 1.8 ± 0.2 mg/dl in both the sensory polyneuropathy group and the sensorimotor polyneuropathy group.

Of the patients detected to have polyneuropathy, 36.3% (n = 29) had an additionally diagnosed complication associated with type 2 DM.

According to these results, 27.2% (n = 22) of the patients with polyneuropathy had coronary artery disease, 11.1% (n = 9) had retinopathy, and 6.2% (n = 5) had nephropathy. There was a statistically significant difference between the Mg levels of patients with and without complications (*P*=0.021). The mean Mg level was 1.82 ± 0.50 mg/dl for the patients with complications while it was 1.88 ± 0.18 mg/dl for those without complications. However, no significant difference was observed in the albumin and phosphor levels according to the presence or absence of complications (*P*=0.227 and *P*=0.993, respectively).

Table 2. Comparison of the various parameters of the patients according to the presence of polyneuropathy

	Total (n =116)	Polyneuropathy+ (n=81)	Polyneuropathy- (n=33)	*P*
HbA_{1C} (%)	8.9 ± 2.3	9.2 ± 2.5	8.0 ± 1.6	0.052
BUN (mg/dl)	36.0 ± 12.8	37.0 ± 13.4	32.6 ± 9.9	0.094
Creatinine(mg/dl)	0.8 ± 0.3	0.8 ± 0.1	0.9 ± 0.6	0.529
Uric acid(mg/dl)	5.1 ± 1.4	5.0 ± 1.5	5.3 ± 1.2	0.205
Albumin (g/L)	44.7 ± 3.4	44.0 ± 3.4	46.5 ± 2.4	0.001*
Magnesium(mg/dl)	1.8 ± 0.3	1.8 ± 0.2	2.0 ± 0.4	0.013*
GFR (mL/min)	88.9 ± 13.9	86.6 ± 13.7	94.1 ± 13.1	0.011*
Calcium(mg/dl)	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.5	0.733
Sodium(mg/dl)	139.8 ± 2.9	139.5 ± 3.2	140.6 ± 2.1	0.162
Potassium(mg/dl)	4.5 ± 0.4	4.5 ± 0.4	4.6 ± 0.3	0.764
LDL (mg/dl)	112.6 ± 38.3	111.6 ± 38.1	112.3 ± 37.9	0.983
HDL (mg/dl)	44.6 ± 12.2	44.5 ± 11	44.7 ± 15.1	0.605
TG (mg/dl)	176.2 ± 82.7	176.2 ± 81.5	164.3 ± 69.0	0.648
TSH (mU/ml)	1.9 ± 1.6	1.9 ± 1.6	2.1 ± 1.7	0.687
Vitamin B12 (pg/ml)	382.9 ± 191.8	397.8 ± 209	334.6 ± 123.5	0.183
Folic acid (ng/ml)	9.2 ± 3.3	9.2 ± 3.6	9.4 ± 2.4	0.719
Hemoglobin (g/dl)	13.6 ± 1.7	13.7 ± 1.8	13.5 ± 1.6	0.825
Vitamin D (ng/ml)	23.3 ± 13.4	23.7 ± 14.1	21.9 ± 11.3	0.655
Phosphor (mg/dl)	3.6 ± 0.6	3.6 ± 0.4	3.7 ± 0.9	0.839
Ferritin (µg/l)	72.7 ± 77.6	76.6 ± 79.7	60.9 ± 72.0	0.446
UACR (mg/g)	37.0 ± 70.1	42.2 ± 79.1	23.6 ± 36.5	0.575

BUN; blood urea nitrogen, LDL; low-density lipoprotein, HDL; high-density lipoprotein, TG; triglyceride, TSH; thyroid-stimulating hormone,GFR; glomerular filtration rate, UACR; Urine albumin to creatinine ratio *P<0.005

DISCUSSION

The severity and length of hyperglycemia are risk factors for the improving of diabetic polyneuropathy in patients with DM (17, 18). In our study, as the mean HbA_{1C}value increased, the frequency of complications and polyneuropathy, as well as the severity of the latter increased.

Electrolyte disorders are common in diabetic patients and closely associated with increased morbidity and mortality. These disorders are more common in diabetics with poor blood glucose regulation and those with impaired renal function. Hyperglycemia, insulin resistance, or impairment in glucose metabolism might induce glomerular hyperfiltration and increased tubular flow, resulting in decreased tubular reabsorption (6). Complex treatment regimens used by patients with diabetes also stimulate the development of electrolyte disorders in these patients (19). Hypomagnesemia is a common electrolyte disorder among diabetics (20). Diabetic polyneuropathy may present as mixed demyelinating, axonal degeneration or segmental demyelinating. ENMG is a very useful method to detect these disorders (21). In our study, the serum Mg level was found to be statistically lower in patients with diabetic polyneuropathy based on ENMG compared to those without polyneuropathy. In a study conducted with 256 patients with type 2 DM, Zhang et al. performed nerve conduction studies and found that the Mg and phosphate levels were lower in patients with peripheral polyneuropathy (22). In another study for which 978 patients with type 2 DM were recruited, a decrease in Mg was found in proportion to the decrease in the Z score in amplitudes according to the nerve conduction examinations, and it was concluded that Mg could cause peripheral nerve dysfunction through axonal degeneration (23).

Mg is an important element play an important regulator of energy metabolism. It triggers the formation of mitochondrial adenosine triphosphate by preserving transmembrane ion gradients in the inner mitochondrial membrane (24). Mg supplementation has a beneficial effect on glucose control, oxidative stress, and prevention of inflammation (25). In a recent randomized controlled study, it was determined that 12 weeks of Mg supplementation among people with diabetic

foot ulcers regulated ulcer size, glucose metabolism, and serum levels of high-sensitivity C-reactive protein (26). An animal study also showed that Mg acetyltaurate had a preventive effect toward axonal degeneration by reducing oxidative stress through caspase-3 inactivation (27).

Corsonello et al. stated that diabetic patients with microalbuminuria or proteinuria had lower serum ionized magnesium concentration compared to patients with normal albumin in urine (28). Wang et al. found a negative correlation between serum Mg levels and diabetes in terms of macrovascular complications (29). In other studies, hypomagnesemia was found to be associated with diabetic retinopathy in patients with diabetes (30, 31).

Another mechanism for the improvement of diabetic complications changes in metabolic pathways. In these pathways, low Mg levels can modify normal functioning. Sorbitol, a mechanism in the polyol pathway, inhibits inositol transport and results in the inhibition of sodium-potassium adenosine triphosphatase (Na+/K+/ATPase) activity, in diabetes. Intracellular Mg is required for the normal activity of membrane-bound Na+/K+/ATPase, especially in cardiac muscle and neural tissues. Low Mg decrease Na+/K+/ATPase activity, leading to the improving of diabetic polyneuropathy and macro-vascular events (32, 33). In our study, consistent with the literature, the serum Mg level was determined to be lower among the diabetic patients with complications.

Several studies have proven that serum albumin has powerful antioxidant properties that inhibit the production of free hydroxyl radicals and can scavenge peroxy radicals (9, 24). In a study comparing 88 patients diagnosed with GBS presenting with peripheral polyneuropathy and 153 healthy controls, the serum albumin levels were shown to be significantly lower in the former (15). In another study investigating the relationship between microvascular complications and serum albumin, the serum albumin levels were found to be significantly lower in patients with nerve conduction damage observed on ENMG (34). Similarly, in our study, the serum albumin levels of the diabetic patients with polyneuropathy were found to be lower compared to those without polyneuropathy.

Limitation

Our study has certain limitations. First, our sample size was too little to confirm the protective effects of serum electrolytes in diabetic polyneuropathy; therefore, there is a need for prospective studies with larger study populations. However, our study shows that Mg levels are significantly associated with the development of polyneuropathy in diabetic patients. This study can provide a new direction for understanding the possible risk factors and mechanism of polyneuropathy in patients with diabetes.

Conflict of interests: No authors have any conflicts of interest.

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