

The correlation between vitamin D deficiency and the severity of painful diabetic neuropathy in patients with type 2 diabetes mellitus (T2DM)

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ABSTRACT

Background: Diabetes and its complications are the major burden health problem worldwide, and diabetic neuropathy is one of the major complications. Vitamin D levels found to be significantly lower in people with painful diabetic peripheral neuropathy compared with healthy people. The data about the vitamin D levels and severity of the neuropathy in Indonesia are very limited.

Objective: This study aims to investigate the possible relationship between vitamin D levels and the severity of diabetic peripheral neuropathy. **Methods:** A cross-sectional study was carried out during the period from October 2019 to December 2019 on 53 subjects with diabetic peripheral neuropathy. The patient's clinical profile including age, gender, and duration of diabetes, HbA1c, and associated microvascular complications was documented. The treatment history was recorded from electronic prescribing data. The severity of neuropathy was measured with the Toronto Clinical Neuropathy Scoring System. Serum 25-OH vitamin D levels were measured by enzyme immunoassays for the quantitative measurement of total serum 25-OH Vitamin D level in ng/mL.

Results: Vitamin D levels based on the severity of neuropathy are divided into mild, moderate, and severe. At mild neuropathy severity, the average patient's vitamin D level was 19 ± 8.85 ng/mL, at moderate severity the patient's vitamin D level was 16.25 ± 6.08 ng/mL, and for severe neuropathy, the average vitamin D level was 13.35 ± 6.20 ng/mL. Spearman correlation test obtained r value = -0.439 and p value = 0.001 . **Conclusions:** There is a moderate, significant, and negative patterned correlation between vitamin D level and diabetic peripheral neuropathy severity.

KEYWORDS: diabetic peripheral neuropathy severity; type 2 diabetes mellitus; vitamin D

INTRODUCTION

Diabetes and its complications is the major burden health problem in worldwide and Indonesia (1,2). The data from national health survey in Indonesia showed that the prevalence of diabetes increase 2% among above 15 years old population (2). Diabetic neuropathy is one of the major complications (2). The prevalence of diabetic peripheral neuropathy in newly diagnosed diabetic patients reaches about 8%. The proportion increase up to 50% in patients with long-standing disease (3). Among 15% of all diabetic patients will develop foot ulcer and nontraumatic amputation of lower limbs (4).

The pathogenesis of diabetic peripheral neuropathy is a multifactorial process and multiple hypotheses have been postulated. Previous basic research showed that abnormal expression of sodium and calcium channels, metabolic and autoimmune disorders which lead to glial cell activation contribute to the pathogenesis (5). Recent studies showed that blood vessel changes and activation of central pain mechanisms also played significant role (5,6).

Low vitamin D levels are associated with obesity and insulin resistance (7). Low 25-hydroxyvitamin D levels have been associated with sensory neuropathy in

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diabetes (8). Vitamin D levels also might be correlated with the severity of the neuropathy (9).

The role of vitamin D in diabetic neuropathy has been studied in previous studies. A recent systematic review showed that vitamin D deficiency is associated with the generation and development of DPN in Caucasian with type 2 diabetes mellitus (T2DM), and in Asian, diabetic patients with vitamin D deficiency are 1.22 times to suffer from DPN compared with normal vitamin D level (10). A study showed that 25-hydroxyvitamin D levels were significantly lower in people with painful diabetic peripheral neuropathy compared with healthy volunteers and no diabetic peripheral neuropathy patients. Lower 25-hydroxyvitamin D level also correlated with lower cold detection thresholds ($r=0.39$, $p=0.02$) and subepidermal nerve fibre densities ($r=0.42$, $p=0.01$) (11). The data about the vitamin D levels and severity of the neuropathy in Indonesia are very limited. This study aims to investigate the possible relationship between vitamin D levels and the severity of diabetic peripheral neuropathy.

METHODS

Study design and participants

A cross sectional study was carried out during the period from October 2019 to December 2019 on 53 subject with diabetic peripheral neuropathy. The study included all patients above the age of 18 years with T2DM with symptoms suggestive of peripheral neuropathy. Patients with neuropathy due to causes other than diabetes and those who refused informed consent were excluded from the study. The sample size was calculated based on estimate of 20% prevalence of neuropathy in diabetes, allowing for an error of 10%, and thereby a total of 50 patients were recruited. After obtaining approval from the institutional ethical committee (498/E/RSB/2019), patients were recruited in the study based on the inclusion criteria. Informed consent was obtained and the patients were subjected to history and physical examination.

Measures

In this study, the diagnosis of diabetic peripheral neuropathy based on systematic measurement by a neurologist with Diabetic Neuropathy Symptom and

Diabetic Neuropathy Examination tools (12). The type 2 diabetes mellitus patients were obtained from outpatient neurology clinic of Bethesda Hospital Yogyakarta Indonesia. A standardized instrument was used to record demographic details of the patients. The patient's clinical profile including age, gender, and duration of diabetes, status of glycemic control reflected by HbA1c and associated microvascular complications were documented. The treatment history was recorded from electronic prescribing data.

The severity of painful diabetic neuropathy. The severity of neuropathy was measured with the Toronto Clinical Neuropathy Scoring System (TCNS) (13). The individual patient's TCNS score was documented out of a total of 19. Severity of neuropathy was classified based on the score as: no neuropathy (0 to 5), mild neuropathy (6 to 8), moderate (9 to 11), and severe diabetic neuropathy (12 to 19).

Vitamin D serum level. The vitamin D level was measured by standardized method in Prodia Research Laboratory. Serum 25-OH vitamin D levels were measured by enzyme immunoassays for the quantitative measurement of total serum 25-OH Vitamin D level in ng/mL. The level < 10 ng/mL is deficiency, 10-30 ng/mL is in-sufficiency, and 30-100 ng/mL is sufficiency (14).

Data analysis

Continuous variables were assessed for normality using Shapiro-Wilk's test. If the variables were normally distributed they were expressed as mean \pm standard deviation, otherwise median (interquartile range). Categorical variables were expressed either as percentage or proportions. A comparison of normally distributed continuous variables was done by independent sample t-test, non-normally distributed continuous variables by Mann-Whitney U test, and categorical variables by either Chi-Square test or Fisher's-exact test based on the number of observations. Data analysis and validation was carried out by SPSS. All p-values less than 0.05 were considered statistically significant.

RESULTS

The study was conducted on 53 T2DM peripheral neuropathy patients, consisting of 11 male patients (20.8%) and 42 female patients (79.2%). The mean age of

observed patients was 57.8±8.8 years. Of the 53 patients who participated in the study, 29 patients had T2DM for more than 15 years (54.7%), 12 patients had T2DM for 10 to 15 years (22.6%), and 12 patients had T2DM for less than 10 years (22.6%) (**Table 1**). In this study, vitamin D levels were measured in all study patients. The mean vitamin D level in male patients was 20.64±3.96 ng/mL and in female patients was 14.24±7.04 ng/mL (**Table 2**). The results of measurement of vitamin D level based on the severity of neuropathy are divided into mild, moderate, and severe. At mild neuropathy severity, the average of patient's vitamin D level was 19±8.85 ng/mL, at the moderate severity the patient's vitamin D level was 16.25±6.08 ng/mL, and for severe neuropathy, the average vitamin D level was 13.35±6.20 ng/mL (**Table 3**). Correlation analysis in Table 3 shows the correlation between vitamin D level and neuropathy severity and the result shows that decreasing vitamin D level correlates with increased neuropathy severity ($r = -0.439$; $p=0.001$).

There was a statistically significant relationship between gender, hypertension, and status of glycemic control as factors that affect patients' vitamin D levels ($p<0.05$). Confounding variables such as duration of DM, history of cardiovascular disease, oral antidiabetic medication, and insulin therapy did not show a significant relationship with the patient's vitamin D level ($p>0.05$).

DISCUSSION

The data showed that only one study subject had sufficient vitamin D levels. The proportion of subjects with a deficiency was 12/53 (22.6%). Most of the study subjects had insufficient vitamin D levels (75.4%). This result is consistent with some previous studies. The study from Bayani, from 120 T2DM patients showed that vitamin D level was deficient in 77 (64.2%), insufficient in 30 (25%), and sufficient in 13 (10.3%) patients (15). A large epidemiological study showed that the overall prevalence of patients with low vitamin D levels (vitamin D deficiency and insufficiency) was 1257 (83.7%); and 1231 (82%) were newly diagnosed cases. Out of 1257 (83.7%) patients with low vitamin D levels, 60.9% of patients had vitamin D deficiency, and 22.9% of patients had vitamin D insufficiency (16).

Table 1. Baseline characteristic

Characteristic	n=53	%
Gender		
Male	11	20.8
Female	42	79.2
Age (years)		
<60	33	62.3
≥60	20	37.7
Duration of DM (years)		
<10	29	54.7
10-15	12	22.6
>15	12	22.6
Hypertension		
Yes	26	49.1
No	27	50.9
Cardiovascular disease		
Yes	13	24.5
No	40	75.5
Vitamin D level (ng/mL)		
Deficiency (10)	12	22.6
Insufficiency (10-30)	40	75.5
Suficiency (30-100)	1	1.9
Toxicity (>100)	0	0
Oral antidiabetic medication		
Yes	50	94.3
No	3	5.7
Insulin		
Yes	20	37.7
No	33	62.3
Status of glycemic control		
Controlled	35	66.0
Uncontrolled	18	34.0

This study showed that patients with severe neuropathy are correlated with low vitamin D status. Some previous studies showed a similar result. The study from 60 patients with diabetes (thirty with neuropathy and thirty without neuropathy) showed that vitamin D levels were significantly decreased in diabetic patients and those with neuropathy when compared to those without neuropathy ($p<0.05$). Vitamin D levels were significantly reduced with increasing severity of neuropathy ($p=0.001$) (17). Another study conducted by Ahmadih reported that the prevalence of diabetic neuropathy increases with a decrease in 25-OH vitamin D level. The percentage of neuropathy increased in patients with 25-OH vitamin D level below 20 ng/mL (18).

There is emerging evidence that vitamin D is a neurotrophic substance, but its role in diabetic neuropathic pain needs further studies (19). Some

Table 2. The vitamin D level comparison based on the characteristic of the subjects

Characteristic	Mean vitamin D level (ng/mL)	SD vitamin D level (ng/mL)	P
Gender			
Male	20.64	3.96	0.003
Female	14.24	7.04	
Duration of DM (years)			
<10	16.17	7.61	0.105
10-15	17.67	5.35	
>15	12.00	5.98	
Hypertension			
Yes	17.73	7.49	0.030
No	13.48	5.91	
Cardiovascular disease			
Yes	15.69	6.63	0.844
No	15.53	7.20	
Oral antidiabetic medication			
Yes	15.68	7.18	0.729
No	13.67	2.08	
Insulin			
Yes	15.45	6.03	0.876
No	15.64	7.62	
Status of glycemic control			
Controlled	17.54	6.89	0.004
Uncontrolled	11.72	5.59	

Table 3. The vitamin D level based on the severity of neuropathy

Vitamin D	Severity of neuropathy		
	Mild	Moderate	Severe
Mean (ng/mL)	19.00	16.26	13.35
Standard deviation (ng/mL)	8.85	6.08	6.20
Significance	0.001		

researcher hypothesized that vitamin D deficiency may potentiate diabetic nerve damage and may impair nociceptor function, resulting in pain at a threshold of serum 25(OH) vitamin D higher than that in the non-diabetic population (20).

The next important question is “should we add vitamin D treatment in patients with painful diabetic neuropathy”. A quasi-experimental trial sixty type 2 DM subjects (30-65 years old) with painful diabetic neuropathy was performed. Patients received

weekly 50000 IU of vitamin D3 for 12 weeks orally. Among 60 T2DM patients, 58 completed the study. At the end of study, HbA1c, vitamin D, and patient’s clinical condition assessed by Michigan Neuropathy Screening Instrument (MNSI) (both questionnaire and physical examination) improved significantly (p-value<0.001). Oral supplementation of vitamin D (50000 IU) once a week for 12 weeks was associated with a significant decrease in the symptoms and signs of diabetic neuropathy (21). Lee and Chen showed that vitamin D supplementation over 3 months improved neuropathic symptoms by 50% in diabetic patients with vitamin D deficiency at baseline (22).

The mean vitamin D level in male patients in this study was 20.64±3.96 ng/mL, and female patients were 14.24±7.04 ng/mL. Gender was found to have a statistically significant effect on vitamin D levels. In previous studies, it was stated that gender affected vitamin D status, in which 25(OH)D level of women were lower than men and played a role in determining the severity of coronary artery disease (23). The duration of T2DM patients in this study were divided into less than 10 years, 10-15 years and more than 15 years. The duration of DM was found to be statistically insignificant due to vitamin D level. Based on theory that the severity of DM associated with prolonged hyperglycemia that can cause nerve damage and exacerbate neuropathy symptoms (24).

Hypertension in this study was significantly related to vitamin D level. Another study also found that every 10% increase in plasma 25(OH)D level was associated with a decrease in diastolic and systolic blood pressure and 8.1% decreased hypertension (OR=0.92, 95% CI: 0.87–0.97; p=0.002) (25). In this study, the history of cardiovascular disease did not significantly influence vitamin D level. Maintaining optimal vitamin D level is important not only for maintaining calcium homeostasis but also for the risk of cardiovascular disease and blood pressure control. Vitamin D has an effect on the cardiovascular system by reducing the activity of the renin angiotensin-aldosterone system, decreases blood pressure, and has anti-inflammatory and antithrombotic effect (26).

Oral antidiabetic medication and insulin therapy do not significantly influence vitamin D level. The status

of glycemic control reflected by HbA1c is significantly related to vitamin D level. The same thing also found in another study that there is a significant relationship in the vitamin D supplementation to decrease HbA1c ($7.9 \pm 1.7\%$ vs $7.4 \pm 1.2\%$, $p=0.001$) (27).

The study has some limitations. It was a hospital-based study and hence the results may not be generalized to the population on a community basis. The authors could not find enough subjects with normal vitamin D status. We also did not compare the vitamin D level in patients without neuropathy. As a preliminary study on the correlation of vitamin D with neuropathy in Indonesia, further studies and clinical trials are warranted.

CONCLUSIONS

There is a moderate, significant, and negative patterned correlation between vitamin D level and diabetic peripheral neuropathy severity.

Declaration of conflicting interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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