Prevalence and Factors Related to Hypovitaminosis D in Type 2 Diabetes Mellitus Patients with Depression

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ABSTRACT

Background: *The prevalence of hypovitaminosis D (hypoD) in patients with type 2 diabetes mellitus (T2DM) and depression has not been documented. In addition, the risk factors are unknown. This study aimed to identify the prevalence of and risk factors for hypoD in patients with T2DM who also have depression.* ***Methods:*** *118 patients with T2DM who visited the outpatient endocrinology clinics at Cipto Mangunkusumo National Hospital between December 2019-September 2022 provided the clinical and demographic data for this cross- sectional study, including body mass index, blood pressure, glycosylated haemoglobin (HbA1c), lipid profiles, therapy, gender, age, marital status, and educational background. We used The Beck Depression Inventory II (BDI-II) to evaluate depression. We used enzyme-linked immunosorbent assay kit to assess the dependent variable: serum vitamin D. We characterized serum vitamin D levels into three groups (normal, 30 ng/mL; insufficient, 20-29 ng/mL; deficient, 20 ng/mL). We also used analyses of variance to examine the anthropometric, clinical, and biochemical factors between the three groups.* ***Results:*** *118 subjects with T2DM. Their median age was 56 years old (48, 75-60 years old), with a BDI-II score of 17 (15-19), and a serum concentration of vitamin D. The D level was 18.3 ng/mL (9.17–29.46 ng/mL). Only 21.8% of patients with T2DM and depression had sufficient levels of vitamin D. We used multivariable analysis of variance model to examine the associations between age, BDI-II score, HbA1c, and systolic and diastolic blood pressure with vitamin D level. Age and BDI-II score both had a statistically significant effect on vitamin D levels.* ***Conclusion:*** *This cross-sectional study discovered that patients with T2DM and depression had a high prevalence (77.7%) of hypoD. Age and BDI-II score both affected differences in vitamin D levels with statistical significance.*

Keywords: *hypovitaminosis D, type 2 diabetes mellitus, depression.*

INTRODUCTION

As a global public health issue, hypovitaminosis D (hypoD) affects people of all ages.[1] Some findings suggest that vitamin D has a significant role in the health of the brain, nervous system, and depression, in addition to its effects on calcium metabolism, bone, proliferation, differentiation, and immunological modulation.[2] Vitamin D deficiency was associated with an 8-14% increase in the prevalence of depression.[3] According to cross-sectional studies,[4,5] serum 25-hydroxyvitamin D or 25(OH)D concentrations and depressive symptoms have an inverse relationship. Vitamin D regulates serotonin levels and vitamin D deficiency causes lower amounts of serotonin.[6] Low serotonin levels may contribute to the development of clinical depression.[7]

Strong evidence has emerged recently linking hypoD to the development of insulin resistance and abnormalities in insulin secretion potentially interfering with type 2 diabetes mellitus (DM).[8] Patients with diabetes and prediabetes were found to have lower serum levels of 25(OH)D than people with normal glucose tolerance.[9,10] Low serum 25(OH)D levels have been associated with an increased risk of metabolic syndrome and type 2 diabetes in epidemiologic research, which may be partially explained by a rise in fat mass.[11] Long-term complications of diabetes include micro- and macrovascular disease. According to a recent systematic review and meta-analysis, depression is connected to an increased risk of incident macro- and microvascular issues, and diabetic complications are linked to an increased chance of developing depression in the future.[12]

A change in vitamin D homeostasis may contribute to the emergence of type 2 diabetes and hypoD is directly related to depression.[13,14] Many studies have examined the effect of abnormal vitamin D levels and depression[5,7,11,14,15] and the effect of hypoD in DM.[8,10,11,16,17] However, the prevalence of hypoD in patients with type 2 DM and depression, and its contributing variables are still poorly understood.

Until now, no study has looked at factors related to hypoD in patients with type 2 DM and depression. The goal of this study was to determine the prevalence of vitamin D insufficiency and deficiency in patients with type 2 DM and depression. We also investigated the factors linked to low vitamin D plasma levels. Our hypotheses for age, gender, BDI-II score, body mass index (BMI), glycosylated haemoglobin (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) were related to low vitamin D levels in patients with type 2 DM and depression.

METHODS

Study Design and Setting

This cross-sectional study used a convenience sampling technique to obtain data from patients in outpatient endocrinology clinics at the Cipto Mangunkusumo National Hospital, Jakarta, from December 2019–September 2022. Patients with type 2 DM aged over 18 years were included in the study cohort. Individuals with pre-existing diseases affecting vitamin D and/or calcium metabolism, such as liver or kidney disease, psychosis, skin disease, or use of high- dose steroids or immunomodulators, were excluded. However, women who were nursing or pregnant were not excluded. The cohort included only participants who provided their signed informed consent. The sample size was calculated using the finding that the prevalence rate of depressive symptoms in patients with type 2 DM in Jogjakarta, Indonesia, was 37.9%. The level of significance was set at 0.05, the allowable error was set at 10%, the invalid questionnaire rate was set at 10%, and the minimum number of samples was 91.

All study procedures and protocols were approved by the institutional ethical review board at Universitas Indonesia Ethics Committee (LB.02.01/2.6.1/0452/2022). Written informed consent was obtained from all participants.

Data Collection Procedure

Patients with type 2 DM were identified using World Health Organisation/American Diabetes Association criteria.[18] Their anthropometric parameters were measured according to standard protocols and their BMI was calculated. HbA1c percentages were measured in whole blood using the immunoturbidometric method.

Serum vitamin D levels were measured using an ELISA kit and categorized into three groups (i.e. normal, 30 ng/mL; insufficient, 20-29 ng/mL; deficient, 20 ng/mL).[19] SBP and DBP were measured using a standard sphygmomanometer while the patients were sitting. LDL, HDL, and triglyceride (TG) levels were determined with an autoanalyzer. Depression was evaluated using the Beck Depression Inventory II (BDI-II). Each item on the scale is scored on a 4-point (0-3) Likert scale, and the total result for the BDI-II is the sum of all 21 items. The BDI-II was analyzed using the following algorithm: depression ranges from mild (score, 14-19), moderate (20-28), to serious (29-63).[20]

Statistical Analysis

The Kolmogorov–Smirnov test was performed to determine the normality of the parameters. Descriptive statistics were used to provide a summary of the demographic characteristics. The arithmetic mean and standard deviation (SD) were used for continuous variables and the count and percentage for categorical variables. We used univariate analyses to compare anthropometric, clinical, and biochemical variables between the two groups (independent *t*-test for quantitative data and chi-square test for categorical data). For the BDI-II score, BMI, HbA1c, SBP, DBP, LDL, HDL, and TG vales were categorized into three groups (i.e. sufficient vitamin D, vitamin D insufficiency, and vitamin D deficiency) using an analysis of variance (ANOVA) test. A p-value of < 0.05 was considered statistically significant in all analyses. To find a potential set of variables that will go into the multivariable (linear regression) model, we used the statistical methodology for variable selection using $p < 0.25$ in the univariable (bivariate) analysis as a threshold.

RESULTS

From December 2019 to September 2022, we performed screening of 170 patients with type2 DM to obtain 118 patients with type 2 DM and depression. We then checked their vitamin D levels (**Figure 1**).

The patients' characteristics are indicated in **Table 1**. The median age was 56 years (48, 75-60 years) with a median BDI-II score of 17 (15-19), while the mean serum 25(OH)D level was 18.3 ng/mL (9.17-29.46 ng/mL).

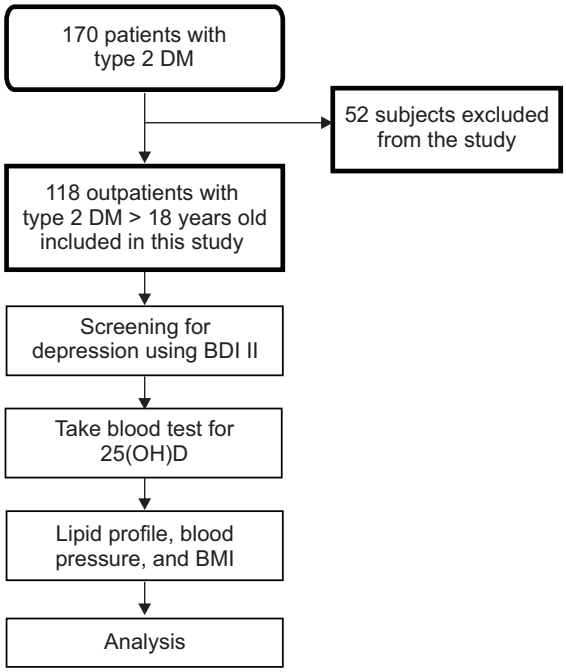

Figure 1. Study recruitment and sampling diagram.

Table 1. Subject characteristics.

Variables	(n = 118)
Age (years), median (IQR)	56 (48.75-60)
Gender, n (%):	
Male	33 (28)
Female	85 (72)
Educational level, N (%)	
Uneducated	2 (1.7)
Primary school	7 (5.9)
Junior high school	10 (8.5)
Senior high school	64 (64.2)
University/college	35 (29.7)
Marital status, n (%)	
Married	94 (79.7)
Unmarried	8 (6.8)
Divorced	16 (13.6)
Religion, n (%)	
Muslim	80 (67.8)
Catholic	4 (3.4)
Christian	32 (27.1)
Buddhist	2 (1.7)
Treatment, n (%)	
Oral antidiabetic drugs (OAD) only	55 (46.6)

Insulin only	14 (11.9)
Combination (OAD + Insulin)	49 (41.5)
Duration of type 2 diabetes mellitus	
< 5 years	77 (65.3%)
> 5 years	41 (34.7%)
With other comorbidities	
Hypertension	59 (50%)
Coronary artery disease	17 (14.4%)
Chronic kidney disease	30 (25.4%)
Stroke ischaemic	7 (5.9%)
Dyslipidemia	78 (66.1%)
Diabetic retinopathy	7 (5.9%)
Diabetic neuropathy	30 (25.4%)
Diabetic ulcer	6 (5.1%)
BDI-II score, median (IQR)	17 (15-19)
BMI (kg/m2), median (IQR)	25.6 (23.4-28.93)
Serum 25(OH)D (ng/mL), mean (SD)	18.3 (9.17-29.46)
HbA1c (%), median (IQR)	7.7 (6,7-9.27)
SBP (mmHg), median (IQR)	135 (117-144.25)
DBP (mmHg), mean (SD)	74.19 (10.32)
LDL-cholesterol, median (IQR)	115.5 (96-138)
HDL-cholesterol, median (IQR)	47.5 (41-55)
TG, median (IQR	140 (97.75-184.5)

Figure 2 shows that among 118 patients, only 22% (n = 26) have a normal/sufficient vitamin D level, with 51.7% having insufficient vitamin D and 26.3% with deficient vitamin D levels.

We compared the age, gender, and metabolic profiles between patients with a normal vitamin D level and those with hypoD (**Table 2**). There was a significant difference in mean HbA1c (p-value = 0.015) and DBP differed between groups (p-value 0.057). and no significant difference in mean of the BDI-II score, BMI, HDL, LDL, and TG. Compared with other variables, HbA1c levels differed between the sufficient/normal, insufficient, and deficient groups with p = 0.015 (**Table 3**).

Table 4 shows that age and HbA1c have a relationship with low vitamin D levels.

Variables with p < 0.25 in the bivariate analysis (i.e. age, BDI-II score, HbA1c, and LDL-cholesterol) were examined further using a multivariate analysis to identify their associations with vitamin D levels. Other factors were not included in this model because they did not show a significant bivariate relationship with vitamin D level. There was a statistically significant difference in vitamin D level based on age and HbA1c. However, the BDI-II score, and SBP and DBP levels did not show statistically significant differences (**Table 5**).

DISCUSSION

Our study found that 77.7% of patients with type 2 DM and depression had hypoD. The

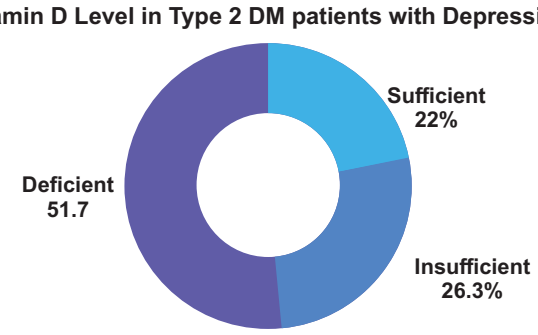

Figure 2. Vitamin D level in type 2 DM with depression.

Table 2. Comparing age and gender with vitamin D grades.

Variable	Sufficient (n = 26)	Insufficient and deficient (n = 92)	p-value
Age in years, median (IQR)	58.5 (55-63.5)	55 (47-60)	0.014*
Gender, N			
Male	8 (24.2)	25 (75.8)	0.910**
Female	18 (21.2)	67 (78.8)	

*Mann–Whitney *U* test; **Chi-square test.

Table 3. Characteristics of patients with sufficient versus Insufficient and deficient vitamin D levels.

Variables	Sufficient (n = 26)	Insufficient (n = 61)	Deficient (n = 31)	p-value
BDI II score, median (IQR)	17 (15-19.2)	17 (14-19)	18 (15-21)	0.072***
BMI (kg/m^2), median (IQR)	25.2 (23.6-28.9)	25.6 (22.9-28.9)	26.9 (23.6-29)	0.834***
HbA1c (%), median (IQR)	6.9 (6.6-7.8)	8 (6.5-9.55)	8.7 (7.5-9.8)	0.015***
SBP (mmHg), median (IQR)	135 (115.5-145)	133 (116.5-143)	138 (118-146)	0.709***
DBP (mmHg), mean	74.65 (9.3)	72.25 (10.01)	77.65 (11.04)	0.057****
LDL-cholesterol, mean	117.35 (25.3)	119.02 (33.6)	112 (30.13)	0.591****
HDL-cholesterol, median (IQR)	49 (41-64.2)	46 (40.5-52.5)	48 (41-53)	0.682***
TG, median (IQR)	130.5 (92.2-178)	125 (106-180.5)	165 (98-201)	0.399***

BDI II, Beck Depression Inventory II; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.
***Kruskal–Wallis test, ****One-way ANOVA.

Table 4. Relationship between of variables with vitamin D.

Variable	R^2	p-value
Age (years)	0.289	0.002*
Gender		
Male	13.73 (6.58-29.67)	0.283**
Female	20.59 (10.45-29.20)	
BDI II score	−0.153	0.098*
BMI (kg/m$^{2)}$	0.000	0.998*
HbA1c	−0.267	0.004*
SBP	0.018	0.846*
DBP	−0.057	0.539*
LDL-cholesterol	0.108	0.243*
HDL-cholesterol	−0.013	0.891*
TG	−0.105	0.259*

*Spearman rho; **Mann–Whitney *U* test.

Table 5. Linear regression analysis of vitamin D status in DM type 2 patients with depression.

Variable	Unstandardized B	Coef. SE	p-value
(Constant)	1.317	10.954	0.905
Age in years	0.567	0.165	0.001*
BDI II score	−0.665	0.326	0.043*

*p-value < 0.05

median age of the group with insufficient and deficient vitamin D levels was younger than that of the patients with normal vitamin D levels. This result was similar to a previous study by Al Quaiz et al. that showed younger adults had a higher prevalence of vitamin D deficiency compared with older participants,[21] which may be because younger patients spend more time indoors and work inside the office, where they do not get enough sunshine, while older patients often have more free time outdoors. This finding may also be due to the use of calcium and vitamin D supplements for osteoporosis among older age groups.[22]

Our study showed no significant difference in vitamin D levels between genders. Yu et al. found that men had higher serum 25(OH)D levels than women,[23] while another study found that men had a higher prevalence of vitamin D deficiency.[21] Lower vitamin D levels in women may be attributed to their clothing style, spending less time outside, and engaging in less physical activity than men.[22]

There were significant differences in age and BDI-II scores, but no differences in HbA1c, SBP, DBP, or TG levels between patients with normal and abnormal vitamin D levels. In various clinical settings, low serum 25(OH)D levels have been linked to depressive symptoms in adults.[24–26] Our patients with deficient vitamin D levels have a slightly higher BDI-II score than other patients, although this was not statistically significant. Lee et al. showed that there was

an inverse association between 25(OH)D levels and depression.[27] Similarly, Khan et al. also showed that depression was more common in individuals with vitamin D deficiency.[25]

Zhao et al. showed that vitamin D deficiency was related to high HbA1c levels.[28] Buhary et al. also showed that HbA1c was inversely related to serum vitamin D levels and vitamin D supplementation will result in better blood glucose control.[29] In our study, the HbA1c levels were slightly higher in the deficient group than the other groups and the findings were statistically significant and supported the results

of previous studies.

Vitamin D deficiency was recently considered a new risk factor for causing hypertension.[30,31] A systematic review and meta-analysis by He and Hao showed that there was no significant difference in SBP and DBP between the control and vitamin D deficiency groups.[32] Vitamin D supplementation also did not lower blood pressure in a study by Zhang et al.[33]

Low serum vitamin D levels have been associated with an atherogenic lipid profile.[34] Chaudhuri et al. showed that vitamin D deficiency was associated with dyslipidemia in Indian subjects.[35] In a retrospective observational study,[36] vitamin D deficiency was associated with higher LDL and lower HDL levels. However, the results of our study showed no significant difference in lipid profiles between groups.

Interestingly, this study found a correlation between age and lack of vitamin D in patients with type 2 DM and depression. According to a study of male and female respondents aged 50 years, Oliveira et al. linked low serum 25(OH)D levels to an increased chance of depressive symptoms, especially in women. Age, economic circumstances, health, habits, bodily and mental abilities, and cognitive abilities all have an impact on depressive symptoms.[37] William et al. reported vitamin D deficiency in 27.8% of children aged 5 to 9 years, 35.4% of children aged 10 to 14 years, and 50.9% of children aged 15 years or older. Vitamin D deficiency was significantly associated with older age, African American ethnicity, winter/spring seasons, a higher insulin level, the total number of comorbidities, and polycystic ovary syndrome (in girls).[37] A study from Qatar found that subjects aged over 60 years have a 61.3% chance of depression and type 2 DM.[38]

A systematic review and meta-analysis showed that vitamin D supplementation may improve depression in patients with type 2 DM.[39] In a recent study of prediabetic patients, the researchers found that new-onset diabetes occurred in 22.7% of adults who received vitamin D and 25% of those who received a placebo over a 3-year period, resulting in a 15% relative risk reduction. Extrapolating their results to the more than 374 million prediabetic adults worldwide indicates that low-cost vitamin D supplementation could prevent the onset of diabetes in more than 10 million individuals.[40]

Limitation the Study

There are a few limitations to our research findings. This cross-sectional study means that any associations may not necessarily indicate causation. We were unable to determine whether our patients' vitamin D status varied from that of the general community because we did not include healthy controls. Our findings might not be very generalizable in regions with different sun exposure patterns.

CONCLUSION

This study showed that patients with type 2 DM and depression had a high prevalence of hypoD (i.e. 77.7%). In addition, age and BDI-II score were associated with low vitamin D levels.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests or conflicts of interest.

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