Journal of General - Procedural Dermatology & Venereology Indonesia

Volume 6
Issue 2 *(December 2022 Edition)*

Article 7

12-31-2022

Correlation Between Serum 25 Hydroxy-vitamin D Levels and The Worst Pain Intensity in Postherpetic Neuralgia

Wizar Putri Mellaratna
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Nelva K. Jusuf
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Ariyati Yosi
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Recommended Citation

Mellaratna, Wizar Putri; Jusuf, Nelva K.; and Yosi, Ariyati (2022) "Correlation Between Serum 25 Hydroxy-vitamin D Levels and The Worst Pain Intensity in Postherpetic Neuralgia," *Journal of General - Procedural Dermatology & Venereology Indonesia*: Vol. 6: Iss. 2, Article 7.
DOI: 10.7454/jdvi.v6i2.1006
Available at: https://scholarhub.ui.ac.id/jdvi/vol6/iss2/7

Original Article

Correlation between serum 25 hydroxy-vitamin D levels and the worst pain intensity in postherpetic neuralgia

Wizar Putri Mellaratna, Nelva K. Jusuf, Ariyati Yosi

Department of Dermatology and Venereology, Faculty of Medicine,
Universitas Sumatera Utara, Medan, Indonesia

Email: mellaratna.iskandar@gmail.com

Abstract

Background: Postherpetic neuralgia (PHN) is persistent pain in the affected dermatome that occurs more than three months after the eruption of the herpes zoster has disappeared. Vitamin D has a role in Schwann cell regeneration and stimulates the release of nerve growth factors.
Methods: Blood sampling was performed to test serum 25(OH)D levels. Patients filled out their worst pain intensity using the Zoster Brief Pain Inventory questionnaire. The score was reported in Likert score (0-10), 0 indicating no pain and 10 indicating the most severe pain. Spearman correlation test was used, and $p < 0.05$ was considered statistically significant.
Results: The PHN patients were mostly aged ≥60 years (50.0%), female (59.4%), had a deficiency of 25(OH)D levels (59.4%), and had the worst pain intensity with a score of 9 (40.6%). There were no differences in serum 25(OH)D levels among age groups ($p > 0.05$) and PHN durations ($p > 0.05$). However, there were significant differences in serum 25(OH)D levels between sex groups ($p < 0.05$). The limitations of this study were that liver function tests were not carried out, and data on the duration of UV exposure were not taken in this study.
Conclusion: No correlation exists between serum 25(OH)D levels and the worst pain intensity in PHN patients. Further research with a control group, liver function tests, and the duration of sun exposure data is needed to conclude the role of 25(OH)D in PHN patients.

Keywords: *pain intensity, postherpetic neuralgia, vitamin D*

Background

Postherpetic neuralgia (PHN) is a complication of herpes zoster with a sensation of stabbing pain and severe allodynia in the affected dermatome that occurs three months after the onset of herpes zoster.[1] Risk factors of PHN include older age that contributes to nutritional deficiencies, including zinc (19%), vitamin C (16%), iron (14%), vitamin D (12%), vitamin B12 (11%), β carotene (11%), vitamin E (10%), vitamin A (8%), folic acid (8%), vitamin B6 (7%), selenium (7%), and copper (3%).[2] Based on research conducted by Bartley et al.,[3] vitamin D has a role as an anti-inflammatory and detoxifying agent in nerves. The anti-inflammatory effect occurs as alpha-melanocyte stimulating hormone (αMSH) decreases the production of proinflammatory cytokines and modulates cytokines, such as IL-10. Vitamin D inhibits the synthesis of nitric oxide (NO), which has a role in neuropathic pain. Vitamin D also increases glutathione and γ-glutamyl peptidase in astrocytes, which is thought to play a role in scavenging the reactive oxygen species (ROS). In patients with PHN, degeneration of Schwann cells and nerve fibers is found in myelinated and lost cells in the dorsal root ganglions (DRG). Vitamin D potentially reduces inflammation of Schwann cells. Vitamin D also increases nerve growth factor (NGF) regeneration in keratinocytes and Schwann cells, triggering Schwann cell regeneration.[3]

Clinical studies assessing the association between decreased vitamin D levels and chronic pain are still limited. However, there is sufficient evidence to suggest the contribution of vitamin D to the anatomy and physiology of pain, which influences the etiology and maintenance of chronic pain status

and associated comorbidities. Vitamin D also has a neuroprotective effect that affects the pathophysiology of chronic pain. Vitamin D reduces TNF-α, macrophage colony-stimulating factors (M-CSF), and nitric oxide levels in astrocytes and microglia. Through inhibition against M-CSF, vitamin D can block pain pathways.[4] Postherpetic neuralgia is chronic neuropathic pain, so researchers are interested in assessing the correlation between vitamin D deficiency with the worst pain intensity in PHN patients to know the significance of vitamin D levels on the pain intensity in PHN patients residing in tropical countries such as Indonesia.

One of the questionnaires to assess pain intensity, especially in PHN, is the Zoster Brief Pain Inventory (ZBPI), which assesses four components of pain intensity in the last 24 hours, including the worst pain, the slightest pain, the average pain, and current pain intensity felt by PHN patients. In this study, the researchers selected the worst pain intensity because it has the highest internal validity (Cronbach's alpha value 0,77 until 0,90) compared to the other domains of pain intensity (the slightest pain, the average pain, and the current pain intensity).[5] Decreased levels of 25(OH)D were accompanied by increased numbers of the worst pain intensity.[6]

Methods

Patients and study design

This was a cross-sectional study conducted at the Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan. Thirty-two patients were included from July 2019 to December 2019. Data on PHN patients were collected from the medical records of Sumatera Utara University Hospital and two public health centers in Medan. Postherpetic neuralgia was defined as a neurologic complication of herpes zoster that causes chronic pain for more than three months after the rash had disappeared. The inclusion criteria were patients who had been diagnosed with PHN from January 2015 to December 2019, aged over 40 years old (categorized as 40-44, 45-49, 50-54, 55-59, and $\geq$ 60 years), and patients who already signed informed consent to be involved in this study. The demographic data included age, sex, and duration of PHN (measured from three months after the rash disappeared until the day of investigation). This study obtained ethics approvals from the Faculty of Medicine, Universitas Sumatera Utara, and Adam Malik Hospital 583/TGL/KEPK FK USU-RSUP HAM/2019.

Researchers recorded patients' data, including age, sex, duration of disease, telephone number, and home address. Then, the researcher asked about the patients' readiness to participate in this study in their houses. The patients filled out the worst pain intensity they felt in the last 24 hours on the ZBPI questionnaire (with permission) in the Likert score. A score of 0 indicated no pain, and a score of 10 indicated the worst pain felt by patients. PHN patients' blood samples were collected, and their serum 25 hydroxyvitamin D levels were measured using the DiaSorin Liaison® instrument. The serum 25(OH)D levels were reported in numerical units. The concentration of serum 25(OH)D levels was interpreted as deficient (20 ng/mL), insufficient (21-29 ng/mL), sufficient (30-100 ng/mL), and toxic ($>$100 ng/mL).

Statistical analysis

Spearman correlation test was used to evaluate the correlation between serum 25(OH)D levels and the worst pain intensity of postherpetic neuralgia patients as the data were abnormally distributed (normality test result). Spearman correlation was also used to investigate the correlation between serum 25(OH)D levels and the duration of PHN. An independent samples t-test was used to determine the differences in serum 25(OH)D levels based on sex as the data were normally distributed, and a one-way ANOVA test was used to determine the differences in serum 25(OH)D levels among age groups as the data were normally distributed. A p-value of <0.05 was considered statistically significant. The statistical correlation was categorized into very weak (r 0,0-< 0,2), weak (r = 0,2-0,4), moderate (r = 0,4- <0,6), strong (0,6 - <0,8), and very strong (0,8-1,0).

Results

This study included 32 PHN patients. The largest proportion of patients (50%) was over 60, and the smallest proportion (3,3%) was in the 50-54 years age group. The majority of patients were females (59.4%). The patients' characteristics are described in table 1.

Table 1. Characteristics of PHN patients

Characteristics	n (N=32)	(%)
Age (years)		
40-44	5	15.6
45-49	4	12.5
50-54	1	3.1
55-59	6	18.8
≥ 60	16	50.0
Sex group		
Female	19	59.4
Male	13	40.6

The results showed that 19 (59.4%) PHN patients had a deficiency in serum 25(OH)D levels, followed by 9 (28.1%) having insufficiency and 4 (12.5%) having normal levels (table 2).

Table 2. Distribution of serum 25(OH)D levels in PHN patients

	Serum 25(OH)D levels	
	n (N=32)	(%)
Deficiency	19	59.4
Insufficiency	9	28.1
Normal	4	12.5
Toxic	0	0

Thirteen (40.6%) patients had the worst pain intensity score of 9, whereas 1 (3.1%) and 1 (3.1%) had the worst pain intensity score of 4 and 6, respectively (table 3).

Table 3. Distribution of worst pain intensity in PHN patients

Worst pain intensity	n (%)	Median (min-max)
0	0 (0)	8.50 (3-10)
1	0 (0)	
2	0 (0)	
3	3 (9.4)	
4	1 (3.1)	
5	2 (6.3)	
6	1 (3.1)	
7	6 (18.8)	
8	3 (9.4)	
9	13 (40.6)	
10	3 (9.4)	

As shown in table 4, there was no significant correlation between serum 25(OH)D levels and the worst pain intensity in PHN patients ($p > 0.05$).

Table 4. Correlation between worst pain intensity and serum 25(OH)D levels

	Worst pain intensity		
	Correlation coefficient (r)	**p**	**n**
Serum 25(OH)D levels	-0.070	0.703	32

*Spearman correlation test

This study also found that the correlation between serum 25(OH)D levels and the duration of PHN was not statistically significant ($p > 0.05$), as described in table 5.

Table 5. Correlation between worst pain intensity and duration of PHN

	Duration of PHN		
	Correlation coefficient (r)	**p**	**n**
Serum 25(OH)D levels	-0.060	0.744	32

*Spearman correlation test

Most PHN patients in this study were over 60 years old with a mean serum 25(OH)D value of 22.3888 ± 7.618 ng/mL. There were no differences in serum 25(OH)D levels among age groups ($p > 0.05$), as shown in table 6.

Table 6. Serum 25(OH)D levels in PHN patients, based on age groups

Ages (Years)	Frequency	Mean ± SD (ng/mL)	p
40-44	5	18.880 ± 4.589	0.213
45-49	4	18.200 ± 7.411	
50-54	1	6.800 ± 0.000	
55-59	6	18.367 ± 6.005	
≥ 60	16	22.388 ± 7.618	

*one-way ANOVA test

The mean value of serum 25(OH)D levels in female patients was lower (17.426 ± 5.658 ng/mL) compared to that in males (23.946 ± 7.614 ng/mL). There were statistically significant differences ($p <0.05$) in serum 25(OH)D levels between female and male PHN patients ($p < 0.05$), as shown in table 7.

Table 7. Serum 25(OH)D levels in PHN patients, based on sex groups

Sex groups	Frequency	Mean ± SD (ng/mL)	p
Female	19	17.426 ± 5.658	0.009
Male	13	23.946 ± 7.614	

*Independent samples t-test

Discussion

Most PHN patients in this study were in the older age group, similar to a study by Lu et al.[7] which reported that most (49.8%) of PHN patients were in the 65-74 age group. This finding corresponds to a study by Chen et al.[8] which proposed that increasing age (> 50 years) is a risk factor for developing nutritional deficiencies, resulting in reduced cellular immunity that would be prone to virus infection (such as VZV reactivation). Munoz-Quiles et al.[9] reported that increasing age is associated with the development of PHN. The study found that compared to the young age group, PHN was twice as many in the 60-69 age group, three times higher in the 70-79 age group, and 3.67 higher in the over 80 age group. In terms of sex, Munoz-Quiles et al.[9] reported that the incidence of PHN in female patients was two folds greater than in males. Yu et al.[10] also reported that most PHN patients were female (53.5%), whereas Lu et al.[7] found that most PHN patients were males.

This study showed that most PHN patients had a deficiency in serum 25(OH)D levels. Chen et al.[11] (reported that most PHN patients (79.3%) had insufficiency in serum 25(OH)D levels with a mean value of 27.584 ± 7.488 ng/mL, compared to healthy control (47%) with a normal concentration of serum 25(OH)D levels (30.052 ± 6,988 ng/mL). Chao et al.[12] (also analyzed the serum 25(OH)D levels in PHN patients and reported that 59.1% had a deficiency, 33% had an insufficiency, and 8% had normal serum 25(OH)D levels. Based on pain intensity experienced by the patients, Schmader et al.[13] stated that the majority of PHN patients (51%) had severe pain (Likert score 8 to 10), whereas moderate pain (Likert score 4 to 7) was found in 20-30% of patients. The study found a correlation between pain intensity and increasing interference in their quality of life. Katz et al.[14] reported that the average score of the worst pain intensity in PHN patients was 6.74. In this study, most PHN patients had the worst pain intensity score of 9. Severe pain intensity felt by PHN patients is probably correlated with the larger proportion of female PHN patients who tended to have a low pain threshold. This finding corresponds to a study by Belfer et al.[15] that stated that females have a low pain threshold, low sensitization to noxious stimuli, and greater curiosity about the pain.

This study showed no significant correlation between serum 25(OH)D levels with the worst pain intensity. Chen et al.[11] reported a significant but weak correlation (r = -0.329) between spontaneous pain and serum 25(OH)D levels. Vicira et al.[16] reported that risk factors influencing chronic pain intensity include older age, female gender, divorce history, low socioeconomic status, low education status, obesity, and history of alcohol consumption and smoking. Mellaratna et al.[17] stated that the worst pain intensity had a very strong and significant ($p < 0.001$) correlation with mood disturbance ($r = 0.846$) and working status ($r = 0.818$). The worst pain intensity also had a strong and significant ($p < 0.001$) correlation with general activity ($r = 0.673$), sleep disturbance ($r = 0.774$), social relationship ($r = 0.653$), and disturbance of enjoyment of life ($r = 0.783$). Additionally, the worst pain intensity had a moderate and significant ($p < 0.001$) correlation with the walking ability ($r = 0.475$).[17]

The researchers have not yet found a correlation between the duration of PHN and serum 25(OH)D levels. In contrast, Shipton et al.[4] found that long-term vitamin D deficiency is associated with persistent chronic pain. Chao et al.[12] proposed that serum 25(OH)D levels have roles in the nerve injury mechanism of PHN patients, such as inflammation reduction in Schwann cells, myelinization, axogenesis stimulation, and improved immunity to prevent virus replication in the dorsal root ganglion.

Postherpetic neuralgia incidence involved older age groups. Twelve percent of elderly patients were reported to have a vitamin D deficiency that contributed to decreased immunity, a risk factor of HZ and PHN.[8] Risk factors of vitamin D deficiency were reduced vitamin D synthesis, minimal UV exposure, and limited mobility in the older age group.[18] This research showed no differences in serum 25(OH)D levels among all age groups.

The mean value of serum 25(OH)D levels was lower in females (22.30 ng/mL) compared to males (24.71 ng/mL), and the difference was statistically significant. The result of linear regression analysis from Zadhsir et al.[19] indicated that the female sex was a risk factor for serum 25(OH)D deficiency. Al-quaiz et al.[20] stated that about 72% of males had a deficiency in serum 25(OH)D levels, 17.3 % had insufficiency, and 49,7% had ≥ 25 to < 50 ng/mL serum 25(OH)D levels. This study showed significant differences in serum 25(OH)D levels between females and males.

This research had several limitations. The history of the duration of sunlight exposure was not taken, and liver function tests were not performed. This study also did not have a control group. Additionally, this study had an inadequate sample size, leading to low statistical power (p= 0,703) to detect a significant correlation between serum 25(OH)D levels and the worst pain intensity in PHN patients.

Conclusion

This study shows no correlation between serum 25(OH)D levels and the worst pain intensity in PHN patients. Further studies with a control group and higher statistical power are needed to detect significant differences between serum 25(OH)D levels and the worst pain intensity in PHN patients.

Acknowledgments

We express our gratitude to Sumatera Utara General Hospital and two public health centers in Medan, which provided the medical record of PHN patients in our study.

Author Contributions

All authors act as guarantors of the manuscript. WPM is the principal investigator of this study. WPM, NKJ, and AY participated in the study's conception, data acquisition, data interpretation, and writing. WPM, NKJ, and AY participated in the study's data analysis and statistical analysis.

Conflict of Interests

There is no conflict of interest in this study.

References

1. Pusponegoro E, Nilasari H, Lumintang H, Niode NJ, Daili SF, Djauzi S. *Buku panduan herpes zoster di Indonesia* [in Indonesian]. Jakarta: Balai Penerbit Fakultas Kedokteran Universitas Indonesia; 2014. p.17
2. Watson CPN, Gershon AA, Oxman MN. Herpes zoster: Post-herpetic neuralgia and other complications [internet]. [cited 2019 Jan 14]. Springer: Canada. 2017. p.36-39. Available from: https://www.researchgate.net/publication/321529440_Herpes_Zoster_Postherpetic_Neuralgiaand_Other_Complications_Focus_on_Treatment_and_Prevention
3. Bartley J. Post-herpetic neuralgia, Schwann cell activation and vitamin D. Med Hypotheses [internet]. 2009 December. [cited 2019 Jan 16];73(6):927-9 Available from: https://www.ncbi.nlm.nih.gov/pubmed/19635651. DOI:10.1016/j.mehy.2009.06.039
4. Shipton EA, Shipton EE. Vitamin D and pain: Vitamin D and its role in the aetiology and maintenance of chronic pain states and associated comorbidities. Pain Res Treat [internet]. 2015 [cited 2020 Aug 4];1-12. Available from: http://downloads.hindawi.com/archive/2015/904967.pdf. DOI: 10.1155/2015/904967
5. Atkinson TM, Mendoza TR, Sit L, et al. The brief pain inventory and its "pain at its worst in the last 24 hours" item: Clinical trial endpoint considerations. Pain Med [internet]. 2010 [cited 2019 Oct 28];11(3):337–46. Available from: https://watermark.silverchair.com. DOI:10.1111/j.1526-4637.2009.00774.x.
6. Dahlan MS. *Statistik untuk kedokteran dan kesehatan* [In Indonesian]. Edisi 6. Jakarta: Salemba Medika; 2014. p.224.
7. Lu WH, Lin CW, Wang CY, Chen LK, Hsiao FY. Epidemiology and long-term disease burden of herpes zoster and postherpetic neuralgia in Taiwan: A population-based propensity score-matched cohort study. BMC Public Health [internet]. 2018. [cited 2020 Mar 7];18:369. Available from: https://search.proquest.com/docview/2049642494/84933ADC3F7D404FPQ/24?accountid=50257. DOI:10.1186/s12889-018-5247-6
8. Chen JY, Chang CY, Song-Lin Y, Lin Hu M. Nutritional factors in herpes zoster, postherpetic neuralgia, and zoster vaccination. Popul Health Manag [internet]. 2012 [cited 2019 Jan 16]; 15(6): 391-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23088666. DOI: 10.1089/pop.2012.1563
9. Muñoz-Quiles C, López-Lacort M, Orrico-Sánchez A, Díez-Domingo J. Impact of postherpetic neuralgia: A six-year population-based analysis on people aged 50 years or older. J Infection [internet]. 2018 [cited 2019 Oct 23]; 77(2): 131 –6. Available from: https://www.sciencedirect.com/science/article/pii/S0163445318301075. DOI:10.1016/j.jinf.2018.04.004.
10. Yu SY, Fan BF, Yang F, et al. Patient and economic burdens of postherpetic neuralgia in China. Clinicoecon Outcomes Res [internet]. 2019 [cited Mar 7]; 11: 539-50. Available from: search.proquest.com/docview/2291222233/1520C3BBFB814EC7PQ/7?accountid=50257. DOI:10.2147/CEOR.S203920
11. Chen JY, Lin YT, Wang LK, et al. Hypovitaminosis D in postherpetic neuralgia, high prevalence and inverse association with pain: A retrospective Study. Nutrients [internet]. 2019 [cited 2020 Feb 9];11(11):2787. Available from: https://search.proquest.com/docview/2315488596/fulltextPDF/24D2BC3DC46F4E51PQ/1?accountid=50257. DOI: 10.3390/nu11112787
12. Chao CT, Chiang CK, Huang JW, Hung KY. Vitamin D is closely linked to the clinical course of herpes zoster: From pathogenesis to

complications. Med. Hypotheses [internet]. 2015 [cited 2019 Jan 22];85:452-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26163058. DOI:10.1016/j.mehy.2015.06.027
13. Schmader KE, Sloane R, Pieper C, et al. The impact of acute herpes zoster pain and discomfort on functional status and quality of life in older adults. Clin J Pain [internet]. 2007 [cited 2019 Nov 12];23(6):490-6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17575488. DOI: 10.1097/AJP.0b013e318065b6c9
14. Katz NP, Gammaitoni AR, Davis MW, Dworkin RH. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: An effectiveness trial. Pain Med [internet]. 2002. [cited 2020 February 10]; 3 (4): 324-32. Available from: https://academic.oup.com/painmedicine/article/3/4/324/1843150 https://doi.org/10.1046/j.1526-4637.2002.02050.x
15. Belfer I. Pain in women. Agri Pain [internet]. 2017 [cited 2018 May 20];29(2):51-4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28895988. DOI: 10.5505/agri.2017.87369.
16. Vicira EB, Garcia JBS, Silva AAM, Aroujo RLT, Jansen RCS. Prevalence, characteristics, and factors associated with chronic pain with and without neuropathic pain characteristics in Sao Luis, Brazil. J Pain Sym Man [internet]. 2012 [cited 2020 May 3];44(2):239-51. Available from: https://www.sciencedirect.com/science/article/pii/S0885392412002126. DOI: 10.1016/j.jpainsymman.2011.08.014
17. Mellaratna WP, Jusuf NK, Yosi A. The impact of pain intensity on quality of life of postherpetic neuralgia patients. Med Glas (Zenica) [internet]. 2020. [cited 2020 Aug 25];17(2):288-293. Available from: https://www.researchgate.net/publication/343366748_The_impact_of_pain_intensity_on_quality_of_life_of_postherpetic_neuralgia_patients. DOI 10.17392/1111-20
18. Nair R, Maseeh A. Vitamin D: The “sunshine” vitamin. J Pharmacol Pharmacother [internet]. 2012. [cited 2020 March 8]; 3(2): 118-26. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3356951/. DOI: 10.4103/0976-500X.95506
19. Zadshir A, Tareen N, Pan D, Norris K, Martins D. The prevalence of hypovitaminosis D among US adults: Data from NHANES III. Ethn Dis [internet]. 2005. [cited 2020 Feb 13]; 15 (5): S5-97-101. Available from: https://pubmed.ncbi.nlm.nih.gov/16315387-the-prevalence-of-hypovitaminosis-d-among-us-adults-data-from-the-nhanes-iii/.
20. AlQuaiz AM, Kazi A, Fouda M, Alyousefi N. Age and gender differences in the prevalence and correlates of vitamin D deficiency. Arch. Osteoporos [internet]. 2018. [cited 2020 Feb 13];13:49. Available from: https://pubmed.ncbi.nlm.nih.gov/29705881-age-and-gender-differences-in-the-prevalence-and-correlates-of-vitamin-d-deficiency/. DOI: 10.1007/s11657-018-0461-5