

Critical Magnesium and HbA1c Cut-off Values for the Development of Polyneuropathy in Type 2 Diabetes Patients in Ankara City Hospital Between 2021-2023

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Abstract *Background and aim:* Our aim was to evaluate the relationship between magnesium and HbA1c levels and the development of polyneuropathy (PNP) in patients with type 2 diabetes and to determine the cut-off values of magnesium (Mg) and HbA1c that may cause PNP. *Methods:* For all 270 patients with type 2 diabetes mellitus were performed electroneurographical examinations according to the polyneuropathy protocol, serum magnesium and HbA1c levels were measured and recorded. *Results:* The mean age was higher in the group with PNP. The distribution of sex ratios among the PNP groups was statistically different, with more males in the PNP group ($P=0.016$). Mg values were statistically lower in patients with PNP ($P<0.001$). HbA1c values were statistically higher in patients with PNP ($P=0.013$). Patients with Mg values less than or equal to 1.95mg/dl were 11.3 times and patients with HbA1c values greater than or equal to 8.95mmol/mol were 3.9 times more likely to develop PNP. *Conclusions:* Although the lower normal limit for Magnesium was 1.6mg/dl and the upper limit for HbA1c was 6.3mmol/mol according to our laboratory standards, we found a more real cut-off value in terms of predisposing to the development of polyneuropathy in our patients.

Keywords: hypomagnesemia, HbA1c, type 2 diabetes mellitus, cut-off, polyneuropathy

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1. Introduction

Diabetic neuropathy, the most frequent complication of diabetes mellitus, is a peripheral nervous system disorder. Approximately 30% of diabetic patients develop diabetic polyneuropathy (PNP), approximately 75% of these are diabetic sensorimotor polyneuropathy and its yearly incidence amounts to 2% [1,2]. Neuropathy can cause a loss of feeling, reduce quality of life due to chronic pain, and cause chronic wounds [3].

Hypomagnesemia is much more common in type 2 diabetic patients than in non-diabetic individuals [4]. Of type 2 diabetic patients, 13.5-47.7% have hypomagnesemia compared with 2.5-15% of non-diabetic individuals. Magnesium, free or bound to protein, is the second most common cation in intracellular compartments and the fourth most common in the human body as a whole [5]. Magnesium is present in three compartments of body; %65 in bones, %34 inside cells, and %1 in extracellular compartment [6,7]. Because it is a cofactor in numerous enzymatic reactions, magnesium plays an important role in neuromuscular stimulation and cellular permeability, but also has antioxidant, anti-inflammatory, and antiapoptotic effects [8]. It regulates ionic channels

and mitochondrial functions, serves as a critical element in cellular proliferation and apoptosis, and assists in both cellular and humoral immune reactions [9].

Hypomagnesemia has been reported to cause glycemic control disturbances, coronary arterial disease, hypertension, diabetic retinopathy, nephropathy, neuropathy, and foot ulcers. In addition, research has shown that hypomagnesemia increases cellular glucose transport, decreases pancreatic insulin secretion, and leads to interaction of insulin with its receptor and/or disturbed post-receptor insulin signaling [3]. Some studies also demonstrated lower levels of intracellular magnesium in diabetic patients with neuropathy whose nerve transmission was then improved by magnesium replacement therapy [10].

Although there are studies in the literature showing that hypomagnesemia and high HbA1c levels are the cause of PNP in type 2 diabetic patients, no study has been found on critical magnesium and HbA1c cut-off levels that may cause PNP development [8,9,11,12,13].

In this study, our primary aim was to evaluate the relationship between magnesium and HbA1c levels and the development of polyneuropathy in diabetic patients, and our secondary aim was to determine the critical magnesium and HbA1c levels that affect the development of polyneuropathy in diabetic patients.

2. Materials and Methods

Our study included 270 patients with type 2 diabetes mellitus who applied to the electrophysiology laboratory of our clinic for polyneuropathy examination within 5 months. During the admission to the clinic, the patients whose polyneuropathy etiology was irrelevant to diabetes were excluded. For all of the patients, electroneurographical examinations were performed according to the polyneuropathy protocol, the presence of type 2 diabetes mellitus was assessed, serum fasting Mg (magnesium) and HbA1c levels were measured and recorded. For measuring the Mg levels was used direct colorimetric assay based on the reaction of magnesium with xylidyl blue in alkaline pH. For the electroneurographic examination MEB-9104 K neuropack device (Tokyo, Japan) was used.

In polyneuropathy protocol the nerves which were examined were as follows: ulnar nerve sensory and motor conductions in upper extremity and deep peroneal motor, posterior tibial motor, and sural nerve conductions in both lower extremities. Based on the results of a study of the Turkish population, the normal limits for nerve conduction evaluations were determined as follows: distal latency for ulnar nerve motor conduction was 3.3 ms, Compound Muscle Action Potential (CMAP) amplitude was 7mV, motor conduction velocity was 39.6m/s; ulnar nerve distal sensory conduction speed was 37.3 m/s, amplitude was 7 mV; deep peroneal nerve motor conduction distal latency was 5.8 ms, amplitude was 3.6 mV, conduction speed was 40.9m/s, F response latency was 52 ms; sural nerve conduction speed was 33.8 m/s, amplitude was 5 mV. At least two pathological nerve conductions, one of which was in the sural nerve, led to symmetric polyneuropathy diagnosis [14].

Statistical analyses of the data were conducted using the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) software. Descriptive statistics of continuous variables were reported using mean $\pm$ standard deviation or median (min-max) depending on the data normal distribution. Frequency distributions of categorical data were reported as numbers and percentages (%). Proportion comparisons

between categorical variables were conducted using the Chi-square test or Fisher's exact test. The normality distribution of the data was evaluated with the Kolmogorov-Smirnov or Shapiro-Wilks test. The student's t-test was used to compare normal distributed data between the two independent groups, and the Mann Whitney U test was used to compare the data that were not distributed normally.

ROC (Receiver Operating Characteristic) analysis was used to determine whether Mg and HbA1c parameters could be prognostic markers in the formation of polyneuropathies (PNP). The area under the ROC curve (AUC) with 95% confidence intervals were calculated. AUC was evaluated as 0.9-1: Excellent, 0.8-0.9: Good, 0.7-0.8: Fair, 0.6-0.7: Poor and 0.5-0.6: very poor. Following the ROC analysis, Youden index (maximum sensitivity and specificity) was used to determine the best cut-off point for the parameters found significant in ROC analysis.

Univariate and multivariate binary logistic regression analysis was used to assess the effects of gender, age, Mg and HbA1c values on the formation of PNP. As a result of the univariate analyses, the parameters found to be significant at <0.05 were included in multivariate models. Odds ratio (OR) with 95% Confidence interval (CI) values were calculated for each parameter found statistically significant in the univariate and multivariate binary logistic regression models. The statistical significance level in all tests was considered $P < 0.05$.

3. Results

A total of 270 patient data were analyzed in the study. 134 (49.6%) of the patients were male and 136 (50.4%) were female. The mean age of the patients was 57.85 ± 10.86 years. Descriptive statistics, mean or ratio comparisons of age, gender, Mg (magnesium) (and HbA1c values among PNP (Polyneuropathies) groups are shown in Table 1. Frequency and percentage of PNP of all patients are shown in Table 1.

Table 1. Mean or proportion comparisons of age, gender, Mg and HbA1c values among Polyneuropathies (PNP) groups

		All patients (n=270)	PNP (Yes) (n=166)	PNP (No) (n=104)	P values
Age (years) (mean $\pm$ SD)	Total	57.85 $\pm$ 10.86	59.35 $\pm$ 11.16	55.46 $\pm$ 9.97	0.004^a
	Female	58.43 $\pm$ 10.54	60.45 $\pm$ 10.71	56.01 $\pm$ 9.89	0.014^a
	Male	57.26 $\pm$ 11.19	58.46 $\pm$ 11.48	54.64 $\pm$ 10.15	0.066 ^a
Gender (n, %)	Male	134 (49.6%)	92 (55.4%)	42 (40.4%)	0.016^b
	Female	136 (50.4%)	74 (44.6%)	62 (59.6%)	
Magnesium (mg/dl) (mean $\pm$ SD)		1.86 $\pm$ 0.32	1.73 $\pm$ 0.32	2.06 $\pm$ 0.19	<0.001^c
Magnesium groups (n, %)	< 1.6	51 (18.9%)	51 (30.7%)	0 (0%)	<0.001^c
	$\geq$ 1.6	219 (81.1%)	115 (69.3%)	104 (100%)	
HbA1c (mmol/mol) (mean $\pm$ SD)		7.7 (5.3-18.1)	8.1 (5.3-18.1)	7.3 (5.3-14.8)	0.013^d
	median (min-max)	8.30 $\pm$ 2.13	8.57 $\pm$ 2.31	7.87 $\pm$ 1.72	
HbA1c groups (n, %)	$\leq$ 6.3	43 (15.9%)	29 (17.5%)	14 (13.5%)	0.381 ^b
	> 6.3	227 (84.1%)	137 (82.5%)	90 (86.5%)	

Mg: Magnesium, HbA1c: Glycated hemoglobin, SD: standard deviation, PNP: Polyneuropathies

^aStudent's t-test

^bChi-square test

^cFisher exact test

^dMann Whitney U test

The mean age of the patients was significantly different between the PNP groups ($P=0.004$). The mean age was higher in the group with PNP. The mean age of female patients was significantly different between PNP groups ($P=0.014$), the mean age of male patients was not significantly different between the groups ($P=0.066$). The distribution of sex ratios among the PNP groups was statistically different, with more males in the PNP group ($P=0.016$). Mg values were statistically lower in patients with PNP ($P<0.001$). In addition, the distribution of the patient ratios in the Mg groups formed according to the 1.6 cutoff point (lower limit of normal Mg values) among the PNP groups was significantly different ($P<0.001$). HbA1c values were statistically higher in patients with PNP ($P=0.013$). The distribution of the patient ratios in the HbA1c groups formed according to the 6.3 cut-off point was similar among the PNP groups ($P=0.381$).

The mean age of the patients in the Mg groups formed according to the 1.6 cutoff point was significantly different ($P=0.001$). In addition, the mean age of female patients and male patients in the Mg groups were significantly different ($P=0.002$, $P=0.049$, respectively). The gender distribution of the patients in the Mg groups was significantly different ($P=0.038$). The mean age of the patients in the HbA1c groups formed according to the 6.3 cut-off point was similar ($P=0.051$). The mean age of the female patients in the HbA1c groups was similar ($P=0.829$). The mean age of male patients was significantly different ($P=0.005$). The gender distribution of the patients in the HbA1c groups was similar ($P=0.376$), Table 2.

ROC analysis results, sensitivity, selectivity, positive-negative predictive values and odds ratio (+) values of Mg and HbA1c values for the prediction of PNP formation are presented in Table 3 and in Figure 1.

Table 2. Comparison of age averages and gender distributions among the subgroups of MG and HBA1C

Age (years) (mean $\pm$ SD)		Mg $\geq$ 1.6 (n= 219)	Mg < 1.6 (n=51)	P values	HbA1c $\leq$ 6.3 (n=43)	HbA1c > 6.3 (n=227)	P values
		56.79 $\pm$ 10.42	62.41 $\pm$ 11.62	0.001 ^a	60.81 $\pm$ 11.74	57.29 $\pm$ 10.62	0.051 ^a
Female	Total	57.3 $\pm$ 10.18	65.36 $\pm$ 10.3	0.002 ^a	57.94 $\pm$ 11.25	58.51 $\pm$ 10.47	0.829 ^a
	Male	56.20 $\pm$ 10.71	60.65 $\pm$ 12.15	0.049 ^a	63.08 $\pm$ 11.86	56 $\pm$ 10.67	0.005 ^a
Gender (n, %)	Male	102 (46.6%)	32 (62.7%)	0.038 ^b	24 (55.8%)	110 (48.5%)	0.376 ^b
	Female	117 (53.4%)	19 (37.3%)		19 (44.2%)	117 (51.5%)	

Mg: Magnesium, HbA1c: Glycated hemoglobin

^aStudent's t-test

^bChi-square test

Table 3. ROC (Receiver Operating Characteristic) analysis results, sensitivity, specificity, positive-negative predictive values and likelihood ratio (+) values for the prediction of PNP formation of Mg and HbA1c values

	Mg	HbA1c
AUC (95%CI)	0.807 (0.757-0.858)	0.590 (0.522-0.658)
P values	<0.001	0.013
Cut-off	1.95	8.95
Sensitivity	78.9% (71.7 – 84.6)	39.1% (31.7 – 47)
Specificity	72.1% (62.3 – 80.2)	80.7% (71.6 – 87.5)
PPV	81.8% (74.8 – 87.3)	76.4% (65.7 – 84.7)
NPV	68.1% (58.5 – 76.5)	45.4% (38.1 – 52.8)
LR +	2.83 (2.05- 3.89)	2.03 (1.31- 3.15)

Mg: Magnesium, HbA1c: Glycated hemoglobin

AUC: Area Under the ROC Curve, CI: Confidence Interval, PPV: Positive Predictive Values, NPV: Negative Predictive Values, LR: Likelihood Ratio

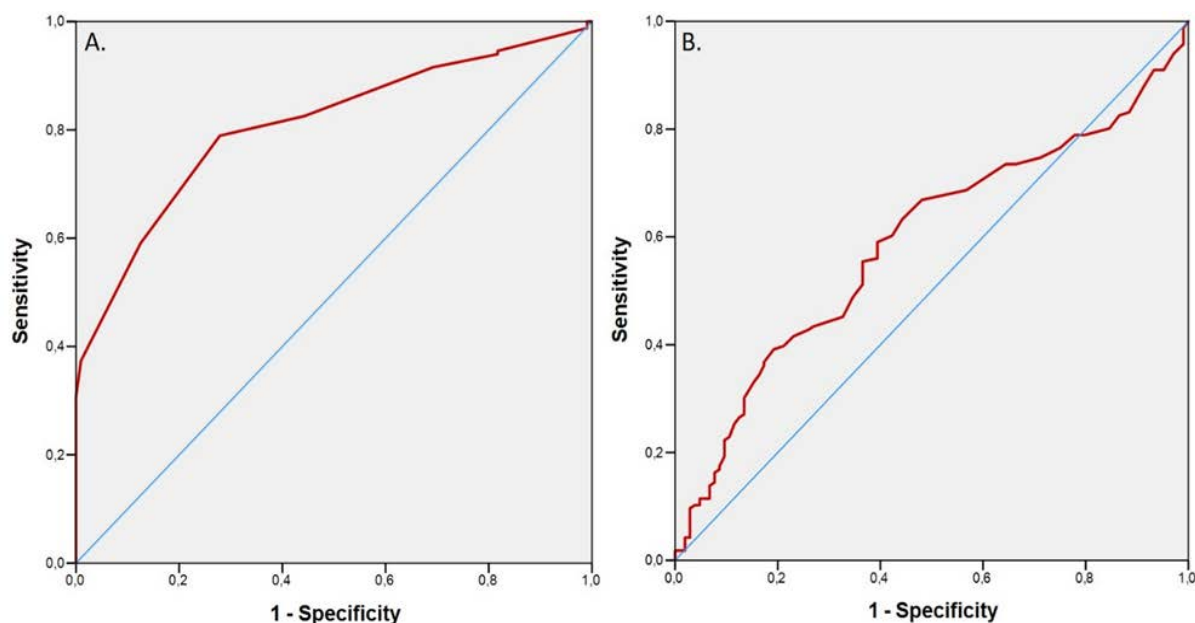


Figure 1. ROC analysis results for the prediction of Polyneuropathies (PNP) of Mg (A.) and HbA1c (B.) values

Mg and HbA1c were statistically significant in predicting PNP formation ($P < 0.001$, $P = 0.013$, respectively). The discrimination power (ROC area under the curve) for Mg was good, the discrimination power (ROC area under the curve) for HbA1c was very poor (AUC 95% CI=0.807 (0.757-0.858, respectively), AUC=0.590 (0.522-0.658)). The best cut-off point for Mg was determined as 1.95, and the sensitivity and specificity values for the prediction of PNP formation for this cut-off were 78.9% (71.7 - 84.6) and 72.1% (62.3 - 80.2) with confidence intervals, respectively. The best cutoff point for HbA1c was determined as 8.95, and sensitivity and specificity values for the prediction of PNP formation for this cutoff were 39.1% (31.7 - 47) and 80.7% (71.6 - 87.5), respectively (Figure 1).

The results of Univariate and Multivariate Logistic Regression analyzes performed to determine whether gender, age, Mg and HbA1c have an effect on the formation of polyneuropathies (PNP) are shown in Table 4.

According to the Univariate model, the effects of

gender, age, Mg and HbA1c variables on PNP formation were significant (respectively, $P = 0.017$, $P = 0.005$, $P < 0.001$, $P = 0.001$, Table 4). According to the results of the multivariate model performed with gender, age, Mg and HbA1c, which were found to be significant in the univariate model, the effects of gender, age, Mg and HbA1c variables on PNP formation were significant (respectively, $P = 0.002$, $P = 0.008$, $P < 0.001$, $P < 0.001$), (Table 4). According to the results of the multivariate model, the probability of occurrence of PNP in men was 2.71 (1.45 - 5.07) times higher than in women. A 1-unit increase in patient age increased the probability of PNP occurrence 1.04 (1.01 - 1.07) times. Patients with a Mg less than or equal to 1.95 were 11.3 (6 - 21.3) times more likely to develop PNP than patients with a Mg greater than 1.95. Patients with an HbA1c value greater than or equal to 8.95 were 3.9 (1.9 - 7.97) times more likely to develop PNP than patients with a HbA1c value less than 8.95 (Figure 2).

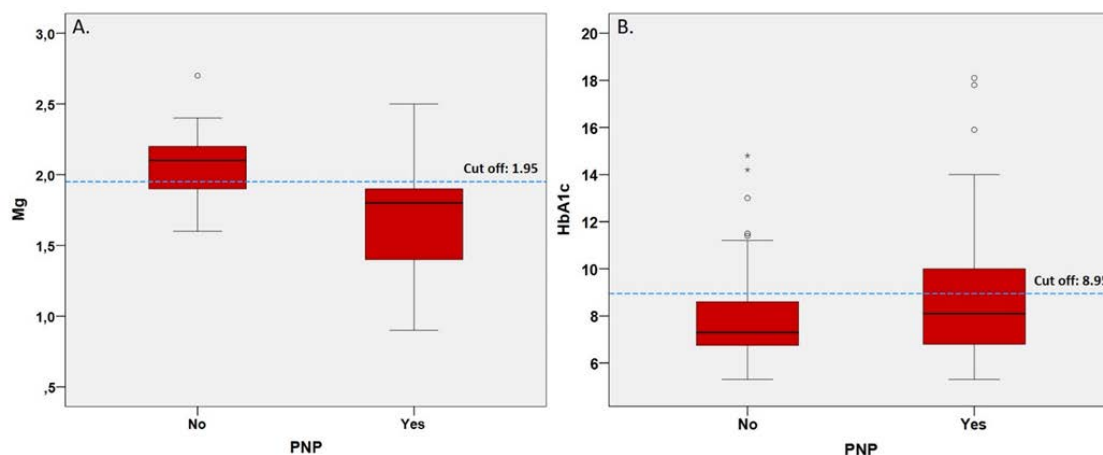


Figure 2. Box plot with cut-off points for the distribution of Mg (A.) and HbA1c (B.) values among Polyneuropathies (PNP) groups

Table 4. Univariate and multivariate binary logistic regression analysis results to determine the effect of gender, age, Mg and HbA1c values on the occurrence of polyneuropathies (PNP)

	Univariate		Multivariate	
	P values	OR (95% CI)	P values	OR (95% CI)
Gender (male vs. female)	0.017	1.83 (1.11 - 3.01)	0.002	2.71 (1.45 - 5.07)
Age	0.005	1.03 (1.01 - 1.06)	0.008	1.04 (1.01 - 1.07)
Mg (≤ 1.95 vs. > 1.95)	<0.001	9.68 (5.48 - 17.1)	<0.001	11.3 (6 - 21.3)
HbA1c (≥ 8.95 vs. < 8.95)	0.001	2.70 (1.51 - 4.82)	<0.001	3.9 (1.9 - 7.97)

Nagelkerke R Square: 0.421, Classification success of multivariate model: 77.4%

Mg: Magnesium, HbA1c: Glycated haemoglobin, OR: Odds ratio, CI: Confidence interval

4. Discussion

Diabetic polyneuropathy is a very common complication of diabetes, and it is very important to evaluate the conditions that may predispose to it. Sensory peripheral neuropathy is the most common type and is closely related to the duration of diabetes. It can occur clinically in mild, moderate or severe levels [15].

Hypomagnesemia is frequently detected in patients with diabetes. It is also accepted that it has an effect on the occurrence and progression of diabetes complications [16].

In our study, Mg (magnesium) levels of diabetic patients with and without polyneuropathy were examined and its relationship with HbA1c levels, which is known to predispose to neuropathy, was also evaluated. It is a known data that susceptibility to polyneuropathy increases with age, and our study also supports this; the rate of polyneuropathy was higher in older age. While peripheral neuropathy occurs at a rate of 2.4% in the general

population, this rate rises to 8% in elderly individuals [17]. However, unlike the information in the literature, our female patients were older than males in the polyneuropathy group, although polyneuropathy was more common in males. The distribution of sex ratios in our patients with polyneuropathy was statistically higher in male gender. The results of previous studies on this have varied [18,19,20,21,22,23]. While some studies report that the rate of polyneuropathy is higher in male gender [21,23], as in our study, some of the others emphasized the opposite [22]. One of them showed that gender based differences in patients with diabetic polyneuropathy are statistically not significant [18,19,20]. These different results in the literature; It also suggests that diabetic polyneuropathy may be related to Mg and HbA1c levels rather than gender. The reason for the differences in the literature is that the development of polyneuropathy in diabetic patients may be due to multiple effects. Age or gender alone are not the factors that trigger the development of polyneuropathy in diabetic patients, and factors such as blood sugar regulation and magnesium level can also be effective.

When we compared our patients in terms of hypomagnesemia and HbA1c elevation, which we know to predispose to diabetic polyneuropathy; hypomagnesemia was more frequent in our male patients ($P=0.038$). But the gender distribution of our patients in the HbA1c groups was similar. It was thought that the polyneuropathy seen in our male patients at an earlier age than females may be related to hypomagnesemia. PNP (polyneuropathy) was detected in all hypomagnesemic diabetic patients. Consistent with previous studies suggesting a link between hypomagnesemia and diabetic complications, in our study, 100% of the diabetic patients without polyneuropathy had normal Mg levels, compared with only 69,3% of those diabetic patients with polyneuropathy. This finding suggested that there may be a "critical magnesium level" within the normal magnesium range in the development of polyneuropathy in diabetic patients. Magnesium is the second most abundant intracellular divalent cation and an important cofactor for carbohydrate metabolism and glycemic control [24]. According to the results of some recent studies, low magnesium levels in individuals have been associated with prediabetes and diabetes [25,26]. It has been reported that the risk and severity of diabetes-related complications may be higher in the presence of hypomagnesemia [16]. In several studies, negative correlation between plasma Mg concentration and the plasma glucose levels and development of polyneuropathy was demonstrated [8,11,12,13]. And some other studies demonstrate that Mg replacement therapy improves nerve transmission [10]. Our results show that, although the normal lower limit of Mg was determined as 1.6 mg/dl, it was observed that the frequency of polyneuropathy was concentrated in patients with values of 1.96 mg/dl and below. On the other hand, although the upper limit of normal for HbA1c was 6.3 mmol/mol, the frequency of polyneuropathy was found to be 8.95 mmol/mol and above. Patients with Mg values less than or equal to 1.95mg/dl were 11.3 times and patients with HbA1c values greater than or equal to 8.95mmol/mol were 3.9 times more likely to develop PNP. In the light of these data, the cut-off values we determined

for the development of diabetic polyneuropathy; are within the limits considered normal for both Magnesium and HbA1c. In previous similar studies, cut-off values corresponding to such an intermediate value were not determined [8,9,11,12,13]. In the follow-up of diabetic patients, these cut-off values may be important data in terms of preventing the development of polyneuropathy.

Despite the contradictory literature results regarding the effect of gender on the development of diabetic polyneuropathy, male gender was found to be a risk factor in our study. This may be due to the fact that modifiable risk factors are more common in male patients, that is, adherence to the diet, which is important in the control of diabetes, is more inadequate in male patients. However, there is a need for studies that evaluate the adherence to diet according to gender in diabetic patients in order to make a definite comment on this issue.

5. Conclusion

As a result, we can say that male gender, hypomagnesemia and high HbA1c levels are effective factors in the development of diabetic polyneuropathy, and keeping the Mg (magnesium) level above 1.96 mg/dl and the HbA1c level below 8.95 mmol/mol may be important in preventing the development of diabetic polyneuropathy.

Statement of Competing Interests

Author declares that she has no conflict of interest.

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