Vitamin D Deficiency as a Factor Associated with Neuropathic Pain in Multibacillary Type Morbus Hansen

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ABSTRACT

Objective: Morbus Hansen (MH), caused by Mycobacterium leprae, is marked by neuropathic pain. Prior studies link low vitamin D levels to diabetic neuropathic pain, yet research on its role in MH-related neuropathic pain is limited. This study investigates the role of vitamin D deficiency in MH-related neuropathic pain.

Materials and Methods: An analytical cross-sectional study was conducted among multibacillary (MB) MH patients at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali from April to August 2023. Neuropathic pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire, while serum 25(OH)D levels determined vitamin D status. The cutoff for deficiency was determined via ROC curve analysis.

Results: Among 42 participants, those without neuropathic pain exhibited higher mean serum vitamin D levels than those with neuropathic pain (28.69 ± 8.16 vs. 22.11 ± 9.54 ng/ml; p=0.021). The ROC curve identified a cutoff value of 30.25 ng/ml, categorizing participants into vitamin D deficiency (<30.25 ng/ml) and non-deficiency (≥30.25 ng/ml) groups. Bivariate analysis revealed a heightened incidence of neuropathic pain among MH patients with serum vitamin D levels below the designated cutoff point (OR: 6.60; 95%CI: 1.484-29.355; p=0.022). Multivariate analysis indicated that two variables significantly correlated with neuropathic pain in MH patients: vitamin D deficiency (OR: 14.337; 95%CI: 2.431-84.542; p=0.003) and peripheral nerve enlargement (OR: 12.564; 95%CI: 2.096-75.307; p=0.006).

Conclusion: Disparities in average vitamin D levels were observed between MH patients with and without neuropathic pain. Vitamin D deficiency, alongside peripheral nerve enlargement, emerged as significant risk factors for neuropathic pain in MH patients.

Keywords: Morbus hansen; multibacillary; neuropathic pain; serum vitamin D; vitamin D deficiency (Siriraj Med J 2024; 76: 488-496)

INTRODUCTION

Morbus Hansen (MH) is a chronic infectious disease caused by *Mycobacterium leprae*, with one of its complications being neuropathic pain. A complete neurological examination is crucial for the early detection of neuropathic pain, including nerve conduction tests capable of detecting nerve damage before symptoms manifest. However, apart from the associated costs, such

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examinations are not universally available, necessitating the exploration of more cost-effective diagnostic alternatives. Vitamin D has been extensively studied in relation to neuropathic pain, particularly in the context of diabetic neuropathic pain. Clinical trial studies by Martin et al. have demonstrated that vitamin D supplementation, in conjunction with exercise, can alleviate symptoms and complications of diabetic neuropathy.[1] Additionally, a meta-analysis by Qu et al. found lower vitamin D levels in individuals with diabetic neuropathic pain compared to healthy subjects, suggesting that vitamin D deficiency increases the risk of diabetic neuropathic pain and that vitamin D supplementation is effective in mitigating its progression.[1,2]

The role of vitamin D in individuals with MH has been explored predominantly as an immunomodulator. Vitamin D levels influence bacterial indices in multibacillary (MB) MH patients. Toruan et al. revealed an intracrine vitamin D disorder in MB MH patients, leading to compromised macrophage phagocytosis of mycobacteria.[3] In their study, the mean serum vitamin D level was 19.15 ± 3.25 in the paucibacillary (PB) type and 14.85 ± 4.26 in the MB type. Moreover, Rusyati et al. observed that lower plasma vitamin D receptor levels correlated with higher bacterial index numbers in MH patients.[4] Vitamin D plays a pivotal role in improving axonogenesis and sensory responses in peripheral nerves. It upregulates the expression of vitamin D receptors, particularly in small-diameter neurons, while downregulating the expression of L-type calcium channels. Furthermore, vitamin D activates the expression of calcium-binding proteins and increases calcium-buffering molecules in cells, thus shielding them from damage and apoptosis.[5,6]

Vitamin D exerts a modulatory effect on inflammation associated with chronic pain by inhibiting nitric oxide synthesis, which contributes to oxidative stress.[7,8] In vitro studies demonstrate that vitamin D controls the expression of the Nerve Growth Factor (NGF) gene in Schwann cells. Calcitriol and vitamin D analogs increase the binding of activator protein-1 (AP-1) to the NGF promoter, stimulating NGF production. NGF, typically produced by basal keratinocytes in normal skin, binds strongly to the Trk A receptor on nociceptor nerve fibers, enhancing their sensitivity, particularly during inflammation.[9] Vitamin D augments NGF production and prevents a decrease in NGF levels, providing the necessary neuroprotective effect for nerve growth, especially in the peripheral nervous system (sympathetic and sensory nerves). Elevated NGF levels also inhibit the release of substance P and calcitonin gene-related peptide (CGRP), mitigating pain.[5,6,10–18] Patients with low vitamin D levels experience impaired nociceptor function and increased nerve damage, resulting in a lower pain threshold. Correcting vitamin D levels can raise the pain threshold once again.[2,11,19–21]

The mechanisms and manifestations of neuropathic pain in MH closely resemble those observed in individuals with diabetes mellitus. Although prior studies have extensively explored the association between low serum vitamin D levels and diabetic neuropathic pain, research directly evaluating the relationship between vitamin D levels and MH neuropathic pain remains scarce. Thus, investigating this correlation presents an intriguing avenue for further exploration.

MATERIALS AND METHODS

Study design

An analytical observational study with a cross-sectional design was conducted at the neurologist clinic and the skin and genital clinic at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali from April to August 2023. This research received approval and ethical clearance from the Research Ethics Commission, Faculty of Medicine, Universitas Udayana (No: 1130/UN14.2.2.VII.14/LT/2023).

Participant selection

Prior to participation, written informed consent was obtained from all enrolled individuals. Inclusion criteria encompassed individuals diagnosed with multibacillary (MB) type Morbus Hansen (MH) who were aged 18 years or older. Exclusion criteria comprised patients with chronic kidney disease, chronic liver disease, diabetes mellitus, HIV/AIDS infection, entrapment neuropathy, history of stroke, multiple sclerosis, undergoing chemotherapy, diagnosed with malignancy, alcoholism, or taking regular medication within the preceding 30 days, including vitamin D supplements, phenytoin, phenobarbital, carbamazepine, and cholestyramine.

Neuropathic pain assessment

Neuropathic pain assessment was conducted using the Douleur Neuropathique 4 (DN4) questionnaire, comprising 7 pain description questions and 3 clinical examinations with sensitivity and specificity rates ranging from 82% to 95% and 78% to 97%, respectively. The questionnaire was administered by trained neurologists following rigorous training and standardization procedures to ensure consistency and accuracy in data collection.

Vitamin D assessment

Venous blood samples were collected from all participants by highly trained phlebotomists, utilizing

aseptic techniques and adhering strictly to established protocols to minimize the risk of contamination and ensure the integrity of the samples. The samples were processed and analyzed for the quantification of serum 25-hydroxyvitamin D [25(OH)D] levels in ng/ml using the highly sensitive and precise enzyme-linked immunosorbent assay (ELISA) method validated and standardized in the Clinical Pathology laboratory at Prof. Dr. I.G.N.G. Ngoerah General Hospital.

Statistical analysis

Statistical analysis was performed using the SPSS 25 for Windows program, with serum 25(OH)D levels considered the independent variable and MH neuropathic pain as the dependent variable. Numerical variables and data were presented as mean or median based on the results of the normality test using the Shapiro-Wilk test. Bivariate analysis utilized the independent parametric t-test for comparison. The threshold for vitamin D deficiency was determined through the receiver operating characteristic (ROC) curve. Variables with a significance value of less than 0.25 from multivariate selection were subjected to multivariate logistic regression analysis to explore associations of confounding variables with neuropathic pain. A p-value ≤0.05 was deemed statistically significant.

RESULTS

In the study, 42 participants meeting the criteria were categorized into two groups: those experiencing neuropathic pain and those without (Table 1). The ROC curve (Fig 1) demonstrates the diagnostic capability of serum vitamin D levels, as the curve surpasses the 50% line. The area under the curve (AUC) value obtained was 71.4% (95%CI: 0.558-0.871; p=0.017), indicating moderate diagnostic efficacy. The ROC coordinates revealed a cut-off value for vitamin D of 30.25 ng/ml using the Youden index, with a sensitivity of 52.4% and a specificity of 85.7%.

The disparity in mean serum vitamin D levels between MH patients with and without neuropathic pain was evaluated using the unpaired T test. Patients without MH neuropathic pain exhibited a higher mean serum vitamin D level of 28.69 ± 8.16 ng/ml (p=0.021). Bivariate analysis examined the relationship between serum vitamin D levels (independent variable) and neuropathic pain in MH patients (dependent variable) using a cut-off point of 30.25 ng/ml. The hypothesis was tested using an unpaired categorical comparative test employing the Chi-square method (Table 2). Additionally, bivariate analysis explored other factors influencing neuropathic pain in MH patients, including gender, body mass index, leprosy reaction, compliance with multidrug therapy (MDT), medication status, peripheral nerve enlargement, and Pittsburgh Sleep Quality Index (PSQI) (Table 3).

Variables such as onset of diagnosis, peripheral nerve enlargement, leprosy reaction, and MDT treatment status exhibited significance in multivariate selection with a p-value <0.25 (Table 4), prompting further analysis in multivariate regression. The final stage of multivariate analysis identified two variables significantly associated with neuropathic pain in MH patients: vitamin D deficiency (OR: 11.398; 95%CI: 2.140-60.698; p=0.004), and peripheral nerve enlargement (OR: 5.68; 95%CI: 1.104-29.213; p=0.038) (Table 5). Although due to the nature of the study, several confounding factors such as duration and severity of MH, comorbidities, and sun exposure could deviate the results.

DISCUSSION

Our study, consistent with prior research, found a predominance of male participants (71.4%), aligning with systematic reviews indicating a higher susceptibility of men to Morbus Hansen (MH) infection. This gender disparity may be attributed to differences in health-seeking behaviors between genders, potentially leading to increased male exposure to MH disease.[22] Using the DN4 screening tool, our research identified tingling (50%) and electric shock sensations (40.5%) as the most frequently reported symptoms.[23] According to Toh et al., patients in Nepal predominantly reported tingling sensations (90%), followed by burning sensations and numbness at 80%.[24] Discrepancies in study results may arise from subjective complaints, limited participants, and variations in screening tools. In MH patients, vitamin D levels have been linked to bacterial indices, with Toruan et al.[3] reporting a mean of 14.85 ± 4.26 ng/ml. In our study, we observed higher levels, averaging 25.4 ± 9.383 ng/ml, possibly due to Indonesia's tropical climate and increased sunlight exposure. Among MH patients with neuropathic pain, mean serum vitamin D levels were lower (22.11 ± 9.54 ng/ml), with a mean difference of 6.586 ± 2.74. Prior studies have explored the association between vitamin D and neuropathic pain, particularly in diabetic neuropathy, where lower vitamin D levels were correlated with neuropathic pain. Vitamin D deficiency can impact nerve growth factor (NGF), myelin production, and inflammatory factors, contributing to axonal and myelin damage and hyperexcitability, ultimately leading to MH neuropathic pain.[9,11,25–27]

Bivariate analysis in our study revealed a significant association between low vitamin D levels and MH neuropathic pain, with a 6.6 times greater risk observed

TABLE 1. Basic characteristics of research participants.

Variables	Neuropathic Pain (n=21)	Without Neuropathic Pain (n=21)
Age (years) (median (min-max)	43 (23-63)	37 (20-81)
Educational Background		
Elementary School	5 (23.8%)	1 (4.8%)
Junior High School	1 (4.8%)	4 (19%)
Senior High School	6 (28.6%)	11 (52.4%)
University	9 (42.9%)	5 (23.8%)
Marital Status		
Single	4 (19%)	7 (33.3%)
Married	17 (81%)	14 (66.7%)
Employment		
Farmer/Labor	3 (14.3%)	3 (14.3%)
Self-employed	5 (23.8%)	3 (14.3%)
Private Employee	7 (33.3%)	9 (42.9%)
Government Employee	2 (9.5%)	0 (0%)
Others	4 (19%)	6 (28.6%)
Numeric Pain Rating Scale (median (min-max)	2 (0-6)	1 (0-5)
Nerve Enlargement		
N. Auricularis	3 (14.3%)	13 (61.5%)
N. Ulnaris	12 (57.1%)	4 (19%)
N. Peroneus	2 (9.5%)	10 (47.6%)
N. Tibialis	9 (42.9%)	8 (38.1%)
DASS- 21		
Depression		
Normal (0-9)	19 (90.5%)	19 (90.5%)
Mild (10-13)	2 (9.5%)	2 (9.5%)
Anxiety		
Normal (0-7)	21 (100%)	20 (95.2%)
Mild (8-9)	0 (0%)	1 (4.8%)
Stress		
Normal (0-14)	21 (100%)	21 (100%)

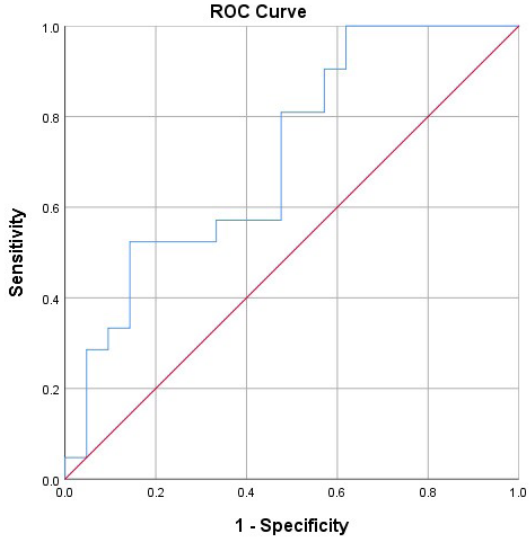

Fig 1. Results of the ROC Procedure - Serum Vitamin D Level Values for MH neuropathic pain

TABLE 2. Bivariate analysis of serum vitamin D levels with neuropathic pain in MH patients.

Variables	Neuropathic Pain	Without Neuropathic Pain	OR (95%CI)	p-value
Serum Vitamin D ng/ml (mean ± SD)	22.11 ± 9.54	28.69 ± 8.16		0.021*
Vitamin D Deficiency (<30.25)	18 (85.7%)	10 (47.6%)	6.6	
Vitamin D No deficiency (≥30.25)	3 (14.3%)	11 (52.4%)	(1.484 - 29.355)	0.022*

TABLE 3. Bivariate analysis of covariate variables with neuropathic pain in MH Patients.

Variables	Neuropathic Pain n (%)	Without Neuropathic Pain n (%)	OR (95%CI)	p-value
Gender				
Male	14 (66.7)	16 (76.2)	0.625	0.733
Female	7 (33.3)	5 (23.8)	(0.161-2.419)	
Body Mass Index				
Overweight-Obesitas	7 (33.3)	4 (19)	2.125	0.483
Underweight-Normoweight	14 (66.7)	17 (81)	(0.515-8.77)	
Leprosy Reaction				
Yes	13 (61.9)	8 (38.1)	2.641	0.217
No	8 (38.1)	13 (61.9)	(0.76-9.176)	
Onset of Diagnosis				
≥ 1 year	10 (47.6)	5 (23.8)	2.909	0.198
< 1 year	11 (52.4)	16 (76.2)	(0.777-10.887)	
MDT Compliance				
Poor	2 (9.5)	2 (9.5)	1	1.00
Good	19 (90.5)	19 (90.5)	(0.127-7.850)	
Treatment Status				
On Treatment	16 (76.2)	19 (90.5)	0.377	0.410
Release from Treatment	5 (23.8)	2 (9.5)	(0.057-1.977)	
Peripheral Nerve Enlargement				
Yes	17 (81)	13 (61.9)	2.615	0.306
No	4 (19)	8 (38.1)	(0.644-10.614)	
Vitamin B Supplementation				
No	16 (76.2)	15 (71.4)	1.28	1.000
Yes	5 (23.8)	6 (28.6)	(0.322-5.088)	
PSQI				
Poor Sleep (>5)	8 (38.1)	5 (23.8)	1.969	0.504
Good Sleep (≤5)	13 (61.9)	16 (76.2)	(0.518-7.488)	

TABLE 4. Multivariate logistic regression selection analysis.

Variables	Adjusted OR	95%CI	p-value
Onset of Diagnosis	2.909	0.777-10.887	0.113*
Peripheral Nerve Enlargement	2.615	0.644-10.614	0.179*
Leprosy Reaction	2.641	0.76-9.176	0.127*
MDT Treatment Status	0.337	0.057-1.977	0.228*
MDT Compliance	1.00	0.127-7.850	1.00
Vitamin D Deficiency	6.6	1.484-29.355	0.013*

NB:
*: statistically significant
Abbreviations: OR: Odds Ratio; CI: Confidence Interval

TABLE 5. Multivariate logistic regression analysis.

Variables	Adjusted OR	95%CI	p-value
Onset of Diagnosis	1.641	0.206-13.061	0.640
Peripheral Nerve Enlargement	5.680	1.104-29.213	0.038*
Leprosy Reaction	4.341	0.775-24.329	0.095
MDT Treatment Status	0.220	0.010-4.704	0.333
Vitamin D Deficiency	11.398	2.140-60.698	0.004*

NB:
*: statistically significant

among MH patients with vitamin D deficiency compared to those without (OR 6.6; CI 95% [1.484-29.355]). This finding aligns with Alam et al.'s study, which reported a 9.8 times increased risk of neuropathic pain in individuals with diabetes mellitus and vitamin D deficiency.[25] Vitamin D plays a crucial role in peripheral nerves by enhancing axonogenesis, sensory responses, and the expression of vitamin D receptors, particularly in small diameter neurons. Additionally, it activates calcium-binding proteins, enhances cellular calcium buffering, modulates inflammation, inhibits nitric oxide synthesis, and reduces oxidative stress.[5,6] Moreover, vitamin D contributes to neuroprotection by promoting nerve growth factor (NGF) production and preventing declines in NGF levels, crucial for peripheral nerve growth and pain modulation.[28] Elevated NGF levels can also inhibit the release of substance P and calcitonin gene-related peptide (CGRP), further influencing pain sensation.[7,8] In a study by Tiago et al., leprosy reaction emerged as a significant risk factor for neuropathic pain occurrence.[22] Lockwood et al. demonstrated that during leprosy reactions, M. leprae antigens trigger chronic neuritis and ectopic nerve activity, leading to chronic neuropathic pain in MH patients.[29] In our study, 61.9% of patients experiencing leprosy reactions reported neuropathic pain; however, bivariate analysis did not yield significance (p = 0.217). This suggests that neuropathic pain may not solely stem from the host's immune response but also from direct Schwann cell damage by M. leprae. The prevalence of neuropathic pain is notably higher in patients with longer MH diagnoses due to persistent nerve inflammation and M. leprae antigen presence.[22] Interestingly, in our

study, neuropathic pain incidence was similar among patients diagnosed with MH for less or more than one year, with no significant relationship observed (p = 0.198). However, Faridi et al. reported a correlation between MH disease duration and neuropathic pain incidence.[30] These discrepancies highlight the complex etiology of neuropathic pain in MH, warranting further investigation. MDT therapy does not guarantee prevention of neuropathic pain in MH patients. Even after completing treatment, patients may still experience neuropathic pain, as observed in studies by Pitta et al.[31] and Riecher et al.[32] Approximately 23.8% of patients experiencing neuropathic pain had completed MDT, consistent with findings from Mumbai.[32] However, Faridi et al. reported a 1.75 times increased risk of MH neuropathic pain at the initiation of antimicrobial therapy compared to after therapy. The majority of neuropathic pain patients in their study were still undergoing MDT, suggesting potential contributions from dead bacterial cells in nerve inflammation.[30,33] However, bivariate analysis in our study did not yield a significant result (p=0.41).

In a study by Giesel et al., nerve enlargement was prevalent in MH cases associated with neuropathic pain, with a higher incidence of sensory disturbances.[23] In our study, 81% of neuropathic pain patients exhibited peripheral nerve enlargement, indicating ongoing nerve inflammation contributing to neuropathic pain. Neuropathic pain can lead to psychological issues such as anxiety, depression, and sleep disorders, impacting patients' quality of life. While approximately 50% of MH patients with neuropathic pain reported insomnia in Giesel et al.'s study[23], only about 61.9% of our study's neuropathic pain patients reported sleep disorders. Bivariate analysis did not yield significance (p = 0.504), possibly due to variations in diagnostic tools. In assessments using the Hamilton Depression scale, depression rates were observed to be approximately 70%, 72.1%, and 77.8% in MH patients with neuropathic pain, diabetic neuropathic pain, and post-herpetic neuralgia patients, respectively. However, in our study utilizing the Depression Anxiety Stress Scales 21 (DASS-21), only four patients exhibited mild depression, with one patient experiencing mild anxiety and no reported stress. It is plausible that our study's assessment spanned varying periods of MH occurrence, which might have hindered a comprehensive depiction of depression within a singular period.[23] Multivariate analysis employing logistic regression revealed that independent risk factors for neuropathic pain in MH included vitamin D deficiency and peripheral nerve enlargement. Conversely, the presence of leprosy reactions, duration of MH affliction, and MDT treatment status did not exhibit statistically significant relationships with neuropathic pain in MB type MH. In this study, vitamin D deficiency (OR 11.398; CI 95% [2.140-60.698]; p=0.004) was identified as a more significant risk factor for neuropathic pain in MH compared to peripheral nerve enlargement (OR 5.68; CI 95% [1.104-29.213]; p=0.038). Within MH, there is an escalation in free radicals and other inflammatory responses, which contribute to macrophage activity, axonal damage, demyelination, and subsequent nerve ischemia. These processes, including peripheral nerve enlargement, can lead to neuropathic pain. However, our findings suggest that vitamin D deficiency poses a greater risk for neuropathic pain manifestation in MH patients compared to peripheral nerve enlargement.

This study is pioneering in exploring the relationship between vitamin D deficiency and MH neuropathic pain in Indonesia, offering valuable insights into risk factors for MB type MH. Employing multivariate analysis, the study expands understanding beyond vitamin D deficiency alone. Additionally, the widespread availability of vitamin D tests enhances the study's practical relevance in medical practice. Establishing a cut-off value for vitamin D deficiency at 30.25 ng/ml provides a basis for future research on neuropathic pain prevention.

However, inherent limitations exist. The study's sample size was constrained by the scarcity of diagnosed MB type MH cases, affecting statistical power and generalizability. Due to the challenge of long-term patient follow-up, a cross-sectional design was employed, preventing the establishment of causal relationships. Nerve conduction studies, considered a gold standard, were not incorporated due to resource constraints, potentially limiting the depth of pain assessment. While some risk factors were matched, resource constraints in a tertiary hospital limited adjustment for all confounding factors. Factors like sunscreen usage and clothing materials may introduce bias in vitamin D level assessments.

CONCLUSION

Neuropathic pain prevalence in this study is 50%, with MB type MH patients having serum vitamin D deficiency below 30.25 ng/ml facing a significant risk. Specifically, individuals with deficient vitamin D levels are 11.398 times more likely to experience neuropathic pain. However, given the limited sample size and cross-sectional study design, caution is warranted in interpreting the results. Early diagnosis of neuropathic pain is crucial, as it often goes undetected, leading to inadequate treatment. Ongoing research aims to identify predictive factors for neuropathic pain, offering potential interventions to alleviate symptoms in MH patients.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

Conceptualization, Formal Analysis, Project administration, Writing – original draft, C.T.; Data curation, Writing – review & editing, B.G.; Investigation Visualization, K.T.; Methodology, A.M., Resources, K.W.; Software, A.S.; Supervision, Validation, I.W.

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