Association between serum level of vitamin D (25-hydroxyvitamin D) and plasma level of vitamin D receptor with bacteriological index in leprosy patients

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Abstract

Macrophages respond against *Mycobacterium leprae* infection through interacting with vitamin D and vitamin D receptor (VDR). There has been no study analyzing the association between vitamin D and VDR with bacteriological index (BI) in leprosy patients in Indonesia. To analyze the serum level of 25-hydroxyvitamin D (25(OH)D) and plasma level of VDR as well as their association with BI in leprosy patients in Indonesia. This is a cross-sectional study. Serum level of 25(OH)D was assessed with *in vitro* chemiluminescent immunoassay. Plasma level of VDR was assessed with enzyme linked immunosorbent assay method. Median serum level of 25(OH)D was 12.68 ng/mL. There was no correlation between serum level of 25(OH)D and BI (r=0.033; p=0.869). Median plasma level of VDR was 1.36 ng/mL. There was no correlation between plasma level of VDR and BI (r=-0.063; p=0.749) and no significant association between BI and serum level of 25(OH) and plasma level of VDR (R^2=0.055). There was no association between serum level of 25(OH)D and plasma level of VDR with BI in leprosy patients.

Introduction

Leprosy is a chronic infectious disease caused by the bacterium *Mycobacterium leprae (M. leprae)*. The number of leprosy cases began to decrease after the use of multidrug therapy (MDT) regimens. However, the management of leprosy is still a challenge because of the lack of early detection, lengthy treatment, non-adherence, and the occurrence of leprosy reactions. In the 2019 Indonesian health data profile, the prevalence rate of leprosy in Indonesia in 2019 was 0.74 cases/10,000 population.[1,2]

The course of leprosy is not only influenced by bacterial factors, but also genetics and immunity. The immune system that first responds to *M. leprae* infection is cellular immunity, namely macrophages. Based on the study, it is known that various macrophage responses to infection, one of which is through the interaction between vitamin D and the vitamin D receptor (VDR). Based on the results of previous studies, it was reported that the incidence of vitamin D deficiency in Indonesia is quite high.[3,4]

The extraskeletal role of vitamin D became known after VDR was found in almost all cells and tissues of the body.[5] The vitamin D and VDR complexes will increase the expression of CYP27B, resulting in the conversion of the inactive form of vitamin D 25-hydroxyvitamin D (25(OH)D) to the active form 1,25-dihydroxyvitamin D (1,25(OH)2D).[6] Kim *et al.* demonstrated that activation of the vitamin D pathway during macrophage differentiation can enhance antimicrobial response against *M. leprae* infection.[7] The interaction of vitamin D with VDR on various immune cells will stimulate the expression of antimicrobial peptides, namely cathelicidin and defensin-2. Cathelicidin functions in destroying

the integrity of the bacterial cell membrane, resulting in bacterial death.[7]

In tuberculoid leprosy, interferon (IFN)-γ and interleukin (IL)-15 are produced. Cytokine IFN-γ is a marker of the Th1 subset which together with IL-15 is a strong inducer of antimicrobial activity mediated by CYP27B1 and vitamin D. Lepromatous leprosy has a cytokine profile of IFN-α and/or IFN-β, IL-10 and IL-4. IL-4 is a marker of the Th2 subset that has an effect on suppressing vitamin D function by increasing CYP24A activity. Based on these differences in immune responses, it can be concluded that the intracrine function of vitamin D plays a greater role in the tuberculoid type of leprosy than in lepromatous leprosy.[8]

Over the past two decades, there have been increasing reports of the association of vitamin D with leprosy. Research by Mandal *et al*. reported that the mean serum vitamin D level in the leprosy group was lower than the control group.[9] Research by Dewi *et al.* found a negative correlation between plasma 25(OH)D levels in MB type leprosy compared to PB type leprosy.[10] Based on the results of these studies, the researchers wanted to know the relationship between serum 25(OH)D levels and plasma VDR with BI in leprosy patients.

Materials and Methods

Research design

This study is an analytical observational study with a cross-sectional design which aims to determine the relationship between serum 25(OH)D levels and plasma VDR levels with BI in leprosy patients. Patients with a diagnosis of leprosy underwent BI examination, examination of serum 25(OH)D levels, VDR plasma levels, and filling out a sun exposure questionnaire.

Research population

Patients aged 18-59 years old diagnosed with leprosy attending the Dermatology and Venereology Outpatient Clinic, Cipto Mangunkusumo National Hospital (RSCM) were taken as research subjects from November 2021 after obtaining ethical approval, until the minimum sample size of 28 is met in April 2022. Subject selection was done in a sequential manner (consecutive sampling). Patients with a history of MDT treatment; took corticosteroids or other immunosuppressive drugs in the 12 days prior to blood collection; took calcitriol, supplements containing vitamin D2, or vitamin D3 supplements in the past month; pregnant or breastfeeding; with obesity, impaired liver function, renal function, malignancy, and malabsorption; and autoimmune diseases were excluded.

Materials and workflow

Initial examination began with the collection of the subjects' data, including sociodemographic, serum levels of 25(OH)D, VDR plasma levels, BI, and weekly sun exposure score questionnaire. Then, enforcement of leprosy diagnosis was conducted by researchers and supervisors. The leprosy diagnosis was brought if they fulfilled at least one of the three cardinal signs, and the bacterial index would be assessed to the Ridley-Jopling logarithmic scale. The content of vitamin D 25-OH in serum/plasma was determined by direct competition chemiluminescence immunoassay (CLIA) with LIASON® (DiaSorin, Saluggia, Italy). VDR plasma level assessment was based on the principle of sandwich ELISA with the LifeSpan BioScience, Inc. (LSBio, Shirley, MA, USA) device which is a Human Vitamin D Receptor/VDR ELISA Kit (ELISA Sandwich) Catalog No. LF-F5306.

Research ethics

This research had been declared to have passed the ethical review by the Health Research Ethics Committee, Faculty of Medicine, University of Indonesia based on letter number KET1045/UN2.F1/ETIK/PPM.00.02/2021 and obtained permission to conduct research from RSCM numbered LB.02.03/2.6.1/204/2021. Researchers maintained the confidentiality of subjects' identity and informed consents were collected from all the subjects.

Data analysis

All subject's data obtained from the examination were recorded. The data that has been collected will be edited, verified and coded, then entered into variables using Microsoft Excel 2016 and SPSS Statistics 20 software. The data were used to determine the distribution of the data and the coefficient of variation. If the data distribution is normal, then the mean value and standard deviation were used, otherwise the median value and the minimum–maximum value were used. Furthermore, the Pearson/Spearman correlation test will be carried out according to the normality of the data. Linear regression analysis was conducted to determine the relationship between levels of 25(OH)D2, levels of VDR and BI using the stepwise method.

Results

Sociodemographic characteristics

The sociodemographic characteristics of subjects are shown in Table 1. Subjects had a mean age of 38.21 years with the youngest age was 18 and the oldest was 53.

Table 1. Sociodemographic characteristics of subjects.

Sociodemographic characteristics	N (%)
Age in years (mean ± standard deviation)	38.21±10.66
Age group	
18-29	8 (28.6)
30-39	7 (25)
40-49	7 (25)
50-59	6 (21.4)
Gender	
Man	18 (64.3)
Woman	10 (35.7)
Occupation	
Not working/retired	8 (28.6)
Employee	12 (42.9)
Self-employed	8 (28.6)
Education	
Low	3 (10.7)
Intermediate	18 (64.3)
High	7 (25)
Financing	
National Health Services	26 (92.9)
Personal	2 (7.1)

Clinical characteristics

The clinical characteristics of subjects are shown in Table 2. In this study, the median score of subject sun exposure was 17 with the smallest score of 12 and the largest score of 42. All subjects in this study were diagnosed with multibacillary leprosy (100%) with BL type (35.6%) as the most common type based on the Ridley-Jopling classification. The median BI was +2 with the smallest value 0 and the largest value +4 with the majority of subjects having BI 0.

Serum 25(OH)D levels in newly diagnosed leprosy patients

In this study, the normality test for 25(OH)D serum levels showed an abnormal distribution so that it was displayed in the form of the median (minimum value - maximum value). The median serum 25(OH)D level was 12.68 ng/mL with a range of 4.88-44.74 ng/mL. Serum 25(OH)D levels in newly diagnosed leprosy patients are shown in Table 3.

Correlation between bacterial index and serum level of 25(OH)D

Numerical data of serum 25(OH)D and BI levels were not normally distributed, so Spearman's test was performed to analyze the correlation. There was no significant correlation between BI and serum levels of 25(OH)D (r=0.033; p=0.869).

Vitamin D receptor plasma levels in newly diagnosed leprosy patients

In this study, the normality test of VDR plasma levels showed an abnormal distribution therefore it was displayed in the form of the median (minimum value - maximum value). VDR plasma levels in newly diagnosed leprosy patients are shown in Table 4.

Correlation between bacteriological index and vitamin D receptor plasma levels

The numerical data of VDR plasma levels and BI were not normally distributed, so Spearman's test was performed to analyze the correlation. There was no significant correlation between BI and VDR plasma levels (r=-0.063; p=0.749).

Relationship between bacterial index and serum 25(OH)D levels and vitamin D receptor plasma levels

The multivariate regression analysis of the independent variables on the BI of patients diagnosed with leprosy is shown in Table 5. Based on the multivariate regression analysis that has been carried out, there are no significant variables on BI.

Correlation of 25(OH)D serum levels with sun exposure score

Numerical data of 25(OH)D serum levels and sun exposure scores were not normally distributed, so Spearman's test was performed to analyze the correlation. Correlation analysis using Spearman's test showed that there was a strong positive correlation between serum 25(OH)D levels and sun exposure scores (r=0.863; p<0.001).

Table 2. Clinical characteristics of subjects.

Clinical characteristics	N (%)
Sun exposure score in points (median, min - max value)	17 (12-42)
BMI in kg/m² (mean ± standard deviation)	22.36±9.85
BMI category	
Thin	4 (14.3)
Normal	20 (71.4)
Pre-obesity	4 (14.3)
Obesity	0
Types of Leprosy based on WHO	
Paucibacillary	0
Multibacillary	28 (100)
Leprosy type based on Ridley-Joppling	
Tuberculoid	0
Borderline tuberculoid	7 (25)
Borderline	2 (7.2)
Borderline lepromatous	10 (35.6)
Lepromatous	9 (32.2)
Bacterial index (median, min - max value)	1.5 (0-4)
Bacteria index category	
0	9 (32.1)
+1	5 (17.9)
+2	7 (25.0)
+3	5 (17.9)
+4	2 (7.1)
+5	0

BMI, body mass index; WHO, World Health Organization.

Table 3. Serum levels of 25(OH)D in newly diagnosed leprosy patients.

25(OH)D serum levels	N (%)
Deficiency	20 (71.4)
Insufficiency	4 (14.3)
Normal	4 (14.3)

Table 4. Vitamin D receptor plasma levels in newly diagnosed leprosy patients.

Parameter	Score
VDR plasma level in ng/mL	1.36 (0.26-8.04)

VDR, vitamin D receptor.

Table 5. Multivariate regression analysis of the independent variables on the BI of patients diagnosed with leprosy.

No	Variable	Bacterial index			
		Coefficient	SE	t	p
1.	Serum 25(OH)D levels	0.133	0.024	0.684	0.500
2.	VDR plasma level	0.191	0.181	0.982	0.336

VDR, vitamin D receptor; SE, standard error. R square 5.5%.

Discussion

Serum 25(OH)D levels in newly diagnosed leprosy patients

In this study, the median serum 25(OH)D level was 12.68 ng/mL with a range from 4.88 to 44.74 ng/mL with the majority of patients experiencing deficiency (71.4%). The research of Darus *et al.* in Medan reported a higher mean serum 25(OH)D level of leprosy patients (22.27 ng/mL).[11] These levels are lower than normal individuals (33.00 ng/mL).[11] The low levels of vitamin D in the majority of the subjects in this study may be able to describe the magnitude of the number of vitamin D deficiency in the Indonesian population. Green et al. reported the incidence of vitamin D deficiency in Indonesia and Malaysia in the female population aged 18-40 years by 60%.[12]

The level of 25(OH)D is mainly influenced by the synthesis of vitamin D in the skin by the help of sunlight, in this study assessed by a weekly sun exposure questionnaire. The majority of the low weekly sun exposure scores in subjects may be one of the causes of low 25(OH) levels in almost all subjects. In this study, it was found that two subjects with high sun exposure had normal levels of 25(OH)D, namely 38.86 ng/mL and 44.74 ng/mL.

Levels of 25(OH)D in leprosy patients in this study were lower than similar studies in Medan, this may be because previous studies were conducted before the COVID-19 pandemic, while this study was conducted during the COVID-19 pandemic. During this pandemic, most activities are carried out at home so that it can lead to lower serum 25(OH)D levels. In addition, the low serum 25(OH)D level in this study may be due to the unhealthy eating habits of the Jakarta population, which includes foods with high sugar or salt content and fatty foods.[13] This unhealthy eating habits can cause the intake of foods rich in vitamin D to decrease so that it may affect the low levels of vitamin D in leprosy patients in this study. Vitamin D acts as an immunomodulator that can increase the natural immune response and trigger antimicrobial activity through binding to VDR. One of the targets of VDR is the LL37 gene (catelicidin) which encodes a protein that plays a role in the elimination of intracellular bacteria. When there is a chronic infection, such as leprosy infection, 25(OH)D is metabolized rapidly therefore serum levels are reduced.[11] The majority of 25(OH)D serum levels in this study were included in the deficient category, in accordance with the above theory.

Correlation between bacteriological index and serum levels of 25(OH)D

No significant correlation was found between BI and serum levels of 25(OH)D (r=0.033; p=0.869). A previous study in Medan reported different findings, namely that there was a moderately significant negative correlation between BI and serum 25(OH)D levels in newly diagnosed leprosy patients (r=-0.510; p<0.05). This correlation indicates that the smaller the BI, the higher the serum 25(OH)D level. Toruan *et al.* also reported that there was a significant relationship between serum 25(OH)D levels and the type of leprosy.[14] The study reported that there were more PB-type MH patients with serum 25(OH)D levels greater than 17.55 ng/mL than MB-type leprosy patients. This study examined 33 subjects with the majority of subjects diagnosed with MB type leprosy (66.7%).[14-16] In addition, Rusyati *et al.* in Bali reported that there was a higher serum 25(OH)D level in PB type leprosy than MB type.[17]

In this study, there was no significant correlation, possibly because there were no subjects diagnosed with PB type leprosy, hence the data needed to obtain a correlation was not sufficient. There are differences in immune responses from the spectrum of leprosy due to differences in the cytokine profiles produced, wherein the tuberculoid type of leprosy has a greater role in the intracrine function of vitamin D compared to lepromatous type of leprosy. In addition, lower exposure to sunlight during the pandemic also affected the subjects' serum 25(OH)D levels, which tended to be low.[15] The unhealthy eating habits of the Jakarta population and mostly rely on fast food can also cause relatively low serum 25(OH)D levels in almost all patients.[13] Another factor that may play a role is the process of examining acid-fast bacilli carried out. False-negative results can result from inadequate preparation, improper staining, and inadequate readings.[16] These factors may cause an uneven distribution of data so that the correlations obtained are not significant.

Vitamin D receptor plasma levels in newly diagnosed leprosy patients

The median VDR plasma level was 1.36 ng/mL with a range of 0.26-8.04 ng/mL. Research on VDR levels in leprosy patients is still very limited, Rusyati *et al.* reported lower VDR plasma levels (0.02780 ng/mL) with the lowest level of 0.01951 ng/mL and the highest level of 0.03456 ng/mL.[17] Another study that assessed VDR expression in leprosy reported that leprosy patients had lower peripheral blood mononuclear cell VDR mRNA expression than healthy individuals.[9]

VDR is widely distributed in various body tissues, one of which is in peripheral blood monocytes.[18] A study states that the regulation of VDR genes is influenced by environmental, genetic, and epigenetic. Vitamin D is known to autoregulate VDR, so vitamin D levels may affect VDR.[19] Polymorphism variations play a role in influencing the VDR response to vitamin D.[20] Luong *et al*. said that polymorphisms in VDR can affect susceptibility to leprosy because it plays a role in the strength of the host immune response and determines the type of leprosy.[21]

Correlation between bacteriological index and vitamin D receptor plasma levels

This study did not find a significant correlation between BI and VDR plasma levels (r=-0.063; p=0.749). This finding contradicts the findings of several previous studies. Rusyati *et al*. reported that there was a strong negative correlation between B and plasma VDR levels in MB type leprosy patients (r=-0.954; p<0.001).[17] These results indicate that the lower the VDR plasma level, the higher the BI. Another study by Mandal *et al.* found that leprosy patients who had low VDR plasma levels generally had high BI although not statistically analyzed.[16] VDR is expressed by immune cells, namely T cells, B cells, neutrophils, and antigen-presenting cells. When 1,25(OH)2D interacts with VDR, chemotaxis, phagocytosis, and B cell proliferation will occur, followed by immunoglobulin production.[17] In addition, Roy *et al*. reported a significant association between VDR polymorphisms and BI.[21] These findings suggest that VDR plays a role in the pathogenesis of leprosy.[9,17,22] The TaqI polymorphism studied in Roy *et al*. consists of 3 genotypes.[22] The tt genotype plays a role in increasing the stability of VDR mRNA which will trigger a cellular immune response, therefore more often to be found in tuberculoid leprosy.[21,22] In this study, all subjects were classified into MB type leprosy with the majority of subjects having lepromatous type leprosy. This may lead to non-significant correlation.

Research by Favus *et al.* reported that an increase in endogenous levels of 1,25(OH)2D can increase VDR levels in the intestine.[23] VDR levels are also thought to be influenced by age.[24]

Different results were obtained by Wood *et al*. that there was no significant change in the levels of unbound VDR in the duodenum with respect to age.[25] Another study also reported that there was no significant difference in VDR levels in the duodenum between young and old women.[26]

The VDR assessment in this study used the ELISA method which can measure both bound and free vitamin D.[27] The non-significant correlation in this study may also be caused by the measurement of the total VDR, a specific measurement of the level of the bound VDR may give better results. Until now there has been no research that explains the relationship between VDR and BI directly. Existing research links the relationship between VDR and BI through vitamin D. Therefore, no conclusions can be drawn regarding the exact cause of the absence of a correlation between VDR plasma levels and BI.

Relationship between bacterial index and serum 25(OH)D levels and vitamin D receptor plasma levels

Based on the multivariate regression analysis that has been carried out, there is no significant relationship between serum 25(OH)D levels and plasma VDR levels on BI. Several previous studies reported a significant correlation and relationship between IB both with serum levels of 25(OH)D and plasma levels of VDR.[11,17] In this study, no significant correlation was found. This finding may be due to the influence of various factors on each variable so that the distribution of data is less evenly distributed, including the COVID-19 pandemic condition, eating habits, quality of smear examination, and genetic factors.

Correlation of 25(OH)D serum levels with sun exposure score

Correlation analysis using Spearman's test showed that there was a strong positive correlation between serum 25(OH)D levels and sun exposure scores ($r=0.863$; $p<0.001$). Nurbazlin *et al*. in Malaysia reported similar results that there was a positive correlation between 25(OH)D serum levels and sun exposure scores.[28] The study also concluded that each 25(OH)D serum level increased by 1.93 nmol/L for each point increase in sun exposure score.[28] Another British study in a South Asian population reported that serum 25(OH)D levels in that population were very low with less sun exposure.[29] When human skin is exposed to sunlight, about 15% of 7-dehydrocholesterol is converted to previtamin D3, the ingredient of vitamin D3. In addition, UVB will be absorbed and converted into suprasterol and 5,6-transvitamin D3.[30] These theories support the findings of the strong positive correlation found in this study.

This study is the first study in Indonesia to assess the relationship between serum 25(OH)D levels and plasma VDR levels with bacterial index in leprosy patients with the study subjects' weekly sun exposure were also assessed. However, this study only involved subjects with MB type of leprosy, so further research is needed for the population of subjects with PB type of leprosy. This study did not examine the duration of leprosy that may be associated with serum 25(OH)D and VDR plasma levels of subjects.

Conclusions

There was no relationship between serum 25(OH)D levels and VDR plasma levels with BI in leprosy patients. Checking vitamin D levels and vitamin D supplementation in leprosy patients therefore is not recommended. Further studies with various types of leprosy to analyze the relationship between serum 25(OH)D and VDR plasma levels with various types of leprosy should be conducted.

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