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Association of Diabetic Peripheral Neuropathy with Vitamin D Levels Depends on Vitamin D Status

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1 Yang Ou
B 2 Zhi Liang
CD 3 Yang Yang
ABG 1 Yi-kun Zhou

1 Department of Endocrinology and Metabolism, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, PR China
2 Information Center, The First People's Hospital of Yunnan Province, The Affiliated Hospital of Kunming University of Science and Technology, Kunming, Yunnan, PR China
3 Department of Urology, Kunming Yan'an Hospital, Kunming, Yunnan, PR China

Corresponding Author: Yi-kun Zhou, e-mail: yikunzhou24@sina.com
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Background: Vitamin D deficiency has been reported to be associated with diabetic peripheral neuropathy (DPN). Our objective here was to evaluate the association between vitamin D levels and neuropathic symptoms in a Chinese population.

Material/Methods: A total of 4435 patients with type 2 diabetes (T2D) were recruited in this cross-sectional study. 25-dihydroxyvitamin D (25-(OH) D) serum concentration was measured by electrochemiluminescence assay (Cobas e601, Roche). DPN was clinically diagnosed by assessing neurological symptoms and performing current perception threshold (CPT) testing. Of all the patients, 2910 were CPT-positive and had assessed neurological symptoms.

Results: In the vitamin D insufficiency group (<30 ng/mL 25-(OH) D), patients with neurological symptoms had higher serum 25-(OH) D levels than those without neurological symptoms (24.65±3.42 ng/mL vs 23.61±4.54 ng/mL, $p \leq 0.001$). The risk of numbness and pain increased by 0.5-fold for every 6 ng/mL increase in 25-(OH) D. In the vitamin D sufficiency group (≥30 ng/mL 25-(OH) D), patients with neurological symptoms had lower serum 25-(OH) D levels than those without neurological symptoms (32.96±3.18 ng/mL vs 33.45±4.27 ng/mL, $p<0.01$). For every 4 ng/mL decrease in 25-(OH) D, the risk of numbness and pain increased by 0.2-fold.

Conclusions: The association of neuropathy symptoms with 25-(OH) D levels differed depending on whether the patients had insufficient or sufficient vitamin D.

Keywords: **25-dihydroxyvitamin D • Diabetes Complications • Diabetic Neuropathies**

Abbreviations: **VDD** – vitamin D deficiency; **DPN** – diabetic peripheral neuropathy; **T2D** – type 2 diabetes; **25-(OH) D** – 25-dihydroxyvitamin D; **25-(OH) D3** – 25-dihydroxyvitamin D3; **CPT** – current perception threshold; **VDI** – vitamin D insufficiency; **VDS** – vitamin D sufficiency; **DN** – diabetic neuropathy; **BMI –** Body mass index; **SG** – symptomatic group; **AG** – asymptomatic group; **NDPN** – non-diabetic peripheral neuropathy; **NDN** – non-diabetic neuropathy; **NGF** – nerve growth factor; **NDS** – neuropathy disability score; **VD** – vitamin D

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Background

Many disorders have been confirmed to be associated with vitamin D, such as cardiovascular diseases, metabolic syndrome, cancer, autoimmune diseases, and Alzheimer's disease [1-3]. Vitamin D insufficiency (VDI) is common in diabetic patients [4]. Several studies have showed that adequate vitamin D intake can prevent or delay the onset of diabetes and reduce complications in diabetic patients [5-7].

Neuropathy is the most common chronic complication of diabetes; about 50% of diabetic patients have various types of neuropathies [8]. Approximately 50% of patients with diabetic neuropathy (DN) experience some degree of neuropathic pain [9]. Diabetic peripheral neuropathy (DPN) is an important cause of non-traumatic foot ulcers and amputations, and also contributes to recurrent hospitalizations, injuries, and decreased quality of life.

Although electrophysiological nerve conduction study (NCS) is the criterion standard of DPN diagnosis, it cannot detect early neurological injuries. Furthermore, NCS has some limitations in assessing DPN patients' clinical manifestations. However, CPT can help distinguish NCS variables from clinical phenotypes according to the grade [10]. It also helps in understanding the functions of sensory fibers by evaluating the functions of Aβ, Aδ, and C from the early asymptomatic stage to the late stage of severe neuropathy [11].

The pathogenesis of DN is not fully understood thus far. Recently, studies have suggested that Vitamin D deficiency (VDD) contributes to the development of neuropathy complications [12-14]. VDD has also been shown to be an independent risk factor for DPN in a recent Chinese study [15]. The potential relationship between vitamin D levels and neuropathy warrants further study. Previous studies have mainly focused on the relation between vitamin D and DPN incidence, However, the relationship between vitamin D and neuropathic symptoms has not been well studied. Here, we aimed to evaluate the association between vitamin D levels and neuropathic symptoms in Chinese type 2 diabetes (T2D) patients with DPN from a different perspective.

Material and Methods

Study Population and Neuropathy Assessment

This study included a total of 4435 patients with T2D hospitalized at the First People's Hospital of Yunnan, Department of Endocrinology, during 2014-2017. Patients were diagnosed according to the 1999 World Health Organization criteria and the 2012 American Diabetes Association standards [16]. Patients with type 1 diabetes mellitus or specific types of diabetes mellitus, acute complications of diabetes, osteomalacia, history of cerebral infarction, degenerative changes in cervical vertebra, osteoporosis, parathyroid conditions including hyperparathyroidism and hypoparathyroidism, and patients receiving oral vitamin D supplements were excluded. We conducted this study in 2019 and had access to information that could identify individual participants during or after data collection. This study was approved by the Ethics Committee of the First People's Hospital of Yunnan Province. Consent was obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

All patients underwent a neuropathic evaluation, including assessment of neurological symptoms and current perception threshold (CPT). All tests were carried out in a quiet room and performed by the same physician or technician. Positive neurological symptoms were defined as any pain, numbness, or tingling. CPT value was measured using a neurothesiometer (CPT/C, Neurotron, American). This device was applied at 2 different test sites: the right index finger and the right big toe. The test procedure used 3 different sinusoidal frequencies: 2000 Hz, 250 Hz, and 5 Hz. The stimulus was applied as a constant alternating current sinusoidal wave ranging in intensity from 0.01 mA to 9.99 mA. The measurements were selectively conducted on thick myelinated sensory nerve fibers (Aβ), fine myelinated sensory nerve fibers (Aδ), and unmyelinated sensory nerve fibers (c nerve fibers). The test results are expressed in CPT units. Normal CPT values measured at the hand were 2000 Hz 174-401, 250 Hz 26-183.5, and 5 Hz 17-104, and those measured at the toe were 2000 Hz 200-526, 250 Hz 62-211, and 5 Hz 18-173. An abnormal CPT value was defined as any value higher than the normal range. Of all the patients, 2910 were CPT-positive and clinically diagnosed as DPN according to the 2019 Expert consensus on diagnosis, treatment, and management of diabetic peripheral neuropathy in primary care [17]. Diagnostic criteria for DPN were: 1) history of diabetes mellitus (DM); 2) clinical manifestations and/or evidence of electrophysiological examination (CPT); and 3) exclusion of other causes.

Data collection and Anthropometric Measurement

Information on sex, age, weight, height, and duration of diabetes was obtained through medical history inquiry and physical examination. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

2Laboratory Measurements and VDI Diagnosis

Blood samples were collected from an antecubital vein, and serum 25-dihydroxy vitamin D (25-(OH) D) concentration was measured by electrochemiluminescence assay (Cobas e601,

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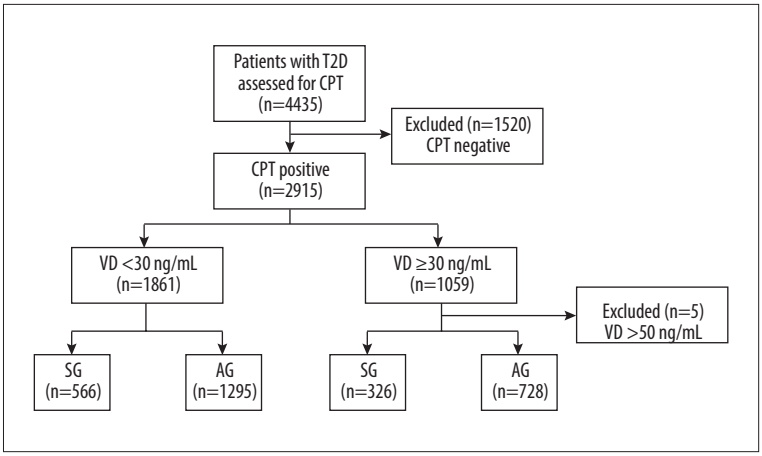

Figure 1. Flow chart.

Table 1. Characteristics of symptomatic and asymptomatic patients.

	Symptomatic group	Asymptomatic group	*P*
Age (years)	55.75±11.21	55.21±11.76	0.227
No. of cases (Male/Female)	516/374	1302/687	<0.001***
Duration of diabetes (years)	8.66±5.55	8.70±6.17	0.038*
BMI (kg/m^2)	24.76±4.71	24.56±4.90	0.914
25-(OH) D (ng/mL)	27.69±5.21	27.15±6.48	<0.001***

Data are expressed as median and range; Significance, *** p<0.001, * p<0.05; BMI – body mass index.

Roche). VDI was defined as a serum circulating 25-(OH) D level of <30 ng/mL, and vitamin D sufficiency (VDS) as a 25-(OH) D level of ≥30 ng/mL. Patients were divided based on the presence of pain and/or numbness symptoms into a symptomatic group (SG) and an asymptomatic group (AG) (**Figure 1**).

Statistical Analysis

SPSS v. 20.0 software was used for statistical analysis. Data are expressed as mean±standard deviation for continuous variables. Differences between the groups were analyzed using an independent-samples *t* test or analysis of variance, as appropriate, for measurement data, or using a chi-squared test for categorical values. Multiple logistic regression analysis was performed to evaluate neuropathic symptoms and associated factors. All *p* values are two-tailed, and p<0.05 was considered to be statistically significant.

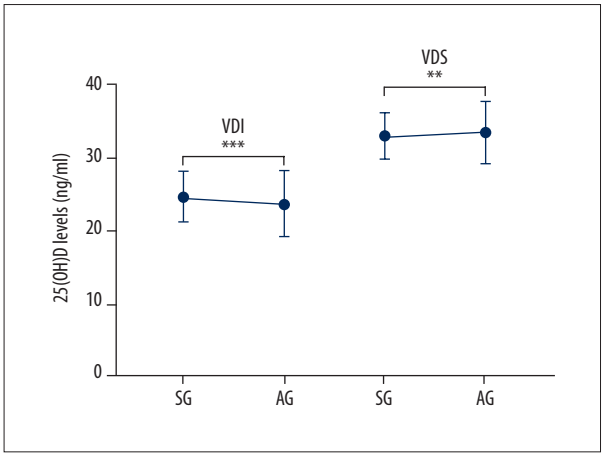

Figure 2. 25-hydroxy vitamin D levels in symptomatic and asymptomatic patients at varying states of vitamin D. Significance, *** p<0.001, ** p<0.01, VDI – vitamin D insufficiency; VDS – vitamin D sufficiency; SG – symptomatic group; AG – asymptomatic group; Figure 2 was made using Graphpad Prism 7 (GraphPad Software).

Results

Comparison of Symptomatic and Asymptomatic Study Groups

A total of 2910 people were enrolled in the study. The age, sex, diabetes duration, BMI, and 25-(OH) D levels were compared and analyzed. There were significant differences in sex, and diabetes duration between SG and AG. The SG patients had higher serum 25-(OH) D levels than AG patients (p≤0.001). A chi-square test showed significant differences according to sex and neurological symptoms (p≤0.001) (**Table 1**).

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Table 2. Logistic regression analysis of neuropathic symptom-related risk factors in VDI (<30 ng/mL 25-(OH) D) patients.

Variable	β	S.E.	Wald	*P*	OR	95%CI
Sex	-0.250	0.119	4.436	0.035*	0.779	0.617-0.983
Age (years)	0.028	0.098	0.083	0.773	1.029	0.849-1.246
Duration of diabetes (years)	-0.095	0.086	1.210	0.271	0.910	0.769-1.077
BMI (kg/m^2)	0.002	0.071	0.001	0.980	1.002	0.872-1.151
25-hydroxyvitamin D (ng/mL)	0.379	0.095	16.017	0.000***	1.461	1.214-1.760

Data are expressed as median and range; Significance, *** $p<0.001$, * $p<0.05$; BMI – body mass index.

Table 3. Logistic regression analysis of neuropathic symptom-related risk factors in VDS (≥30 ng/mL 25-(OH) D) patients.

Variable	β	S.E.	Wald	*P*	OR	95%CI
Sex	-0.302	0.171	3.115	0.078	0.740	0.529-1.034
Age (years)	0.036	0.138	0.067	0.796	1.036	0.790-1.359
Duration of diabetes (years)	0.050	0.118	0.181	0.671	1.052	0.834-1.326
BMI (kg/m^2)	0.114	0.095	1.455	0.228	1.121	0.931-1.349
25-hydroxyvitamin D (ng/mL)	-0.225	0.110	4.150	0.042*	0.798	0.643-0.992

Data are expressed as median and range; Significance, * $p<0.05$; BMI – body mass index.

Comparison of Symptomatic and Asymptomatic Study Groups with Different Levels of 25-(OH) D

Diabetic patients were divided into 2 groups according to 25-(OH) D levels: less than 30 ng/mL, and greater than or equal to 30 ng/mL. In the VDI group (<30 ng/mL 25-(OH) D), 1295 patients had no diabetic neurological symptoms and 566 patients had diabetic neurological symptoms. The SG patients had relatively higher serum 25-(OH) D levels than AG patients (24.65±3.42 ng/mL vs 23.61±4.54 ng/mL, $p\leq0.001$). In contrast, the VDS group (≥30 ng/mL 25-(OH) D) showed the opposite association; the 326 SG patients had a lower 25-(OH) D level than the 728 AG patients (32.96±3.18 ng/mL vs 33.45±4.27 ng/mL, $p<0.01$) (**Figure 2**).

Logistic Regression Analysis of Neuropathic Symptom-Related Risk Factors

There was a statistically significant difference between SG and AG in the VDI (25-(OH) D <30 ng/mL) group, so we performed further regression analysis of sex, course of disease, age, BMI, and 25-(OH) D levels. We found that in this 25-(OH) D range, the risk of neurological symptoms was higher with relatively higher 25-(OH) D levels. For every 6 ng/mL increase in 25-(OH) D, the risk of numbness and pain increased by 0.5-fold (**Table 2**). At the same time, we found that sex was related to neurological symptoms and women were more prone to neurological symptoms than men.

We also performed similar regression analysis in the VDS (≥30 ng/mL 25-(OH) D) group. We found that in this 25-(OH) D range, the risk of neurological symptoms was higher with relatively lower levels of 25-(OH) D. For every 4 ng/ml decrease in 25-(OH) D, the risk of numbness and pain increased by 0.2-fold (**Table 3**).

Discussion

In this study, we aimed to investigate the relationship between serum 25-(OH) D levels and neuropathic symptoms in T2D patients with DPN. This retrospective study revealed that the level 25-(OH) D was lower in AG patients than in SG patients. Additionally, in VDI patients (<30 ng/mL 25-(OH) D), the risk of neurological symptoms was higher with relatively higher levels of 25-(OH) D. For every 6 ng/mL increase in 25-(OH) D, the risk of numbness and pain increased by 0.5-fold. The opposite correlation was found in the VDS (≥30 ng/mL 25-(OH) D) group; the SG patients had relatively lower serum 25-(OH) D levels than AG patients. For every 4 ng/mL decrease in 25-(OH) D levels, the risk of numbness and pain increased by 0.2-fold. This suggests that relative vitamin D levels in different vitamin D states (VDI vs VDS) are reversely correlated with symptoms of diabetic neuropathy. As such, treating DPN patients with vitamin D may contribute to various degrees of diabetic peripheral neurological symptoms. These insights provide a new potential pathway for treating DPN.

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Recent studies have reported that VDD is associated with the development of DPN in patients with T2D, and Asian diabetic patients with VDD are 1.22 times more likely to suffer from DPN [18]. Fan et al [19] also found that 25-(OH) D3 levels were lower in DPN and DN groups than in non-diabetic peripheral neuropathy (NDPN) and non-diabetic neuropathy (NDN) groups. VDD is an independent risk factor for DPN and DN [19].

The pathogenesis of DPN remains unclear. NGF deficiency can lead to the development of clinical diabetic small fiber neuropathy [20], and has been indicated as a potential therapeutic for peripheral neuropathies [21]. Vitamin D can promote NGF secretion. A vitamin D3 derivative was shown to induce NGF and prevent neurotrophic deficits in streptozotocin-diabetic rats [22-24]. 1,25-dihydroxyvitamin D3 regulates the synthesis of NGF in primary glial cultures [25], and vitamin D analogs have also been reported to be effective in inducing NGF in human cell lines [20,26].

There was a positive correlation reported between vitamin D and serum NGF in patients with type 1 diabetes and neuropathy recently [27]. Serum 25-(OH) D3 was inversely correlated with neuropathy, but positively correlated with NGF levels [28]. Vitamin D was deactivated by the CYP24A1 enzyme in the presence of glucotoxicity in Schwann cells, which can lead to decreased vitamin D-mediated NGF secretion [28], which can result in small nerve fiber neuropathy.

Our results in the VDS (≥30 ng/mL 25-(OH) D) group were consistent with many previous studies [18,19]. It was suggested that adequate 25-(OH) D can alleviate neurological symptoms. With the decrease of vitamin level, the cold detection threshold also was significantly reduced [29]. In addition, the decreased secretion of NGF mediated by vitamin D can also lead to small nerve fiber neuropathy [20]. Under the influence of the above factors, the lower the level of vitamin D, the more serious the symptoms of DPN.

The most unexpected finding was that the risk of diabetic neurological symptoms increased with relatively higher of vitamin D levels in the VDI group. Similarly, Abdelsadek et al found that serum levels of 25-(OH) D in patients with painless DPN were lower than in patients with painful DPN [30]. Also, the serum level of 25(OH) vitamin D had a statistically significant negative correlation with severity of DPN as regards to neuropathy disability score (NDS) and nerve conduction studies [30]. Blocking NGF activity has been to shown to have potential for normalizing neuronal hyperactivity and producing sustained clinical pain relief [31-35]. However, serum 25-(OH) D3 was positively correlated with NGF. We speculate that, in the VDI group, a slight increase in vitamin D levels led to severe symptomatic reactions because they may be more sensitive to NGF increases resulting from long-term VDI than VDS. Furthermore, vitamin D deficiency also impairs nociceptor function, worsens nerve damage, and lowers the pain threshold. As vitamin D levels increased, the risk of pain increased, and further investigation is needed to explore this. Alam et al found that high-dose intramuscular treatment with vitamin D3 improved neuropathy-specific quality of life in patients with painful diabetic neuropathy, particularly those with VDD, but did not change painful symptoms, paresthesia, loss of temperature sensation, or loss of touch sensation [36]. As vitamin D levels increased, the risk of pain increased, and more research on this is needed.

In previous studies [36-38], some subjects were DPN patients with VDI, and some studies did not group subjects according to vitamin D levels, but the proportion of DPN patients with VDD was more than 40%. Neurological symptoms were measured more than 1 week after vitamin D supplementation; however, these studies did not mention whether any of the symptoms actually worsened during the initial stage of treatment. Our results suggest that vitamin D supplementation can lead to worse diabetic peripheral neurological symptoms in diabetic peripheral neuropathy patients with VDI. Therefore, when type 2 diabetes patients are given vitamin D supplements, particularly for those with VDI, we should consider starting at lower vitamin D doses; or in the early stage of vitamin D treatment for patients with VDI, we should pay more attention to communicating with patients, informing them that pain may increase in short term, and advising them to persist in treatment for a long time.

This study also has some limitations. It was a cross-sectional study, lacking data about long-term supplementation of vitamin D in patients. Future follow-up studies should address whether supplementation with vitamin D aggravates neuropathic symptoms in patients with VDI. The effect of vitamin D supplementation on the symptoms of diabetic neuropathy should be observed after correcting the VDI. When VDI is corrected, will diabetic neurological symptoms decrease with higher levels of vitamin D?

Conclusions

Relative vitamin D levels in different vitamin D states were reversely correlated with symptoms of DPN. Relatively higher vitamin D levels are associated with neurological symptoms in VDI diabetes mellitus patients. We should consider that vitamin D supplementation may lead to increased neurological symptoms in diabetic patients with VDI; however, if VDI is corrected to sufficient levels, this risk of increased neurological symptoms may no longer exist.

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Conflict of Interest

None declared.

Data Availability

The data used to support the findings of this study have not been made available.

Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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