Optimal screening value of vitamin D deficiency for distal symmetric polyneuropathy in patients with diabetes

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Abstract

Aim: The cut-off value of serum 25-hydroxy-vitamin D level for bone-skeletal and cardiovascular diseases are well defined. However, there is no current study defining the optimal cut-off value of serum 25(OH)D levels for preventing diabetic distal symmetric polyneuropathy (DSP). We aimed to evaluate the relationship between the 25(OH)D levels and the parameters of electrophysiology and Toronto Clinical Scoring System (TCSS) to obtain a cut-off value of serum 25(OH)D levels in diabetic DSP patients.

Materials and Methods: This is a case-control study included 90 diabetic patients with or without diagnosed DSP who were visiting the outpatient Physical Therapy and Rehabilitation Clinic. The patients' demographic data and vitamin D levels were recorded. The patients were classified according to serum 25(OH)D levels as having optimal, insufficiency, and deficiency. The electrophysiological study was conducted for the diagnosis and staging of polyneuropathy. TCSS was used to evaluate the patients' neuropathic symptoms.

Results: From the results of this study conducted on the 90 patients that were diagnosed with diabetes, it was found that the electrophysiological study and TCSS were significantly different in the three vitamin D groups. Regression analysis test demonstrated that 25 (OH) D level with 0.845 odds ratio is the only risk factor for the development of DSP. The serum levels of 25(OH)D below 15 ng/mL is associated with DSP.

Conclusion: This study indicate that vitamin D deficiency is a risk factor for the development of DSP, and serum 25(OH)D level $\leq$ 15 ng/ml is crucial in assessing the severity of neuropathic symptoms.

Introduction

Diabetic distal symmetric polyneuropathy (DSP) is a major cause of peripheral neuropathy, which affects 50% of diabetic patients [1]. DSP increases the mortality and morbidity in diabetic patients, such as sleep disturbance and silent myocardial ischemia [2].

25(OH)D is critical in preventing metabolic and cardiovascular diseases [3]. Previous study demonstrated that a low 25(OH)D level is a risk factor for diabetes [4]. Additionally, low 25(OH)D levels have been revealed to be related to paresthesia, numbness, neurological deficit, abnormal neurophysiological studies, and parasympathetic dysfunction in diabetic patients [5, 6]. Thus, this mechanism is crucial in inducing DSP in diabetic patients [7, 8].

In the literature, the cut-off values of serum 25(OH)D level

for bone-skeletal and cardiovascular diseases are well defined [9]. Vitamin D deficiency found to be related with DSP. However, there is no current study defining the optimal screening value of serum 25(OH)D for DSP in Turkish patients with diabetes. During vitamin d screening, patient with diabetes may benefit from an established cut off point in order to early diagnose of DSP. Therefore, we aimed to obtain a cut-off value of serum 25(OH) D levels in Turkish diabetic patients to able to early diagnose DSP and also evaluate the relationship between 25(OH)D levels and DSP using the parameters of electrophysiology and severity of DSP through the Toronto Clinical Scoring System (TCSS).

Materials and Methods

Patient characteristics

Informed consent was obtained from all the patients, and this study was approved by the local ethics committee of Ataturk Training and Research Hospital, Turkey. This

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is a case-control study included 90 diabetic patients with or without diagnosed DSP who were visiting the outpatient Physical Therapy and Rehabilitation Clinics presented with neuropathic symptoms. A pre-hoc sample size was measured for sensitivity and specificity analysis using a 30% prevalence and 0.810 power, according to Bujang et al. [10]. After 15% of data loss, 90 voluntary patients from the outpatient clinic were included in the study.

The inclusion criteria were: having a diagnosis of diabetes mellitus (DM) according to the American Diabetes Association, and showing neuropathic symptoms, such as burning, numbness, and tingling in any extremity. The exclusion criteria were: having any severe disabilities (functional ambulation category ≤ 4), receiving dialysis, having a liver derangement or chronic infectious disease (such as AIDS), being addicted to alcohol or drugs, receiving chemotherapy, radiotherapy, or antipsychotics; and having any other diseases that can cause polyneuropathy such as radiculopathy or neurological diseases.

Data collection

Information on sex, age, weight, height, and duration of diabetes were collected using a questionnaire. The body mass index was calculated as the weight (kg) divided by the square of height (m). Th laboratory parameters, serum hemoglobin A1c (HgbA1c) (µg/mL), and serum 25(OH)D levels (ng/mL) were recorded. Patients were classified according to serum 25(OH)D levels as having optimal vitamin D, vitamin D insufficiency (VDI), or vitamin D deficiency (VDD) if their 25(OH)D levels were > 20, 11–20, or ≤ 10 ng/mL, respectively [11].

The TCSS was used to evaluate patients' neuropathic symptoms [12]. The Turkish validity and reliability of TCSS were performed according to Kaymaz et al. [13], which consisted of three parts: neuropathic symptoms, reflexes, and sensation of the big toe. The total score ranged from a minimum of 0 (no neuropathy) to a maximum of 19 points. According to TCSS score > or = 6 interpreted as sign of neuropathy.

The electrophysiological study was carried out following the same methods explained as previously in [14]. Patients were categorized as follows: (1) DSP, presence of clinical evidence of polyneuropathy and abnormal results on nerve conduction tests, (2) non- DSP, no presence of clinical or electrophysiological evidence of polyneuropathy.

Statistical analysis

Statistical Package for the Social Sciences 20.0 was used for performing the statistical analysis. Descriptive statistics (frequency, mean, and standard deviation) were used for analyzing the sociodemographic and clinical features. Categorical parameters were assessed through Fisher's exact test. For two independent groups, the Mann–Whitney U test was used, whereas the Kruskal–Wallis test was used for more than two independent groups. A post-hoc Bonferroni analysis was performed to assess the statistical significancy. The Spearman correlation was used to analyze the relationship of quantitative data to each other. Receiver operator characteristic (ROC) curves were utilized

Table 1. Demographic and clinical characteristics of patients with/out DSP

Variables	Non-DSP (n=50)	DSP (n=40)	p
Female %	70%	67.5%	0.800
Age	57.08 ± 10.40	59.93 ± 10.03	0.193
Diabetes Type II %	96%	95%	0.99
Duration of diabetes(years)	11.23 ± 7.21	13.10 ± 10.25	0.313
HbA1c, µg/mL	8.14 ± 2.20	9.25 ± 1.98	0.015
TCSS	8.54 ± 4.59	14.63 ± 3.95	<0.001
Peroneal motor nerve			
Amplitude, mV (mean ± SD)	4.02 ± 3.71	1.96 ± 1.74	<0.001
Latency, ms (mean ± SD)	3.83 ± 1.07	5.20 ± 1.76	<0.001
CV, m/s (mean ± SD)	45.56 ± 8.48	32.46 ± 15.07	<0.001
Tibial motor nerve			
Amplitude, mV (mean ± SD)	8.33 ± 3.71	3.52 ± 2.90	<0.001
Latency, ms (mean ± SD)	4.36 ± 1.08	5.37 ± 1.312	<0.001
CV, m/s (mean ± SD)	44.27 ± 8.23	30.34 ± 14.66	<0.001
Sural sensory nerve			
Amplitude, mV (mean ± SD)	9.05 ± 5.35	0.60 ± 2.65	<0.001
Latency, ms (mean ± SD)	3.18 ± 0.83	6.96 ± 1.88	<0.001
CV, m/s (mean ± SD)	43.71 ± 8.34	2.15 ± 9.50	<0.001
25(OH)D levels	21.80 ± 11.55	11.39 ±6.17	<0.001
VDI%	12%	35%	<0.001
VDD%	42%	57.5%	<0.001

Continuous variables were shown as mean ± standard deviation, categorical variables were shown as percentage. CV, conduction velocity; DOD, duration of diseases; DSP, distal symmetric polyneuropathy; HgbA1c; Hemoglobin A1c; mV, millivolt; ms, millisecond; m/s, meter per second; VDI: Vitamin D insufficiency; VDD, Vitamin D deficiency; TCSS, Toronto clinical scoring system.

to detect the cut-off scores, sensitivity, and specificity. Logistic regression analysis was performed to test the risk of having DSP. The results were analyzed using a 95% confidence interval and a significance level of p < 0.05.

Results

Demographic and laboratory characteristics of patients with non-DPN and DPN

In this study, 90 patients that were diagnosed with DM (28 males and 62 females) with a mean age of 58.3 ± 10.2 years were included. The mean duration of diagnosis was 12.6 ± 8.6, and 86 (95.6%) patients were known to have Type 2 diabetes. The mean 25(OH)D level was 33.18 ± 22.93 ng/ml, and the mean TCSS was 42.74 ± 11.84. There

Table 2. The risk factor assessment for DSP

Univariate analyses	p value	Odds ratio (95% C.I.)
Age	0.174	1.035 (0.985-1.088)
Sex	0.909	1.066 (0.360-3.156)
25 (OH) D level	<0.001*	0.845 (0.777-0.920)
HbA1c	0.549	1.078 (0.843-1.378)
DOD	0.556	0.982 (0.924-1.043)

* P<0.05. DOD, duration of diseases; DSP, distal symmetric polyneuropathy; HgbA1c, Hemoglobin A1c; F, Female; SD, standard deviation.

Table 3. Comparison of variables according to Vitamin D status

Variables	VDD (n=29)	VDI (n=35)	Optimal (n=26)	p
Sex †				
Female (%)	38.7%	30.6%	30.6%	0.046*
Age, (years)	59.79 ± 9.90	57.66 ± 11.09	57.65 ± 9.76	0.419
HbA1c, µg/mL	9.42 ± 2.11	8.87 ± 2.19	7.40 ± 1.65	0.001*
DOD (years)	14.32 ± 11.83	14.13 ± 7.57	13.54 ± 5.75	0.824
DSP †, (%)	58.9%	35.8%	5.1%	<0.001*
TCSS	13.26 ± 1.48	11.46 ± 3.26	12.23 ± 1.48	0.015*
Peroneal motor nerve				
Amp, mV	2.10 ± 1.92	3.22 ± 2.11	4.06 ± 2.01	0.001*
Latency, ms	5.17 ± 1.77	4.38 ± 1.33	3.71 ± 1.48	0.002*
CV, m/s	31.83 ± 17.88	41.29 ± 9.88	46.44 ± 5.86	<0.001*
Tibial motor nerve				
Amp, mV	2.91 ± 2.51	4.26 ± 7.06	8.69 ± 2.95	<0.001*
Latency, ms	5.45 ± 1.43	4.73 ± 1.26	4.22 ± 0.74	0.005*
CV, m/s	30.51 ± 16.67	39.06 ± 11.43	45.18 ± 5.58	<0.001*
Sural sensory nerve				
Amp, mV	3.46 ± 1.69	7.31 ± 6.41	7.82 ± 4.60	<0.001*
Latency, ms	6.37±2.03	4.84±2.22	3.200±1.64	<0.001*
CV, m/s	17.28±8.63	29.02±23.16	38.66±14.87	<0.001*

Continuous variables were shown as mean ± standard deviation, categorical variables were shown as percentage.

* P<0.05. † Fisher Exact test used. Amp, amplitude; CV, conduction velocity; DOD, duration of diseases; DSP, distal symmetric polyneuropathy; HgbA1c; Hemoglobin A1c; ; mV, millivolt; ms, millisecond; m/s, meter per second; VDI: vitamin D insufficiency; VDD, vitamin D deficiency; TCSS, Toronto clinical scoring system; Kruskal-Wallis test used.

were statistically significant differences in TCSS, parameters of electrophysiological studies, 25(OH)D levels and prevalence of VDI and VDD among two groups (Table 1).

Association of variables with DSP

The regression analysis test results demonstrated that vitamin D deficiency is the risk factor responsible for the development of DSP in patients with DM (Odds Ratio = 0.845; p < 0.001) (Table 2). Serum 25(OH) vitamin D levels were lower in patients with DSP, in contrast to patients without DSP (p<0.001).

Comparison of variables according to vitamin D status

According to the 25(OH)D levels, the differences between the various variables were evaluated, and the neurophysiological studies, TCSS, and HbA1c were significantly different for the 25(OH) vitamin D levels (p<0.05). From the post-hoc test using the Bonferroni correction, the differences between the optimal and VDD groups were found to be statistically significant in the tibialis motor nerve latency (p = 0.004), peroneal motor nerve amplitude (p = 0.001), latency (p = 0.001), and conduction velocity (p < 0.001). The differences in TCSS (p < 0.001, p = 0.004), HghA1c (p = 0.01, p = 0.021), tibialis motor nerve amplitude (p < 0.001, p < 0.001), conduction velocity (p < 0.001, p = 0.024), sural sensory nerve amplitude (p < 0.001, p = 0.007), latency (p < 0.001, p = 0.012), and conduction velocity (p < 0.001, p < 0.001) were found to originate from the paired groups, i.e., optimal and VDD, and optimal and VDI, respectively (Table 3).

Correlation of 25(OH)D level with the disease's activity

In this study, we showed that the severity of DSP -TCSS-, duration of diseases, HgbA1c, and latency values of neurophysiological studies (p < 0.001) had a statistically significant negative correlation. In addition, the amplitude and conduction velocity of neurophysiological studies (p < 0.001) had a statistically significant positive correlation with the serum level of 25(OH) vitamin D (Table 4).

The optimal screening value of vitamin for DSP

The fact that vitamin D is the only independent factor and correlated with all electrophysiological parameters and TCSS, to predict DSP receiver operating characteristic analysis was executed to reveal the optimal cut-off point of 25(OH)D. The ROC analysis results show that the serum levels of 25(OH)D were a good predictor of DSP diagnoses in patients with DM (AUC = 0.825) with an established cut-off level of ≤ 15.2 ng/mL (sensitivity = 82%; specificity = 70%, likehood ratio: 2.75). Also, due to non-DSP patients had a mean of 8.54 ± 4.59 TCSS, we concluded to execute second roc analysis where DSP patients accepted as TCSS > 5. This analysis revealed with an established cut-off level of ≤ 15.2 ng/mL (sensitivity = 62%; specificity = 88%, likehood ratio: 5) (Fig 1).

Discussion

This study showed that low serum vitamin D levels are associated with DSP. Also, the VDD is found to be related to increase electrophysiological, physical, and clinical symptoms with DSP. To the best of our knowledge, this is the first study in Turkish patients that attempted to evaluate the cut-off value of serum 25(OH)D levels for DSP and

Table 4. Correlation of 25 (OH) D levels and the disease's activity.

Variables	25 (OH) D level	
	r	*p*
HbA1c †	-0.356	0.001*
Duration of disease †	-0.233	0.027*
TCSS †	-0.405	<0.001*
Peroneal motor nerve		
Amp, mV	0.444	<0.001*
Latency, ms	-0.415	<0.001*
CV, m/s	0.416	<0.001*
Tibial motor nerve		
Amp, mV	0.623	<0.001*
Latency, ms	-0.411	<0.001*
CV, m/s	0.543	<0.001*
Sural sensory nerve		
Amp, mV	0.503	<0.001*
Latency, ms	-0.558	<0.001*
CV, m/s	0.510	<0.001*

* P<0.05. † Spearman correlation coefficient used. mV, millivolt; ms, millisecond; m/s, meter per second; SD, standard deviation; TCSS, Toronto clinical scoring system, Spearman correlation coefficient used.

Figure 1. ROC curve analysis of Vitamin D for DSP. (a) ROC curve analysis of Vitamin D for DSP AUC = 0.825 (p = 0.001), 95%CI: 0.739 – 0.911. Cut point of Vitamin D= 15.20 ng/mL. Sensitivity: 82.5%; Specificity: 70.00%, Likehood ratio:2.75 (b) ROC curve analysis of Vitamin D for TCSS>5. AUC = 0.753 (p = 0.001), 95%CI 0.646-0.861. Cut point of Vitamin D = 15.20 ng/mL, Sensitivity: 62.22%; Specificity: 87.50%, Likehood ratio:4.97.

determine the relationship between the parameters of the electrophysiological study and vitamin D deficiency.

The serum 25(OH) D level is the indicator used for assessing vitamin D status [15]. There is no consensus on what the serum 25(OH) D level should be in defining vitamin D deficiency. The Endocrine Society classifies serum 25(OH) D level as deficiency, insufficiency, and optimal based on the following levels: ≤ 20, 21–29, and ≥ 30 ng/ml, respectively. However, the American Association of Clinical Endocrinologists classifies serum 25(OH) D level as < 30 and 30–50 ng/ml for deficiency and optimal, respectively. The American Institute of Medicine (IOM) suggests that a serum 25(OH) D level > 20 ng/ml is optimal for bone and skeletal health, but sometimes, a cut-off value of 30 ng/mL is used to describe the optimal status in some societies, as described [16]. In our study, owing to the low number of patients (10 patients) with > 30 ng/ml, we used the IOM recommendation for classifying vitamin D status [9].

In this study, HgbA1c levels were found to be negatively correlated with serum 25(OH)D levels, and HgbA1c levels decreased among the vitamin D groups (optimal vitamin D, vitamin D insufficiency, and vitamin D deficiency, respectively). In the literature, several known mechanisms have been reported, which explained the relation of DM with serum 25(OH)D levels. It has been shown that owing to the destruction of pancreatic βcells and the increase in insulin resistance, T2DM risk is increased with low serum vitamin D [17]. The low 25(OH) D levels were found to be related to the increase in HgbA1c levels [18]. Guo et al. declared that vitamin D deficiency increases serum calcium levels, causing hyperglycemia [19].

Worldwide, the association between vitamin D deficiency and DSP in people with Type 2 diabetes has been demonstrated in a meta-analysis of six observational studies [20].
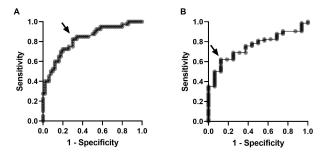
Even though Turkey is a sunny Mediterranean country, vitamin D deficiency is common. Bilir et al. and Celikbilek et al. confirm that low vitamin D level is an independent risk factor for DSP in Turkey; however, in both studies, electrophysiological investigations were not performed, and a screening value of serum 25(OH)D level for DSP was not provided [21, 22]. The only study focused on optimal screening value of vitamin D for diabetic polyneuropathy is from He et al. [26]. The study concluded serum 25(OH) vitamin D level below 16.01 ng/mL increases the risk of DSP three fold. This current study regarding 25(OH) vitamin D level below 15.2 ng/mL increases the risk of DSP 2.75 fold supports the results from He et al. with higher sensitivity and specificity, and also, come to a level of thinking vitamin D levels may be used as screening value for DSP. The relationship between the vitamin D levels and the electrophysiological study parameters was shown by Alamdari et al. [5], and vitamin D supplementation was shown to improve electrophysiological studies [23]. In this study, that the latency values of neurophysiological studies had a statistically significant negative correlation, and, the amplitude and conduction velocity of neurophysiological studies had a statistically significant positive correlation with the serum level of 25(OH) vitamin D.

TCSS is a well-known scoring system for evaluating the severity of neuropathy in DSP patients. Lee et al. used a visual analog score and an abridged form of McGill pain questionnaire of Type 2 diabetes to show that vitamin D supplementation decreases pain [8]. Other studies also showed the relationship between the severity of DSP and vitamin D [24]. In this study, TCSS was used owing to its validity for Turkish DM patients and ease of use and found that TCSS is correlated with vitamin D status, consistent with the findings reported in the literature.

The need for screening item for DSP is questionable. In the countries with high volume of out-patient clinics may be overlooked DSP and the window of early diagnosis for successful treatment can be exuded [24] . Vitamin D is al-

ways at physiatrist's elbow with easy to use. Osteoporosis screening is recommended for diabetic patients with age over 50 years [24]. Physicians may interpret vitamin D results not only from osteoporosis window but also DSP side.

Limitations of this study need to be discussed. Firstly, this study had a cross-sectional design without follow-up. It is important to design studies with long-term outcome of DSP with vitamin D replacement to increase the clinical efficacy of vitamin D for screening. Secondly, this current study only accounted vitamin d levels and HbA1c, other factors such as cholesterol, creatinine and uric acid may be involved in multivariate analysis will affect the results. Lastly, duration of the diabetes may be another important factor, patients in our study had nearly 10 years of duration, adding patients with newly diagnosed diabetes may show different screening value. In conclusion, this data indicate that vitamin D deficiency is a risk factor for DSP, and serum 25(OH) D levels $\leq$ 15 ng/ml are important in assessing neuropathic symptoms. Therefore, we recommend that the serum 25(OH)D levels under 15ng/ml should alert physicians in diabetic patients to detect and treat DSP.

Ethical approval

Informed consent was obtained from all the patients, and this study was approved by the local ethics committee of Ataturk Training and Research Hospital, Turkey (Date: 09/20/2017 Number:26379996 - 172).

Informed consent

Informed consent was obtained from all the patients.

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