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Research Article

The role of Vitamin D deficiency in neuropathic pain following Herpes Zoster: a retrospective cohort study

Herpes zoster sonrası nöropatik ağrıda D vitamini eksikliğinin rolü: retrospektif kohort çalışması

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Abstract

Aim: Postherpetic neuralgia (PHN) is the most common complication of herpes zoster infection that significantly impacts quality of life. In this context, the objective of this study is to investigate the relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and the severity, duration, and neuropathic symptoms of PHN.

Material and Methods: The sample of this retrospective observational cohort study consisted of 71 patients who were followed up with a diagnosis of PHN between January 2020 and June 2024. Patients were stratified into three groups according to their serum 25(OH)D levels as patients with vitamin D deficiency (≤20 ng/mL, n=24), vitamin D insufficiency (21-29 ng/mL, n=26), and vitamin D sufficiency (≥30 ng/mL, n=21). Patients' neuropathic pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire and the Numeric rating scale (NRS). Inflammatory parameters such as C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and leukocyte count were recorded for each patient, and the diagnostic performance of their serum 25(OH)D levels was evaluated by receiver operating characteristic (ROC) curve analysis.

Results: The mean DN4 and NRS scores and pain duration of the patients with vitamin D deficiency were significantly higher than those of other patients (5.83±1.76 vs. 1.71±0.96, p<0.001; 8.92±1.59 vs. 6.29±2.43, p=0.001; 93.54±41.23 vs. 31.86±35.80 days, p<0.001; respectively). Serum 25(OH)D level was strongly correlated with DN4 score (r=-0.758; p<0.001), pain duration (r=-0.640; p<0.001) and NRS score (r=-0.497; p<0.001) in the negative direction. Pins-and-needles sensation and brush-evoked pain were significantly more common in patients with vitamin D deficiency than in other patients (p<0.001). Mean CRP and ESR values of patients with vitamin D deficiency were significantly higher than those of other patients (11.99±14.56 vs. 6.99±12.38 mg/L, p=0.046 and 25.71±16.58 vs. 13.75±7.01 mm/hour, p=0.007; respectively). ROC analyses revealed that the optimal serum 25(OH)D cut-off levels to predict patients with a DN4 score ≥4 and pins-and-needles sensation were 21.15 ng/mL (area under the curve [AUC]=0.862) and 25.85 ng/mL (AUC=0.930), respectively.

Conclusion: Low serum vitamin D levels were associated with increased neuropathic pain intensity, prolonged pain duration, and increased inflammatory response in patients with PHN. In conclusion, vitamin D level may be a valuable biomarker for predicting the clinical course of PHN and determining appropriate treatment strategies.

Keywords: postherpetic neuralgia, vitamin D deficiency, DN4 score, neuropathic pain, herpes zoster

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Öz

Amaç: Postherpetik nevralji (PHN), herpes zoster enfeksiyonunun yaşam kalitesini önemli ölçüde etkileyen en yaygın komplikasyonudur. Bu bağlamda, bu çalışmanın amacı serum 25-hidroksivitamin D [25(OH)D] düzeyleri ile PHN'nin şiddeti, süresi ve nöropatik semptomları arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif gözlemsel kohort çalışmasının örneklemi, Ocak 2020 ile Haziran 2024 arasında PHN tanısı ile takip edilen 71 hastadan oluşmaktadır. Hastalar serum 25(OH)D düzeylerine göre D vitamini eksikliği (≤20 ng/mL, n=24), D vitamini yetersizliği (21-29 ng/mL, n=26) ve D vitamini yeterliliği (≥30 ng/mL, n=21) olan hastalar olarak üç gruba ayrılmıştır. Hastaların nöropatik ağrıları nöropatik ağrı 4 (DN4) anketi ve Numerik derecelendirme ölçeği (NRS) kullanılarak değerlendirilmiştir. Her hasta için C-reaktif protein (CRP) düzeyi, eritrosit sedimentasyon hızı (ESR) ve lökosit sayısı gibi inflamatuar parametreler kaydedilmiş ve serum 25(OH)D düzeylerinin tanısal performansı alıcı işletim karakteristiği (ROC) eğrisi analizi ile değerlendirilmiştir.

Bulgular: D vitamini eksikliği olan hastaların ortalama DN4 ve NRS skorları ile ağrı süreleri diğer hastalara göre anlamlı derecede yüksekti (5,83±1,76'ya karşı 1,71±0,96, p<0,001; 8,92±1,59'a karşı 6,29±2,43, p=0,001; 93,54±41,23'e karşı 31,86±35,80 gün, p<0,001; sırasıyla). Serum 25(OH)D düzeyi, DN4 skoru (r=-0,758; p<0,001), ağrı süresi (r=-0,640; p<0,001) ve NRS skoru (r=-0,497; p<0,001) ile negatif yönde güçlü korelasyon gösterdi. İğnelenme hissi ve fırçayla uyarılan ağrı, D vitamini eksikliği olan hastalarda diğer hastalara göre anlamlı derecede daha yaygındı (p<0,001). D vitamini eksikliği olan hastaların ortalama CRP ve ESR değerleri diğer hastalara göre anlamlı derecede yüksekti (11,99±14,56'ya karşı 6,99±12,38 mg/L, p=0,046 ve 25,71±16,58'e karşı 13,75±7,01 mm/saat, p=0,007; sırasıyla). ROC analizleri, DN4 skoru ≥4 olan hastaları ve iğnelenme hissini tahmin etmek için optimal serum 25(OH)D kesme düzeylerinin sırasıyla 21,15 ng/mL (eğri altında kalan alan [AUC]=0,862) ve 25,85 ng/mL (AUC=0,930) olduğunu ortaya koydu.

Sonuç: Düşük serum D vitamini düzeyleri PHN hastalarında artmış nöropatik ağrı yoğunluğu, uzamış ağrı süresi ve artmış inflamatuar yanıt ile ilişkilendirilmiştir. Sonuç olarak, D vitamini düzeyi PHN'nin klinik seyrini tahmin etmek ve uygun tedavi stratejilerini belirlemek için değerli bir biyobelirteç olabilir.

Anahtar kelimeler: postherpetik nevralji; d vitamini eksikliği; dn4 skoru; nöropatik ağrı; herpes zoster

Introduction

Vitamin D plays a vital role in regulating calcium and phosphate metabolism and maintaining a healthy mineralized skeleton. Vitamin D exists in two main forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), and each form has different sources. Vitamin D3 is synthesized in vertebrates, including humans, by the conversion of 7-dehydrocholesterol in the skin due to exposure to ultraviolet B light. Vitamin D3 is also found in animal-sourced foods, including fatty fish such as salmon, mackerel, and sardines. On the other hand, vitamin D2 is found in plants and fungi, primarily in those exposed to sunlight or UV light, and in yeast. Vitamin D2 is synthesized from ergosterol, a compound found in fungi and yeast [1].

The Endocrine Society's Clinical Practice Guidelines for Preventing Vitamin D Deficiency state that serum 25-hydroxyvitamin D 25(OH)D3 levels below 20 ng/mL (50 nmol/L) and between 21 and 29 ng/mL (52.5–72.5 nmol/L) indicate vitamin D deficiency and insufficiency, respectively [2]. Serum 25-hydroxyvitamin D 25(OH)D3 levels below 30 ng/mL (75 nmol/L) are considered to indicate hypovitaminosis D [3]. Major risk factors for hypovitaminosis D include poor nutrition, limited sunlight exposure, and low physical activity. Suboptimal vitamin D levels have been associated with calcium imbalance, impaired glucose and lipid metabolism, increased oxidative stress, inflammation, and endothelial dysfunction [4]. Vitamin D not only plays a role in establishing calcium and phosphate balance, but also has versatile effects on the immune system. Specifically, vitamin D strengthens the first line of defense against infections, particularly by increasing the synthesis of antimicrobial peptides such as cathelicidin and defensin within the scope of innate immune response. Vitamin D also contributes to the limitation of viral replication by supporting the expression of interferon-alpha and antiviral microribonucleic acids (miRNAs). In the context of the adaptive immune system, vitamin D helps prevent excessive immune reactions such as cytokine storms by suppressing the proinflammatory type 1 T helper (Th1) response and promoting

the immune system's shift to a more regulatory type 2 T helper (Th2) response [5]. Given these effects, vitamin D is considered to play a critical immunomodulatory role in the control of viral infections and the alleviation of related immunopathologies. Following the healing process after varicella-zoster virus (VZV) infection, viral particles migrate to the dorsal root ganglion of the relevant dermatome and become latent there. VZV reactivates with weakening of cellular immunity, leading to herpes zoster (HZ) infection. During the reactivation process of HZ, VZV causes inflammation in the dorsal root ganglion, which has significant effects on both the involved nerve fibers and the dermatomal region. Necrosis and scar tissue developing in the dorsal root ganglion lead to secondary degeneration of motor and sensory nerves. The axonal and myelin damage that occurs during this process disrupts nerve conduction, progresses towards the periphery, and causes a decrease in the density of nerve endings in the skin. The reduction in nerve endings leads to the decline in inhibitory sensory input, especially from A-β fibers. According to the gate control theory of pain, the lack of these inhibitory inputs results in inadequate suppression of pain signals carried via C and A-δ fibers in the dorsal horn. Clinically, patients describe burning pain, itching, and dynamic mechanical allodynia [6,7]. The painful vesicle clusters that initiate on an erythematous base, characterizing the HZ disease, are the clinical reflection of these neuropathological processes. These lesions pustule over time and usually crust over within 7–10 days. Complete shedding of these crusts is generally completed within 4 weeks. Patients in this process are prescribed acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) for mild-to-moderate (NRS score 4–6) pain, in addition to antiviral treatments. In cases where NSAIDs are insufficient, opioid analgesics may be necessary [8]. Rashes are often accompanied by pain and dysesthesia in the affected dermatome area. These symptoms may persist in some patients even after the rashes have healed. This prolonged pain, lasting more than three months from the onset or resolution of the rashes, is called postherpetic neuralgia (PHN) [9].

It has been suggested that vitamin D may affect neuropathic pain at both peripheral and central levels by suppressing proinflammatory cytokines and regulating the synthesis of neurotrophic factors such as nerve growth factor (NGF) in dorsal root ganglion neurons[10,11]. Observational studies have suggested that individuals with low serum 25-hydroxyvitamin D [25(OH)D] levels may be at higher risk of developing PHN [3,9,12–16]. Vitamin D inhibits concentration-dependent nitric oxide (NO) production in glia and astrocytes while increasing phosphorylated N-methyl-D-aspartate (NMDA) receptors in spinal dorsal horn neurons. It has been reported that these receptors are necessary for the initiation of central sensitization and the development of mechanical allodynia [3]. However, the available evidence is conflicting. Some randomized controlled trials and meta-analyses have supported this relationship, while others have reported no statistical significance [17]. Furthermore, it remains unclear whether low vitamin D levels are a causative factor in the development of PHN or merely a comorbid condition. Considering the worldwide prevalence of vitamin D deficiency and the clinical burden caused by PHN, investigating the relationship between serum vitamin D levels and characteristics of pain, such as its severity and duration, in HZ patients is becoming increasingly important from a clinical perspective.

In light of this information, this study's primary objective is to analyze the potential relationship between serum 25(OH)D levels and the severity, duration, and neuropathic components of postherpetic pain, and the secondary objective is to evaluate the potential relationship between the inflammatory response and vitamin D levels.

Material and Methods

Study Design and Setting

This study was designed as a retrospective observational single-center cohort study. The study protocol (Protocol Number: E-60116787-020-548385) was elaborated in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Date: 02.07.2024, Decision No: 12). The study was conducted between January 2020 and June 2024 at the Algology Polyclinic of Pamukkale University Faculty of Medicine in Denizli, Türkiye. The study was reported per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Population and Sample

Patients' medical records, including demographic characteristics, comorbidities, HZ involvement area, and season of admission, were retrospectively accessed from the electronic records system and evaluated. The study population consisted of 87 consecutive patients with PHN who were diagnosed with HZ by the dermatology clinic and subsequently referred to the algology unit. The study's inclusion criteria were having a clinically confirmed HZ

diagnosis by a dermatologist, having been examined at least twice in the algology outpatient clinic due to PHN, having serum 25(OH)D level measured at first admission, having been assessed using standardized pain assessment tools, having being started on pharmacological pain treatment, and that other causes of neuropathic pain were excluded after clinical evaluation. On the other hand, the study's exclusion criteria were having a history of human immunodeficiency virus (HIV) infection or organ transplantation, not having attended regular follow-up visits after treatment, not having given consent to participate in the study, and having been using medications that affect vitamin D metabolism, such as glucocorticoids, antiepileptics, hydralazine, and thiazide diuretics. Accordingly, a total of 16 patients, 2 with a history of organ transplantation, 4 who did not give consent, 5 who did not attend follow-up visits, and 5 who did not meet the study's other inclusion criteria, were excluded from the study. In the end, the study sample consisted of 71 patients, who were stratified into three groups based on their serum 25(OH)D levels according to the Endocrine Society's Clinical Practice Guidelines for Preventing Vitamin D Deficiency [2], as patients with vitamin D deficiency (≤20 ng/mL, n = 24), vitamin D insufficiency (21-29 ng/mL, n = 26), and vitamin D sufficiency (≥30 ng/mL, n = 21) (Figure 1).

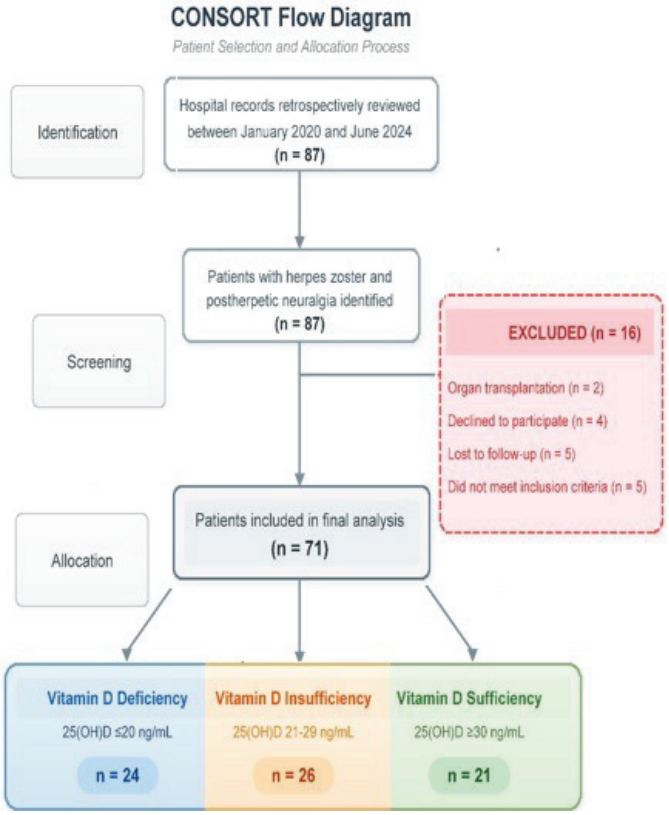

Figure 1. Flow diagram of patients included in the study.

Evaluation of Patients' Pain Levels

Patients' pain levels were assessed using two standardized assessment tools. The first of these, the neuropathic pain in 4 questions (DN4) questionnaire, is a validated tool that assesses the presence and characteristics of neuropathic pain through seven symptoms, i.e., burning pain, cold-evoked pain, electric shock-like pain, tingling, pins-and-needles sensation, pricking, numbness, and itching, and three clinical examination findings, i.e., touch hypoesthesia, pinprick hypoesthesia, and brush-evoked pain. Total DN4 scores of 4 or above indicate the presence of neuropathic pain. The second of these assessment tools, the numeric rating scale (NRS), assesses patients' average pain intensity over the last 24 hours on a scale of 0 (no pain) to 10 (unbearable pain).

Laboratory Tests

Patients' serum 25-hydroxyvitamin D levels were measured by chemiluminescence immunoassay test. Additionally, patients' inflammatory responses were assessed through their C-reactive protein (CRP) levels, erythrocyte sedimentation rates (ESR), and leukocyte counts.

Treatment Protocol

A stepwise approach is adopted in the treatment of HZ. The first-line treatment protocol for HZ includes antiviral agents, i.e., 3 x 1000 mg valacyclovir or 5 x 800 mg acyclovir for 7 days, maximum 3 g/day acetaminophen, and/or NSAIDs. Antiepileptic agents such as gabapentin or pregabalin were administered as second-line treatment to patients in whom adequate analgesia could not be achieved as a result of first-line treatment, i.e., patients with an NRS score or DN4 score of 4 and above.

Gabapentin treatment was initiated by administering 300 mg in the evening on the first day, 300 mg in the morning and evening on the second day, and 300 mg in the morning, noon, and evening on the third day. In the following days, the daily gabapentin dose was adjusted in three equal doses ranging from 1800 to 3600 mg, based on patient tolerance and clinical response. Patients were closely monitored for side effects and regularly followed up.

Pregabalin treatment was initiated with a daily dose of 150 mg divided into two equal doses and titrated up to 300 mg/day according to the tolerance and clinical response of the patients. Pregabalin was not primarily preferred as it could cause euphoria and withdrawal symptoms, and was thus used in patients who did not respond to gabapentin or developed side effects. Opioid analgesics such as tramadol or codeine were added to the treatment protocol if deemed necessary in patients with moderate-to-severe pain (NRS score 4-10) at any phase of the treatment.

Statistical Analysis

The statistical analyses of the collected data were conducted using SPSS 27.0 (Statistical Product and Service Solutions for Windows, Version 27.0, IBM Corp., Armonk, NY, U.S., 2020) software package. The results of the statistical analyses were reported using descriptive statistics, i.e., mean and standard deviation values in the case of normally distributed continuous variables, median values with interquartile ranges in the case of non-normally distributed continuous variables, and numbers and percentage values in the case of categorical variables. The conformity of continuous variables to normal distribution was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as visual tools, including histograms and Q-Q plots. Various statistical methods were used in the comparison of variables among the three study groups created according to serum 25(OH)D levels. Accordingly, one-way analysis of variance (ANOVA) test was used for comparing normally distributed continuous variables such as age and CRP level; Kruskal-wallis H test was used for comparing non-normally distributed continuous variables such as body mass index (BMI), pain duration, DN4 and NRS scores and ESR; and chi-square test was used for comparing categorical variables such as gender, presence of comorbidity, medication use and DN4 symptoms. Additionally, in multiple comparisons, Bonferroni correction was conducted to control the Type I error rate. The relationships between serum 25(OH)D levels and clinical and laboratory parameters were analyzed using correlation analyses. To this end, Pearson correlation coefficients were calculated for correlations involving normally distributed variables, and Spearman correlation coefficients were calculated for correlations involving non-normally distributed variables. In comparing serum 25(OH)D levels according to the presence of DN4 symptom components, the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic performance of serum 25(OH)D level in predicting neuropathic pain characteristics. To this end, Optimal serum 25(OH)D level cut-off levels were determined by the Youden index, and the corresponding area under the curve (AUC), sensitivity, and specificity values were calculated to assess the predictive power for brush-evoked pain, pins-and-needles sensation, and having a DN4 score of 4 and above. All statistical tests conducted were two-tailed and probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance. Missing data were addressed with the listwise deletion method. Imputation methods were not used since there was no data loss in relation to the study's primary outcomes.

Results

The distribution of patients' demographic and clinical characteristics by the study groups is given in Table 1. Accordingly, the mean age of the sample, 56.3% of which was male, was 66.70 ± 12.35 years. There was no significant difference between the groups in terms of gender and age ($p = 0.752$ and $p = 0.203$, respectively). On the other hand, the mean BMI of patients with vitamin D deficiency was significantly higher than those of patients with vitamin D insufficiency and insufficiency (29.05 ± 5.47 kg/m^2 vs. 24.98 ± 2.81 kg/m^2 and 24.82 ± 3.50 kg/m^2; $p=0.005$). There was no significant difference between the groups in terms of the presence of comorbidities. However, coronary artery disease was significantly more common among patients with vitamin D deficiency than in other patients ($p = 0.019$). The rate of patients using gabapentin among pharmacological treatments was significantly higher in patients with vitamin D deficiency (65.5%) than in other patients ($p = 0.001$), whereas the rate of patients using NSAIDs/acetaminophen was highest in patients with vitamin D sufficiency (72.7%) ($p < 0.001$).

The distribution of patients' pain scores and inflammatory marker levels by the study groups is given in Table 2. Overall, both neuropathic pain intensity and pain duration increased significantly as vitamin D levels decreased ($p \leq 0.05$). Specifically, the mean DN4 score of patients with vitamin D deficiency was significantly higher than those of patients with vitamin D insufficiency and sufficiency (5.83 ± 1.76 vs. 3.92 ± 2.68 and 1.71 ± 0.96, $p < 0.001$). Similarly, the mean NRS score and pain duration of patients with vitamin D deficiency were significantly higher than those of other patients ($p = 0.001$ and $p < 0.001$, respectively). Inflammatory markers such as CRP level and ESR were also significantly higher in patients with vitamin D deficiency than in other patients ($p = 0.046$ and $p = 0.007$, respectively).

The dermatome most commonly affected by HZ in PHN patients was the thoracic dermatome (52.1%; n = 37), followed by cranial (22.5%; n = 16), lumbar (12.7%; n = 9), cervical (8.5%; n = 6), and sacral (4.2%; n = 3) dermatomes.

Table 1. Demographic and clinical characteristics of patients according to serum 25(OH)D levels.

	Serum 25(OH)D concentration			
Variables	≤20 ng/mL (n=24)	21-29 ng/mL (n=26)	≥30 ng/mL (n=21)	p-values
Sex				
Female	9 (37.5)	12 (46.2)	10 (47.6)	0.752
Male	15 (62.5)	14 (53.8)	11 (52.4)	
Age (years)	68.67 ± 11.79	68.15 ± 11.90	62.67 ± 13.13	0.203
BMI (kg/m^2)	29.05 ± 5.47	24.98 ± 2.81	24.82 ± 3.50	0.005[a,b]
Smoking, present	12 (50.0)	7 (26.9)	6 (28.6)	0.175
Comorbidity, present	21 (87.5)	19 (73.1)	16 (76.2)	0.430
Hypertension, present	8 (33.3)	8 (30.8)	10 (47.6)	0.452
Coronary artery disease, present	10 (41.7)	2 (7.7)	5 (23.8)	0.019
Diabetes mellitus, present	8 (33.3)	6 (23.1)	2 (9.5)	0.162
Medications used				
Medications used				
Gabapentin, present	19 (65.5)	8 (28.6)	4 (18.2)	0.001
Pregabalin, present	4 (13.8)	3 (10.7)	1 (4.5)	0.581
NSAIDs/Acetaminophen, present	1 (3.4)	16 (57.1)	16 (72.7)	<0.001
Opioids, present	5 (17.2)	1 (3.6)	1 (4.5)	0.166
Season of zoster onset				
Winter	7 (29.2)	7 (26.9)	6 (28.6)	0.412
Spring	5 (20.8)	5 (19.2)	7 (33.3)	
Summer	3 (12.5)	6 (23.1)	6 (28.6)	
Autumn	9 (37.5)	8 (30.8)	2 (9.5)	

Abbrev.: BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs.
Data presented as n (%) or mean ± standard deviation. Bold p-values indicate statistical significance (p≤0.05). [a]Significant difference between ≤20 ng/mL and 21-29 ng/mL groups (p<0.05); [b]Significant difference between ≤20 ng/mL and ≥30 ng/mL groups (p<0.05).

Table 2. Pain parameters and inflammatory markers according to serum 25(OH)D levels.

	Serum 25(OH)D Concentration			
Variables	≤20 ng/mL (n=24)	21-29 ng/mL (n=26)	≥30 ng/mL (n=21)	p-values
DN4 score	5.83 ± 1.76	3.92 ± 2.68	1.71 ± 0.96	<0.001[a,b,c]
DN4 ≥4, present	24 (100.0)	10 (38.5)	0 (0.0)	<0.001
NRS score	8.92 ± 1.59	7.04 ± 2.25	6.29 ± 2.43	0.001[a,b]
Pain duration (days)	93.54 ± 41.23	38.35 ± 17.41	31.86 ± 35.80	<0.001[a,b]
CRP (mg/L)	11.99 ± 14.56	6.91 ± 4.38	6.99 ± 12.38	0.046
ESR (mm/hour)	25.71 ± 16.58	19.64 ± 10.81	13.75 ± 7.01	0.007
WBC count (×10^3/μL)	6.75 ± 2.54	7.91 ± 2.54	6.73 ± 1.66	0.133

Abbrev.: DN4: Douleur Neuropathique 4; NRS: Numeric Rating Scale; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell.
Data presented as n (%) or mean ± standard deviation. Bold p-values indicate statistical significance (p≤0.05). [a]Significant difference between ≤20 ng/mL and 21-29 ng/mL groups (p<0.05); [b]Significant difference between ≤20 ng/mL and ≥30 ng/mL groups (p<0.05); [c]Significant difference between 21-29 ng/mL and ≥30 ng/mL groups (p<0.05).

Correlation analysis of the relationships between serum 25(OH)D level and clinical and laboratory parameters revealed a strong negative correlation between vitamin D level and all pain parameters (Table 3). Accordingly, serum 25(OH)D level was most strongly correlated with DN4 score ($r = -0.758$; $p < 0.001$), followed by pain duration ($r = -0.640$; $p < 0.001$) and NRS score ($r = -0.497$; $p < 0.001$), and significantly correlated in the negative direction with inflammatory markers, i.e., ESR ($r = -0.473$; $p < 0.001$) and CRP level ($r = -0.367$; $p = 0.002$), and was moderately correlated in the negative direction with BMI ($r = -0.404$; $p < 0.001$).

Evaluation of neuropathic pain symptoms revealed that serum 25(OH)D levels were significantly lower in the presence of pins-and-needles sensation and brush-evoked pain (Table 4). Accordingly, the mean vitamin D level of patients with pins-and-needles sensation was significantly lower than that of patients without pins-and-needles sensation (17.06 ± 7.58 ng/

mL vs. 35.30 ± 10.80 ng/mL, p < 0.001). Patients with brush-evoked pain had the lowest mean vitamin D level (14.79 ± 8.06 ng/mL, p < 0.001). The mean vitamin D level of patients with a DN4 score ≥4 was significantly lower than that of those with a DN4 score <4 (15.25 ± 7.31 ng/mL vs. 29.78 ± 12.09 ng/mL, p < 0.001). The mean vitamin D level of patients with burning pain was also lower, albeit not significantly, than that of patients without burning pain (p = 0.056).

Table 3. Correlation analysis between serum 25(OH)D levels and clinical/laboratory parameters.

Parameters	Correlation coefficient (r)	p
BMI	-0.404	<0.001
CRP	-0.367	0.002
ESR	-0.473	<0.001
NRS score	-0.497	<0.001
DN4 score	-0.758	<0.001
Pain duration	-0.640	<0.001

Abbrev.: BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NRS: Numeric Rating Scale; DN4: Douleur Neuropathique 4. Bold p-values indicate statistical significance (p≤0.05).

Table 4. Serum 25(OH)D levels according to neuropathic pain symptoms.

DN4 Symptoms	Symptom Presence	Serum 25(OH) D (ng/mL)	p
Burning pain	Present	20.81 ± 10.62	0.056
	Absent	26.63 ± 13.80	
Cold-evoked pain	Present	22.15 ± 11.71	0.244
	Absent	25.71 ± 12.72	
Electric shock-like pain	Present	26.33 ± 12.88	0.288
	Absent	23.74 ± 11.63	
Tingling	Present	24.69 ± 12.10	0.913
	Absent	24.19 ± 11.24	
Pins and needles sensation	Present	17.06 ± 7.58	<0.001
	Absent	35.30 ± 10.80	
Numbness	Present	25.05 ± 12.63	0.742
	Absent	23.81 ± 11.13	
Itching	Present	23.35 ± 11.75	0.889
	Absent	24.60 ± 11.66	
Touch hypoesthesia	Present	24.75 ± 12.51	0.181
	Absent	23.56 ± 10.09	
Pinprick hypoesthesia	Present	25.63 ± 12.42	0.711
	Absent	24.40 ± 11.58	
Brush-evoked pain	Present	14.79 ± 8.06	<0.001
	Absent	30.06 ± 11.42	
DN4 score	≥4	15.25 ± 7.31	<0.001
	<4	29.78 ± 12.09	

Abbrev.: DN4: Douleur Neuropathique 4. Data presented as mean ± standard deviation. Bold p-values indicate statistical significance (p≤0.05).

ROC curve analyses performed to evaluate the diagnostic performance of serum 25(OH)D level in predicting neuropathic pain parameters revealed that an optimal cut-off level of 21.15 ng/mL predicted patients with a ≥4 DN4 score with 81.5% sensitivity and 84.1% specificity (AUC: 0.862), an optimal cut-off level of 25.85 ng/mL predicted patients with pins-and-needles sensation with 86.0% sensitivity and 85.7% specificity (AUC: 0.930), and an optimal cut-off level of 20.5 ng/mL predicted patients with brush-evoked pain with 77.8% sensitivity and 86.4% specificity (AUC: 0.873) (Figure 2). These findings indicate that serum vitamin D level has high diagnostic value, especially in predicting the presence of pins-and-needles sensation.

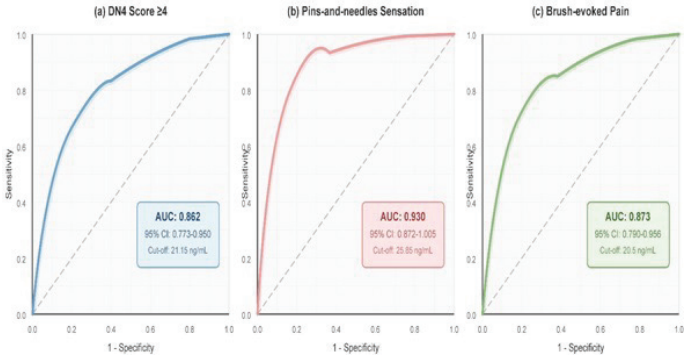

Figure 2. ROC curves showing the diagnostic performance of serum 25(OH)D levels in predicting neuropathic pain parameters. (a) 25(OH)D level for predicting patients with DN4 score ≥4 (AUC: 0.862, cut-off value: 21.15 ng/mL, sensitivity: 81.5%, specificity: 84.1%). (b) 25(OH)D level for predicting pins-and-needles sensation (AUC: 0.930, cut-off value: 25.85 ng/mL, sensitivity: 86.0%, specificity: 85.7%). (c) 25(OH)D level for predicting brush-evoked pain (AUC: 0.873, cut-off value: 20.5 ng/mL, sensitivity: 77.8%, specificity: 86.4%). ROC: Receiver operating characteristic; AUC: Area under the curve.

Discussion

The mean age of our sample was over 60, supporting literature findings that hypovitaminosis D is more common in older age groups. Factors such as decreased exposure to sunlight with age, inadequate nutrition, and decreased synthesis of 7-dehydrocholesterol in the skin are among the main reasons that facilitate vitamin D deficiency [1]. Women experience chronic pain more frequently, more severely, and for longer periods than men, and serum vitamin D levels are generally lower in women than in men [18,19]. In contrast, we did not find any significant difference in serum vitamin D levels between genders. On the other hand, in line with literature data indicating that serum 25(OH)D levels are lower in individuals with a higher BMI [19], we found that serum vitamin D levels decreased significantly as patients' BMI increased. This decrease in serum vitamin D levels with increasing BMI has been attributed to the reduction of the biologically active form of vitamin D in circulation due to its storage in adipose

tissue [6]. While the incidence of comorbidities has differed between the groups determined by vitamin D levels, these differences did not reach statistical significance. Then again, the fact that we found the incidence of coronary artery disease to be significantly higher in patients with vitamin D deficiency than in other patients indicates the effects of vitamin D deficiency on the cardiovascular system. Indeed, significant relationships have been reported in the literature between 25(OH)D levels, hypertension, and coronary artery disease [2,4]. Saguil et al. [8] reported that HZ most frequently affects the thoracic and cranial dermatomes. In parallel, we found that the dermatomes most commonly affected by HZ in PHN patients were the thoracic and cranial dermatomes (52.1%, n=37, and 22.5%, n=16, respectively). Recent studies have shown that vitamin D exhibits anti-inflammatory effects by reducing proinflammatory cytokine release and suppressing T cell responses, and also inhibits prostaglandin E2 (PGE2) synthesis in vitro and modulates the activity of immune cells [20]. Current studies suggest that vitamin D may impact pain intensity and thus may play a potential role in pain management in different clinical settings [1,4,7–9,16].

We found that both DN4 and NRS scores increased significantly as vitamin D levels decreased in PHN patients. The mean DN4 and NRS scores were 5.83 ± 1.76 and 8.92 ± 1.59, respectively, in PHN patients with vitamin D deficiency and 1.71 ± 0.96 and 6.29 ± 2.43, respectively, in PHN patients with vitamin D sufficiency ($p<0.001$ and $p=0.001$, respectively). Similarly, the mean pain duration was also significantly longer in PHN patients with vitamin D deficiency than in PHN patients with vitamin D sufficiency (93.54±41.23 days vs. 31.86±35.8 days, $p<0.001$). These findings suggest that vitamin D deficiency may impact the duration and severity of pain. Pharmacological treatment preferences also reflect this impact. Gabapentin use was significantly higher in patients with low vitamin D levels, whereas NSAIDs/acetaminophen use was significantly higher in patients with high vitamin D levels.

Hypovitaminosis D causes deterioration in nerve regeneration and myelin loss, triggering the central sensitization process characterized by excessive activation of glial cells and proinflammatory cytokine release at the spinal cord level, and consequently, causing neuronal dysfunction, which can lead to both increased severity and prolonged pain [16].

We found a significant decrease in both ESR and CRP levels with increasing vitamin D levels in PHN patients. In particular, these inflammatory markers were significantly elevated in individuals with vitamin D deficiency. These findings are consistent with literature findings indicating that vitamin D levels are inversely related to inflammation [21]. In contrast, Srikanth et al. [22] reported that CRP levels were not significantly associated with 25OHD or $1,25(OH)_2D$ levels, but instead were positively correlated with vitamin D-binding protein levels. They attributed their finding, which differs from the relevant findings in the literature, to the fact that their sample consisted of healthy elderly males and that their CRP levels were generally low (<1.5 µg/mL), suggesting that factors such as the severity of the inflammatory response and the clinical profile of the sample may affect the relationship between vitamin D and inflammation.

We found a significant increase in both overall pain severity and neuropathic pain symptoms with decreasing serum vitamin D levels in PHN patients in our sample, indicating that hypovitaminosis D may be related not only to the presence of pain but also to the type of pain. In a study, where confounding variables such as age, BMI, physical activity, and sun exposure were controlled, Shillo et al. [23] demonstrated that vitamin D levels were significantly lower in patients with painful diabetic peripheral neuropathy (DPN). In line with the strong negative correlation we found between serum 25(OH)D level and DN4 pain score ($r = –0.758$; $p < 0.001$), they found a negative correlation ($r = –0.30$, $p = 0.02$), which they attributed to the fact that vitamin D deficiency may have led to the development of a small fiber neuropathy affecting small diameter (Aδ and C type) sensory fibers, especially nociceptors. They stated that the significant decrease in cold perception threshold in patients with painful DPN reflected the deterioration in the function of Aδ fibers and increased sensory sensitivity. They also emphasized that vitamin D deficiency may increase nociceptor sensitivity by reducing NGF production, contributing to the exacerbation of neuropathic pain [23]. Necrosis, scar formation, axonal and myelin damage that develop in the dorsal root ganglion after HZ infection lead to a decrease in nerve density in the skin in the relevant dermatome. In addition, activation of Schwann cells in the peripheral nervous system contributes to nerve damage by triggering the release of neuroexcitatory and proinflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Furthermore, activation of nociceptive fibers called nervi nervorum located in peripheral nerves contributes to the pain process by causing neurogenic inflammation [7].

In a study conducted with patients with rheumatoid arthritis, serum 25(OH)D cut-off level of ≤13.9 ng/mL was shown to significantly predict neuropathic pain assessed by the Leeds assessment of neuropathic symptoms and signs (LANSS) pain scale with 48.4% sensitivity and 85.5% specificity (AUC 0.71) [24]. In comparison, we determined that a serum 25(OH)D cut-off level of ≤21.15 ng/mL significantly predicted patients with a ≥4 DN4 score with 81.5% sensitivity and 84.1% specificity (AUC:

0.862). Our finding of a higher correlation coefficient between vitamin D level and DN4 score, along with a higher 25(OH)D cut-off level predicting DN4≥4 score, compared to those reported in the literature, may be attributed to the fact that patients' pain levels were assessed in the early period of HZ infection.

In contrast, in a study evaluating the effects of intramuscular injection with 600,000 international unit (IU) vitamin D in patients with Type 1 or Type 2 diabetes, Basit et al. [23] found no significant relationship between baseline serum 25(OH) vitamin D levels and the McGill pain questionnaire (MPQ) score, DN4 score, and positive symptoms, even though they observed significant improvements in patients' pain levels [25]. They attributed their findings to mechanisms such as changes in calcium signaling, adjustments in neurotrophic factor levels, and the production of active vitamin D metabolites, and suggested that the vitamin D dose and duration of application may have been insufficient to correct neuropathic disorders.

On the other hand, in a study examining the effects of vitamin D replacement therapy in patients with DPN and low vitamin D levels, Sarı et al. observed significant reductions in burning pain and electric shock-like pain symptoms and non-significant reductions in tingling, numbness, itching, touch hypoesthesia, and pinprick hypoesthesia, but no change in cold-evoked pain, pins-and-needles sensation, and brush-evoked pain symptoms from baseline to the end of the study in patients in the treatment group [26]. They interpreted these findings as indicating that vitamin D replacement therapy may be effective on some symptoms related to small fiber neuropathy, but that it does not provide a homogeneous improvement in all neuropathic symptom subgroups. A retrospective analysis of PHN patients found significantly higher rates of brush- and cold-evoked pain in individuals with serum 25(OH)D levels ≤67.0 nmol/L ($p = 0.002$ and $p<0.001$, respectively), but found no significant relationship between serum 25(OH)D levels and pins-and-needles sensation ($p = 0.220$) [3]. They explained these findings by the activation of transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) ion channels by reactive oxygen species (ROS), which increase with vitamin D deficiency, and stated that sensitization of TRPA1, particularly through ROS, is an effective mechanism in the development of cold-evoked pain. In contrast, we found that as patients' vitamin D levels decreased, neuropathic symptoms, especially brush-evoked pain and pins-and-needles sensation, among DN4 components became more severe, and DN4 scores increased significantly. The discrepancy between our findings and some findings reported in the literature may be attributed to the inclusion of patients with a DN4 score below 4 and the individual variability created by genetic polymorphisms on pain perception and response. Increased inducible NO synthase expression in astrocytes in response to VZV infection and a consequent significant increase in NO levels may also be a factor in this discrepancy [27]. Vitamin D may limit NO production by suppressing inducible NO synthase activity at both messenger RNA (mRNA) and protein levels under physiological conditions. However, hypovitaminosis D abolishes this regulatory effect, leading to NO accumulation. Increased NO levels trigger the activation of N-methyl-D-aspartate (NMDA) receptors in the spinal dorsal horn via phosphorylation, initiating central sensitization and thus facilitating the development of mechanical allodynia [3].

This study had some limitations, including its retrospective design. Another limitation of the study was its single-center design and limited sample size, which have limited the generalizability of its results. Additionally, potential confounding factors that could affect vitamin D levels, such as sun exposure, physical activity, and dietary habits, were not fully controlled. Lastly, the fact that the pharmacological treatments used in the study, such as gabapentin, pregabalin, NSAIDs, etc., differed according to clinician preferences may have led to heterogeneity in the interpretation of the results of the study.

Our study investigating the relationship between serum 25(OH)D levels and pain severity, pain duration, and neuropathic symptoms in PHN patients revealed that low vitamin D levels were significantly associated with higher DN4 and NRS scores and longer pain duration. Particularly, brush-evoked pain and pins-and-needles sensation were observed more frequently in PHN patients with serum 25(OH)D levels ≤20 ng/mL. These findings suggest that vitamin D may contribute to neuropathic pain through both inflammatory processes and central sensitization mechanisms. However, the study's retrospective design, limited sample size, incomplete control of confounding factors, and differences in medication use limit the generalizability of its findings. Future prospective and multicenter studies will more clearly demonstrate the role of vitamin D levels in the management of PHN.

Ethics Committee Approval

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee (Date: 02.07.2024, Decision No: E-60116787-020-548385).

Conflicts of Interest

The authors declare they have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Authors Contribution

Study Design: Sİ, ÇE; Data Collection: Sİ, ÇE; Statistical Analysis: Sİ; Data Interpretation: Sİ, ÇE; Manuscript Preparation: Sİ, ÇE; Literature Search: Sİ, ÇE; Critical Review: Sİ, ÇE.

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