Vitamin D Levels are Associated with Painful Diabetic Peripheral Neuropathy in Chinese Patients with Type 2 Diabetes Mellitus

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ABSTRACT

This study was aimed to evaluate the relationship between vitamin D and painful diabetic peripheral neuropathy (painful-DPN) in Chinese patients with type 2 diabetes mellitus (T2DM). A total of 478 patients with T2DM were enrolled in this cross-sectional study, 127 of whom had painful-DPN and 351 of whom had painless diabetic peripheral neuropathy (painless-DPN). Detailed data including basic information, anthropometric measurements, laboratory examinations and neurological assessments were collected for all patients. Painful-DPN was diagnosed through neurological assessments, including neuropathy symptom score (NSS), neuropathy disability score (NDS), nerve conduction studies and the visual analogue scale. The results showed that serum vitamin D levels were significantly lower in patients with painful-DPN than patients with painless-DPN (p=0.012). Pain scores, NSS and NDS were negatively associated with vitamin D levels, while motor nerve conduction velocities, motor and sensory nerve amplitudes were positively associated with vitamin D levels (all p<0.05). After adjustment for age, sex, diabetes duration, smoking, diabetic kidney disease and diabetic retinopathy, diabetic blood pressure, parathyroid hormone and HbA1c, serum vitamin D levels were independently associated with painful-DPN based on logistic regression assessments (p=0.039). Moreover, diabetic retinopathy and sex were independently associated with painful-DPN (p=0.031; p=0.005, respectively). Receiver operating characteristic analysis demonstrated that serum vitamin D levels <10.3 ng/mL were predictive of the risk of painful-DPN (p<0.05). These findings revealed that lower serum vitamin D levels were significantly associated with painful-DPN. Further studies are needed to explore the causal relationship and pathophysiology of painful-DPN.

Abbreviations: Painful-DPN: Painful Diabetic Peripheral Neuropathy; DPN: Diabetic Peripheral Neuropathy; T2DM: Type 2 Diabetes Mellitus; RCTs: Randomized Controlled Trials; painless-DPN: Painless Diabetic Peripheral Neuropathy; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Glycosylated Hemoglobin;UA: Uric Acid; hs-CRP: Hypersensitive C-Reactive Protein; Ca: Calcium; P: Phosphorus; Mg: Magnesium; PTH: Parathyroid Hormone; eGFR: Estimated Glomerular Filtration Rate; 25(OH)D: 25-Hydroxyvitamin D; NSS: Neuropathy Symptom Score; NDS: Neuropathy Disability Score; HRV: Heart Rate Variability; VAL: Valsalva; VAS: Visual Analogue Scale; SD: Standard Deviation; CI: Confidence Interval; OR: Odds Ratio; AUC: Area Under The Curve; NGF: Nerve Growth Factor
Introduction

Painful diabetic peripheral neuropathy (painful-DPN) is one of the most common phenotypes of diabetic neuropathies. According to the literature, the prevalence of painful-DPN ranges from 3.3% to 65.3% in patients with diabetes [1-3]. Painful-DPN affects patients’ health-related quality of life and social function and increases their health care costs [4]. Although many studies have investigated the mechanism of pain in patients with diabetic peripheral neuropathy (DPN), the specific pathophysiology of painful-DPN is not well understood [5].

Vitamin D has a well-known role in the regulation of bone metabolism and calcium homeostasis. During recent years, studies have suggested that vitamin D is associated with dozens of diseases, such as cardiovascular diseases, autoimmune diseases, cancers, and metabolic syndrome, including type 2 diabetes mellitus (T2DM) [6-8]. Many studies have further evaluated the relationship between serum vitamin D levels and DPN in patients with type 2 diabetes [9-12]. A meta-analysis including 1368 individuals with type 2 diabetes showed a significant association between vitamin D deficiency and DPN [13]. Those findings link vitamin D with DPN. Meanwhile, several observational studies have reported that patients with chronic pain have low serum vitamin D levels [14,15]. A number of Randomized Controlled Trials (RCTs) using vitamin D for the treatment of pain have been conducted. A meta-analysis including 19 RCTs found that vitamin D supplementation led to a significantly greater mean decrease in pain score compared to placebo in patients with chronic pain [16].

Based on these findings, we hypothesize that serum vitamin D levels may be related to painful-DPN. However, most studies reporting the relationship between vitamin D and DPN have not assessed the differences in serum vitamin D levels between painful-DPN and painless diabetic peripheral neuropathy (painless-DPN) in patients with T2DM. There is also a lack of reports in Chinese patients. Therefore, the aim of this study was to investigate the association between serum vitamin D levels and painful-DPN in T2DM in Chongqing, China.

Patients and Methods

Study Design and Patients

This was a cross-sectional study, and patients with T2DM were consecutively recruited from the First Affiliated Hospital of Chongqing Medical University from May 2018 to January 2019. The diagnosis of T2DM was based on World Health Organization criteria. Participants ≥18 years old who were using oral hypoglycemic agents and (or) insulin were included in the study. The exclusion criteria were as follows:

a) Non-diabetic neuropathies
b) Non-neuropathic pain
c) Neuropathic pain due to other causes than DPN
d) Central nervous system lesions
e) Regular or high-dose vitamin D or calcium supplementation. This study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (number 2018-008). All participants provided written informed consent.

Basic Information and Anthropometric Measurements

Patients’ basic information including age, sex, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), duration of diabetes, smoking, family history of diabetes and hypertension, and presence of diabetic retinopathy and diabetic kidney disease were collected through a questionnaire. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. Current smokers or ex-smokers were defined as smokers. The diagnosis of diabetic kidney disease and diabetic retinopathy was performed according to the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China [17].

Laboratory Measurements

The laboratory profile included Glycosylated Hemoglobin (HbA1c), Uric Acid (UA), Hypersensitive C-Reactive Protein (hs-CRP), Calcium (Ca), Phosphorus (P), Magnesium (Mg), Parathyroid Hormone (PTH), Estimated Glomerular Filtration Rate (eGFR) and 25-hydroxyvitamin D [25(OH)D]. HbA1c was measured through high-pressure liquid chromatography (premier Hb9210, Primus, USA). UA was evaluated through an enzymatic method, and hs-CRP was tested through immunoturbidimetry (Cobas c701, Roche, Germany). Ca, P and Mg levels were measured according to colorimetry (Cobas c701, Roche, Germany). PTH was detected through a chemiluminescence assay (Beckman Coulter, USA). The eGFR was calculated using the CKD-EPI equation [18]. The levels of 25(OH)D in serum or plasma indicated the vitamin D status. A Liaison® 25 OH Vitamin D TOTAL Assay (DiaSorin Inc, USA) was used to measure the serum levels of 25(OH)D.

Neurological Measurements

The Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS) have been widely used for screening of DPN in recent years [19-21]. Symptoms of DPN were assessed by the NSS, including symptoms of pain, cramps, numbness or aching in the legs, location of symptoms (feet, calves, elsewhere), timing of symptoms (present only during the day, both day and night, nocturnal exacerbation, ever awaken the patient from sleep) and ways to relieve the pain or discomfort (walking, standing, sitting or lying down). Signs of DPN were evaluated on the basis of the NDS, including an examination of pin-pricks, temperature sensation, vibration sensation with a 128-Hz tuning fork, and ankle reflexes.
The diagnostic criteria for DPN according to the NSS and the NDS scores were as follows:

a) Moderate or severe neuropathic signs (NSS≥7, NDS≥9)
b) Mild neuropathic signs (NSS=5–6; NDS=3–5)

c) Mild neuropathic symptoms (NSS=5–6 or NSS=7–9). Of note, mild neuropathic signs or symptoms were not diagnostic criteria for DPN (NSS=3–5, NDS=3–4) [19]. DAN was diagnosed according to heart rate variability (HRV) during deep breathing (≥10 times/min) and the valsalva (VAL) maneuver (ratios≥1.10).

Electrophysiological examinations were performed on each participant with a Dantec Keypoint full-function electromyographic evoked potential machine (Dantec Dynamics A/S, Denmark, Copenhagen). Nerve conduction of the tibial, peroneal, ulnar, radial, and median motor nerves, and the tibial, sural, ulnar, radial, and median sensory nerves on both sides, including nerve conduction velocity, amplitude, and latency, was assessed. All participants’ limb temperatures were maintained between 33℃ and 35℃. Diagnosis of neuropathy was performed according to the corresponding reference for Chinese people [22]. If participants had previous results, electrophysiological examinations were not repeated.

### Pain Assessment

Pain was evaluated with the Visual Analogue Scale (VAS) [23], a 1–10 cm long ruler. We assessed current pain intensity, and minimum and maximum pain intensity during the preceding 2 weeks. The participants were instructed to place a sliding gauge at a point on the ruler representing their pain experience. Patients with DPN were further divided into two groups on the basis of the VAS scores:

a) Painless-DPN: VAS=0
b) Painful-DPN: VAS>0; respectively.

### Statistical Analysis

All analyses were conducted in the statistical package SPSS Version 23.0 (SPSS, IBM Corp, Armonk, NY, USA). The normality of the data was evaluated by using the Shapiro–Wilk test. Histograms, Q–Q plots, and variance homogeneity were evaluated by using Levene’s test. Continuous variables with normal distribution are described as mean [Standard Deviation (SD)] and compared using independent samples t-tests. Non-normal continuous variables are presented as median and interquartile range and are compared with Mann–Whitney U tests. Categorical variables are presented as frequencies and percentages and compared with chi-square analyses. Spearman’s correlation analyses were used to evaluate the relationships between vitamin D and pain scores, NSS, NDS and nerve conduction studies. Logistic regression analysis was performed to identify the effects of independent factors on painful-DPN. Candidate variables that had a p-value <0.1 in univariate analyses or that were considered clinically relevant were entered into a multivariable model. By considering the number of events available, we carefully chose the variables included to ensure parsimony of the final model. A receiver-operating characteristic curve was used to find the best cut-off of vitamin D for predicting the risk of painful-DPN. The threshold for statistical significance was set at p<0.05.

### Results

#### Sample Characteristics

A total of 478 patients with T2DM (painful-DPN: n=127; painless-DPN: n=351) participated in the study. Table 1 summarizes the demographic and laboratory data for each group. The patients with painful-DPN included more women (p=0.001), more smokers (p=0.001), and more patients with diabetic kidney disease and diabetic retinopathy (p=0.044 and p=0.001, respectively). Painful-DPN patients were also older and had a longer duration of diabetes (p=0.046, p=0.026, respectively). Patients in the painless-DPN group had higher DBP and higher levels of HbA1c (p=0.011, p=0.026, respectively). Serum vitamin D levels in patients with painful-DPN were lower than those in patients with painless-DPN (p=0.012). Moreover, patients with painful-DPN had higher pain scores (VAS), NSS and NDS than patients with painless-DPN (all p<0.01). The conduction velocity of peroneus motor nerve and tibialis, median sensory nerves in patients with painful-DPN was lower than those in patients with painless-DPN (all p<0.01). The amplitude of tibialis and median motor nerves in patients with painful-DPN was lower than those in patients with painless-DPN (all p<0.01). There was no significant difference in amplitude of all sensory nerves between groups (all p>0.05) (Table 1&2).

### Table 1: Demographic and laboratory data.

| Characteristic          | Painful-DPN(n=127) | Painless-DPN(n=351) | P  |
|------------------------|--------------------|---------------------|----|
| Female, n (%)          | 80(63.0)           | 133(37.9)           | <0.001 |
| Age (year)             | 66(39.7)           | 62(34.7)            | 0.046  |
| BMI(kg/m²)             | 24.1(21.9,26.1)    | 23.8(22.2,26.0)     | 0.888  |
| SBP(mmHg)              | 136.8(18.9)        | 134.9(20.7)        | 0.330  |
| DBP(mmHg)              | 74.2(10.1)         | 77.0(12.4)         | 0.011  |
| Diabetes duration(year)| 12(7,19)           | 10(5,17)            | 0.026  |
| Smoker, n (%)          | 35(27.6)           | 163(46.4)           | <0.001 |
| DM family history, n (%) | 48(37.8)         | 132(38.0)           | >0.999 |
The association of serum vitamin D levels with Neuropathy parameters

Spearman’s correlation analysis showed that the pain scores (VAS), NSS and NDS were negatively associated with serum vitamin D levels ($p<0.05$). There was no significant correlation between serum vitamin D and DAN and HRV during deep breathing ($p=0.858$; $p=0.379$, respectively). VAL showed a positive correlation with serum vitamin D levels ($p=0.008$). There was a significant positive correlation between serum vitamin D levels and conduction velocity of the tibial, peroneal, ulnar, and median motor nerves ($p<0.05$). All sensory nerve conduction velocities showed no significant correlation with serum vitamin D levels (all $p>0.05$) (Table 2). There is also a significant positive correlation between serum vitamin D levels and amplitude of tibialis, peroneus, ulnar and median motor nerves and amplitude of tibialis, ulnar sensory nerves ($p<0.05$) (Table 3).

Table 2: Spearman’s correlation analysis between vitamin D and neuropathy parameters.

| Characteristic                          | r    | p   |
|----------------------------------------|------|-----|
| VAS score                              | -0.114 | 0.013 |
| NSS                                    | -0.120 | 0.018 |
| NDS                                    | -0.145 | 0.004 |
| Autonomic neuropathy (%)               | 0.056 | 0.135 |
| HRV                                    | 0.064 | 0.379 |
| Results of VAL                         | 0.191 | 0.008 |
| Motor nerve conduction (m/s)           |      |     |
| Right tibialis                         | 0.011 | 0.863 |
| Left tibialis                          | 0.138 | 0.030 |
| Right peroneus                         | 0.211 | 0.001 |
| Left peroneus                          | 0.226 | <0.001 |
| Right ulnar                            | 0.010 | 0.905 |
| Left ulnar                             | 0.232 | 0.006 |
| Right radial                           | 0.046 | 0.580 |
| Left radial                            | 0.048 | 0.570 |
| Right median                           | 0.117 | 0.184 |
| Left median                            | 0.179 | 0.041 |

The Relationship between Vitamin D and Painful-DPN

The effects of ten independent variables (age, sex, diabetes duration, smoking, diabetic kidney disease and diabetic retinopathy, DBP, PTH, HbA1c and vitamin D) on painful-DPN were explored by logistic regression analysis. The full model was statistically significant ($P<0.001$). As shown in Table 3, the serum vitamin D levels were significantly associated with painful-DPN ($p=0.039$, OR=0.964, 95% confidence interval (CI): 0.932-0.998). For every 1 ng/mL increase in serum vitamin D level, the odds ratio (OR) of painful-DPN was reduced by 3.60%. Furthermore, diabetic retinopathy and sex were independently associated with painful-DPN ($p=0.031$, OR=1.813, 95%CI: 1.057-3.110; $p=0.005$, OR=2.211, 95%CI: 1.277-3.830; respectively). In receiver-operating characteristic curve analysis, the Area Under the Curve (AUC) was 0.674 (95%CI: 0.620 to 0.728, $p<0.001$). The optimal cut-off of vitamin D was 10.3ng/mL, and the corresponding Youden index was 0.26 (sensitivity: 78.0%; specificity: 48.0%) (Figure 1).
Table 3: Logistic regression for related factors of painful-DPN.

| Parameter                   | OR(95% CI)     | p   |
|-----------------------------|----------------|-----|
| vitamin D                   | 0.964(0.932-0.998) | 0.039 |
| Gender                      | 2.211(1.277-3.830) | 0.005 |
| Diabetic retinopathy        | 1.813(1.057-3.110) | 0.031 |

Discussion

This study demonstrated that patients with painful-DPN had lower serum vitamin D levels than patients with painless-DPN. Pain scores and neuropathy parameters were significantly associated with vitamin D levels. Serum vitamin D levels were independently associated with painful-DPN in patients with T2DM. Moreover, diabetic retinopathy and sex were independently related to painful-DPN. A serum vitamin D level <10.3 ng/mL was a significant predictor of the risk of painful-DPN. Previous studies have found that lower vitamin D levels are prevalent in patients with T2DM, especially in those with DPN [9-11,24]. Shillo et al. have reported that serum vitamin D levels were lower in patients with painful-DPN than in those with painless-DPN, and pain scores were negatively correlated with serum vitamin D levels [25]. These findings are in line with our results. However, the finding of Alkhatabeh et al. was inconsistent with above findings [26]. Meanwhile, the relationship between serum vitamin D levels and neuropathy parameters in type 2 diabetics with painful-DPN is also controversial. In patients with DPN, lower vitamin D levels have been reported to correlate with NDS and nerve conduction studies. For every 1 ng/mL increase in vitamin D, there was 2.2% and 3.4% lower risk of the presence and severity of NCV impairment, respectively [27,28].

In patients with painful-DPN, Shillo et al. did not find a significant association between nerve conduction studies, DAN, and serum vitamin D levels, although HRV during deep breathing was significantly correlated with serum vitamin D levels [25]. However, our results showed that serum vitamin D levels were significantly associated with VAL, motor nerve conduction velocity and motor and sensory nerve amplitude, but not with DAN and sensory nerve conduction velocity. In addition, NSS and NDS showed a negative correlation with serum vitamin D levels in our study. The discrepancies between the results of our study and previous studies may be due to the different races and sample sizes. Furthermore, a research letter and an interventional study (without control group) have reported that vitamin D supplementation can relieve neuropathic pain in patients with T2DM, and vitamin D may play a role in the treatment of painful-DPN [29,30]. In addition, a recent observational study found that lower vitamin D levels were significantly associated with painful-DPN, compared to painless-DPN, no-DPN, and healthy volunteers [25].

The findings of our study are consistent with those results. Consequently, vitamin D may play a role in the pathophysiology of painful-DPN. Some possible mechanisms are as follows. Nerve growth factor (NGF) is well known to be beneficial for neurons [31,32]. A vitamin D3 derivative (CB1093) has been found to increase NGF concentrations in diabetic rats [33], and active Vitamin D3 (tacalcitol) has been shown to promote expression of NGF [34]. After correction of the vitamin D deficiency, NGF production increases. Therefore, vitamin D3 may be useful for preventing and treating neurotrophic deficits. Importantly, vitamin D3 (cholecalciferol) supplementation has been found to relieve neuropathic pain in rats by inducing the dysregulation of multiple genes, an effect associated with modulating opioid signaling [35]. Interestingly, another cross-sectional study using the PainDETECT questionnaire to assess neuropathic pain showed that serum vitamin D was not associated with neuropathic pain in patients with T2DM [26]. The inconsistency may be due to the different races, sample sizes and different diagnosis criteria of painful-DPN.

Diabetic retinopathy was independently associated with painful-DPN in the present study. A previous study in the Middle East has demonstrated that diabetic retinopathy was significantly related to painful-DPN, using the Douleur Neuropathique-4 [36]. Microangiopathy is an important basis of DPN [37]. Diabetic retinopathy is one of the most common microangiopathies in diabetes mellitus. These findings suggest that microangiopathy may also play a role in the development of painful-DPN. In agreement with our results, sex was independently associated with painful-DPN in several studies [2,26,36,38,39]. Females experienced a higher frequency of neuropathic pain among diabetic patients, possibly because they have higher sensitivity and exhibit protective effects in multiple sensory domains [40]. Therefore, sex should also be considered in the detection and treatment of painful-DPN. He et al. reported the cut-off value of vitamin D for predicting the occurrence of DPN to be 16.01 ng/mL [11]. However, our study found a lower cut-off value of serum vitamin D for predicting the risk of painful-DPN (10.3 ng/mL). Notably, the cut-off value of vitamin D did not have strong sensitivity or specificity in screening for painful-DPN. This result may be because painful-DPN is a multifactorial disease, and vitamin D levels are susceptible to other factors, such as diet and sunlight exposure.

Our study demonstrated that serum vitamin D levels were significantly associated with painful-DPN, a finding that may support future exploration of the mechanisms of painful-DPN and provide a new direction for the prevention and treatment of painful-DPN. However, there are several limitations to this study. First, this study was a lack of more sensitive measures for small fiber neuropathy (than HRV and VAL) such as skin biopsy. Due to the lack of translated and sinicized neuropathic pain questionnaires in China, no neuropathic pain questionnaires were used to screen for painful-DPN in this study. Moreover, because of the cross-sectional design, a conclusion of cause and effect between the variables and painful-DPN cannot be inferred. In addition, the cutoff value of vitamin D in predicting painful-DPN could not be confirmed. Furthermore, we did not assess the effects of confounding factors.
including sunlight exposure and diet on serum vitamin D levels. Finally, this was also a single-center study, and more studies are necessary to verify our findings.

**Conclusion**

In this cross-sectional study, we found that higher serum vitamin D levels may play a protective role in painful-DPN in Chinese individuals with type 2 diabetes. Serum vitamin D levels <10.3 ng/mL may predict the risk of painful-DPN. Further large studies are needed to verify our findings and explore the underlying mechanisms.

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**Conflict of Interest**

The authors have no conflicts of interest to disclose.

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