Vitamin D Deficiency as a Factor Associated with Cognitive Impairment in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: Vitamin D as an essential nutrient is increasingly being studied and reported to have roles in diabetes and cognitive function through its antioxidant, anti-inflammatory, and neuroprotective functions. This study aimed to investigate vitamin D deficiency as a factor associated with cognitive impairment in Type 2 Diabetes Mellitus patients.

Materials and Methods: This case-control study was conducted at the diabetic center and neurology outpatient clinic at Prof. Dr. I.G.N.G Ngoerah Hospital in Denpasar, Indonesia between September and December 2022. Cases had a score of < 26 on the Montreal Cognitive Assessment questionnaire (Indonesian version) controls had a score ≥26. Vitamin D levels were assessed using serum 25-hydroxyvitamin D levels. The cut-off for vitamin D deficiency was obtained through the receiver operating curve characteristic.

Results: In total 31 cases and 31 controls were included. The cut-off for vitamin D deficiency was <24.6 ng/ml. Patients with T2DM and vitamin D deficiency had an increased association with cognitive impairment (OR 3.8; 95% CI [1.1 to 13.4]) compared to patients without vitamin D deficiency. Other independent factors associated with cognitive impairment in T2DM were low education levels (OR 5.4; 95% CI [1.3 to 22.2]) and diabetes duration of more than 5 years (OR 4.1; 95% CI [1.1 to 14.4]).

Conclusion: Vitamin D deficiency is one of the factors associated with cognitive impairment in T2DM patients.

Keywords: Cognitive impairment; type 2 diabetes mellitus; vitamin D (Siriraj Med J 2024; 76: 1-7)

INTRODUCTION

Type 2 diabetes mellitus (T2DM) carries a high risk of mortality and morbidity in the community.[1] Various complications can be caused by T2DM, including cognitive impairment.[2,3] Insulin dysregulation is a key element of neurodegeneration in T2DM. Insulin binds to its receptors on the blood-brain barrier and is transported into the central nervous system. Insulin appears to have a neurotropic role in the brain.[2]

Several previous studies indicate an association between vitamin D deficiency and a higher prevalence of diabetes.[4–6] Vitamin D is also reported to be associated with cognitive function.[7] This association is supported by the anti-inflammatory, antioxidant, and neuroprotective functions of vitamin D. These substances increase neurotrophic factors such as nerve growth factor (NGF) which maintains better brain health. Vitamin D also helps to prevent amyloid accumulation and supports amyloid clearance.[8]

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Evidence regarding an association between vitamin D status and dementia risk in patients with diabetes is scant, although several epidemiological studies have linked lower vitamin D concentrations to dementia risk in the general population. A recent cohort study showed that a higher serum vitamin D level in type 2 DM patients was associated with a lower risk of dementia.[9]

No studies have been published analysing the association between vitamin D levels and cognitive impairment in patients with T2DM in Indonesia . Therefore the aim of this study was to analyse the impact of vitamin D levels in T2DM patients with and without cognitive impairment

MATERIALS AND METHODS

The research was conducted at the neurology outpatient clinic and diabetic center of Prof. Dr. I.G.N.G Ngoerah Hospital from September to December 2022 using a case-control design. The study was reviewed and approved by the Institution Review Board of Faculty of Medicine Universitas Udayana/ RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar No.2553/UN14.2.2.VII.14/LT/2022 on September, 22nd 2022. Written informed consent was obtained from each patient prior to the study.

Inclusion criteria were T2DM and age between 45 and 65 years. Exclusion criteria were chronic hepatic impairment, gastrointestinal disease (ulcerative colitis or Crohn's disease), having vitamin D supplementation regularly in the last 1 month, immobilization, history of stroke, central nervous system (CNS) infection, HIV-AIDS, brain tumor, Parkinson's disease, epilepsy, depression, pre-diabetic cognitive impairment, recurrent severe hypoglycemia, head trauma, heart failure, alcohol drinkers, and severe visual and hearing impairment.

The Montreal Cognitive Assessment questionnaire, Indonesian version, (MoCA-Ind) was applied to determine cognitive impairment. It is a brief, validated, and easy-to-use tool to identify mild and early Alzheimer's dementia with good sensitivity and specificity.[10,11] A scores of <26 indicate cognitive impairment[7]. The Hamilton Depression Rating Scale (HDRS) was applied to determine presences of depression (score of ≥8).[12] The Ascertain Dementia 8 – Indonesian version (AD 8-Ina) questionnaire answered by family or caregivers was applied to determine pre-diabetic cognitive impairment.[10]

All participants then underwent venous blood sampling by experts for laboratory examination of serum 25(OH)D levels measured in ng/ml using the Enzyme-Linked Immunosorbent Assay (ELISA) method in the Clinical Pathology Laboratory of Prof. Dr. I.G.N.G Ngoerah Hospital.

Potential confounding variables were poor glycemic control (HbA1c ≥7%), T2DM duration >5 years, hypertension, dyslipidemia, obesity, chronic kidney disease (CKD), and low education level (<12 years).

The data analysis was carried out using IBM SPSS Statistics version 25. All of the analyzed variables are presented in nominal variables. Bivariate associations were analysed using Chi-Square test. The cut-off for vitamin D deficiency was obtained through the receiver operating curve (ROC) characteristics. All variables with a significance value of less than 0.25 from the bivariate analysis will be included in the multivariate or logistic regression analysis. Logistic regression analysis was applied to explore associations of confounding variables with cognitive impairment. A p-value ≤ 0.05 was regarded as statistically significant.

RESULTS

There were 71 patients eligible for the study but 9 patients refused to participate. Thirty-one patients from each of the case and control groups were included in the study (Table 1). The ROC method yielded an Area Under the Curve (AUC) value of 75.3% [95% Confidence Interval (CI) 63.3 to 87.2%] (Fig 1). A vitamin D cut-off value of 24.6 ng/ml resulted in a sensitivity of 61.3% and specificity of 64.5% (Fig 2).

T2DM patients with vitamin D deficiency had a significantly higher risk of experiencing cognitive impairment compared to the control group (OR 2.8; 95% CI [1.1 to 8.1]; p=0.042) (Table 1). Confounding variables significantly associated with cognitive impairment in T2DM were education level, diabetes duration, hypertension, and gender (Table 2). The obesity variable has a significance value of less than 0.25 so it also be analyzed in the multivariate analysis. In the multivariable logistic regression analysis vitamin D deficiency, low education level, and T2DM duration >5 years were associated with cognitive impairments (Table 3).

DISCUSSION

The mean serum vitamin D level in the case group was significantly higher than in the control group (Table 1). These results are in line with a study by Rui-Hua et al. which found that the average vitamin D level in patients with T2DM with mild cognitive impairment (MCI) was 15.75 ng/ml and significantly lower than the normal cognitive group (23.04 ng/ml) (p<0.001).[7]

Vitamin D deficiency is associated with cognitive impairment in T2DM patients in this study. A cohort study involving 13,486 patients in the United Kingdom used a 20 ng/ml limit for all outcomes in measuring the association between vitamin D levels and the risk

TABLE 1. Characteristics of cases and controls.

Characteristics	Cases Cognitive Impairment (n= 31)	Controls Without Cognitive Impairment (n=31)	*p*
Age, (mean ± SD) years	55.1 ± 6.2	56.1 ± 5.2	0.507†
Gender, Female, n (%)	16 (52%)	8 (26%)	0.037*‡
Duration of education, median (25th; 75th percentile) years	12 (6 ; 15)	12 (12 ; 14)	0.217§
BMI, median (min-max) kg/m²	25.80 (19.7-36.7)	25.5 (18.3-36.7)	0.068‡
Occupation,			
Civil workers, n (%)	3 (9.7%)	2 (6.5%)	0.364‡
Teacher	1 (3.2%)	1 (3.2%)	
Unemployed	9 (29%)	4 (12.9%)	
Farmer	0 (0%)	1 (3.2%)	
Medical workers	3 (9.7%)	1 (3.2%)	
Entrepreneur	15 (48.4%)	22 (71%)	
MoCA-Ina score, median (min-max)	22 (11-25)	27 (26-30)	0.000*§
HbA1c, median (min-max) %	7.2 (5.2-14)	6.6 (5.9-14)	0.866§
Vitamin D serum, (mean±SD) ng/ml	20.5 ± 7	28.6 ± 9	0.000*†
Vitamin D category			
Deficiency, n (%)	20 (64.5%)	12 (38.7%)	0.042; OR (95% CI) 2.9 (1.1 to 8.1)
Without deficiency	11 (35.5%)	19 (61.3%)	

**p<0.05 †independent T-test, ‡chi-square test, §mann-whitney test.* BMI, Body Mass Index; MoCA-Ina, Montreal Cognitive Assessment-Indonesian Version; HbA1c, glycated hemoglobin; SD, standard deviation

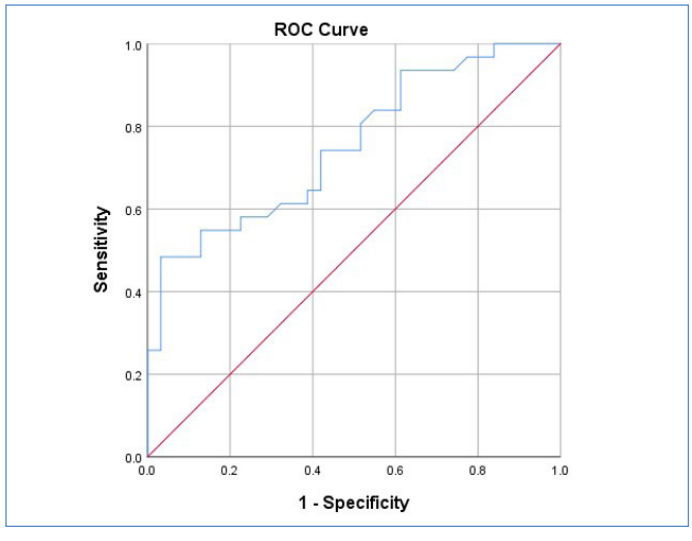

Fig 1. ROC characteristic of vitamin D level, and cognitive impairment in T2DM patients. The AUC based on this curve is 75.3%. ROC, receiver operating curve; AUC, area under the curve.

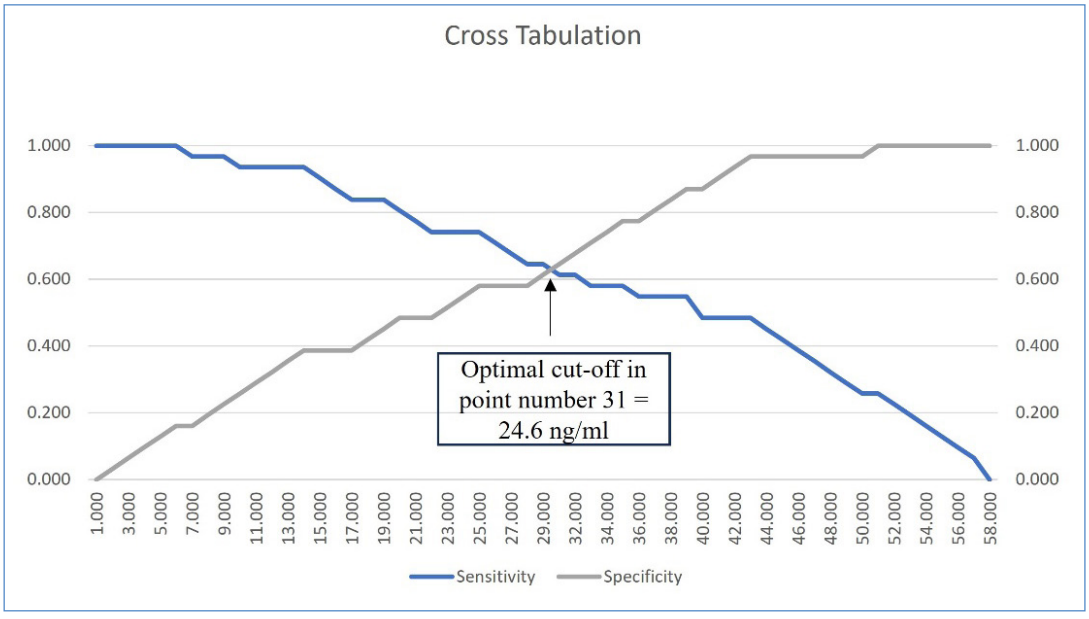

Fig 2. The results of the ROC coordinates for vitamin D deficiency cut-off level

TABLE 2. Results of the bivariate analysis between potential confounding variables and cognitive impairment in T2DM patients.

Variables	Cases n (%)	Controls n (%)	OR (95% CI)	*p*
Duration of education				
Low (<12 years)	13 (21%)	5 (16.1%)	3.8	0.025*
High (≥12 years)	18 (58.1%)	26 (83.9%)	(1.1 to 12.4)	
Duration of T2DM				
> 5 years	15 (48.4%)	7 (22.6%)	3.2	0.034*
≤ 5 years	16 (51.6%)	24 (77.4%)	(1.1 to 9.6)	
Glycemic control				
Poor	17 (54.8%)	13 (41.9%)	1.7	0.309
Good	14 (45.2%)	18 (58.1%)	(0.6 to 4.6)	
Hypertension				
Present	19 (61.3%)	11 (35.5%)	2.9	0.042*
Not present	12 (38.7%)	20 (64.5%)	(1.1 to 8.1)	
Dyslipidemia				
Present	11 (35.5%)	9 (29%)	1.3	0.587
Not present	20 (64.5%)	22 (71%)	(0.5 to 3.9)	
Obesity				
Present	10 (32.3%)	4 (12.9%)	3.2	0.068
Not present	21 (67,.7%)	27 (87.1%)	(0.9 to 11.7)	
CKD				
Present	7 (22.6%)	7 (22.6%)	1	1.000
Not present	24 (77.4%)	24 (77.4%)	(0.3 to 3.3)	
Gender				
Female	16 (51.6%)	8 (25.8%)	3.1	0.037*
Male	15 (48.4%)	23 (74.2%)	(1.1 to 8.9)	

*$p<0.05$. OR, Odd Ratio; CI, Confidence Interval; T2DM, type 2 Diabetes Mellitus; CKD, Chronic Kidney Disease.

TABLE 3. Results of the multivariable logistic regression analysis to statistically predict cognitive impairment in patients with T2DM

Variables	B	S.E	*Adjusted* OR Final step	95% CI	*p*
Vitamin D deficiency	1.3	0.6	3.8	1.1 to 13.4	0.036
Duration of T2DM >5 years	1.4	0.6	4.1	1.2 to 14.4	0.030
Duration of education <12 years	1.7	0.7	5.4	1.3 to 22.2	0.019
Hypertension	1.3	0.6	3.5	1 to 12.3	0.050
Obesity	1.5	0.8	4.3	0.9 to 19.8	0.061

B, Beta; S.E, Standard Error; OR, Odd Ratio; CI, Confidence Interval; T2DM, type 2 Diabetes Mellitus

of dementia in T2DM. The results obtained from this 8-year cohort study showed that higher serum 25(OH)D levels were significantly associated with a lower risk of Alzheimer's dementia (AD), vascular dementia (VD), and all-cause dementia.[9]

The exact mechanism underlying the relationship between vitamin D and dementia in diabetics still needs further research, the most frequently suggested pathways from are the neurodegenerative and vascular pathways.[9] Experimental studies show that vitamin D can enhance the clearance of amyloid plaques by stimulating macrophages[13], in addition, vitamin D can suppress macrophage migration among patients with diabetes.[9]

In vivo studies demonstrated increased vitamin D receptors in diabetic mice neurons indicating that the vitamin D signaling system could be a potential therapeutic target for diabetic neuropathy.[14] In addition, there is mounting evidence that vitamin D can improve glycemic control, blood pressure, and lipid metabolism in diabetic patients.[9]

Vitamin D can play an important role in normal neural function supported by the presence of vitamin D3 25-hydroxylase and 25-hydroxyvitamin D3-1α-hydroxylase in brain tissue.[15] Observations showed that the cultured microglia of mice could produce $1,25(OH)_2D_3$, and there were findings of $1,25(OH)_2D_3$ in human cerebrospinal fluid.[16] $1,25(OH)_2D_3$ is thought to bind and act on vitamin D receptors found in the brain and spinal cord, while vitamin D receptor (VDR) gene expression was observed in neuronal and glial cells. It was found that $1,25(OH)_2D_3$ therapy increases choline acetyltransferase activity in the brain nuclei of mice.[17] Another relatively direct effect of vitamin D on normal neural function is through increased neurotrophin synthesis as demonstrated by the finding that $1,25(OH)_2D_3$ stimulates the synthesis of NGF, glial cell line-derived neurotrophic factor (GDNF), and neurotrophin 3 (NT3) in various non-clinical studies.[18]

Vitamin D appears to protect the brain from free radical-induced damage by inhibition of $1,25(OH)_2D_3$ inducible Nitric Oxide Synthase (iNOS) synthesis.[17] Moreover, protection against oxygen-derived free radicals can come from increasing glutathione levels through upregulation of gamma-glutamyl transpeptidase as seen in the mice brain treated with $1,25(OH)_2D_3$.[19]

Low education level and diabetes duration of more than 5 years were also significantly associated with risk of cognitive impairment. Educational level is widely used as an indicator of cognitive reserve capacity. Individuals with greater cognitive reserves can tolerate a higher neuropathological burden than those with smaller cognitive reserves.[20] A low education level is also associated with a lack of ability to control vascular risk factors, maintain healthy diets and a lack of affordability to access health services.[21]

A study by Sun et al. also found that T2DM patients experienced an average of MCI after having diabetes for 6.34±2.53 years, whereas patients who had severe cognitive dysfunction had an average of T2DM for 10.14±8.24 years. Along with diabetes duration, there is an increase of neuronal damage which comes from macrovascular and microvascular disease, oxidative stress, and insulin resistance.[22]

In this study glycemic control, hypertension, dyslipidemia, obesity, chronic kidney disease, and female gender were not associated with cognitive impairment in T2DM patients. Poor glycemic control is thought

to be one of the risk factors for cognitive impairment in patients with T2DM, however, previous studies still show contrasting results to date.[23,24] Analysis of mean HbA1c and fasting blood glucose over a certain period is suggested to be more important than static measurements.[25] Glycemic variability is not represented completely by HbA1c values especially in patients with good metabolic control.[26] Hypertension is a risk factor for cardio-cerebrovascular disease, cerebral small vessel disease (CSVD), and cerebral atrophy but the direct association between hypertension and cognitive decline is uncertain.[27]

The association between obesity and cognitive impairment was not significant. Both case and control groups in this study had a greater percentage of patients without obesity. A meta-analysis showed that being underweight, overweight, and obese in middle age increases the risk of dementia.[28] Obesity is stated by Xiu et al. not an independent factor of cognitive impairment in T2DM.[29]

Chronic kidney disease was not associated significantly with cognitive impairment in this study. This could be due to the incidentally balanced proportion of CKD sufferers in the case and control groups. The accumulation of advanced glycated end products (AGEs) triggers vascular endothelial dysfunction which can lead to increased fragility and permeability of cerebral vessels.[30] The direct neuronal toxicity effect of uremic toxins on the cerebral vasculature will accelerate vascular calcification and endothelial dysfunction.[31]

Female gender in multivariable analysis was not significantly related to cognitive impairment in T2DM. Results of previous research regarding the role of gender in cognitive impairment risk in T2DM are varying. That could be the result of different eligibility criterias and the presence of confounding factors.[32,33] A meta-analysis showed that women have a higher relative risk of developing vascular dementia associated with T2DM than men, however, in non-vascular dementia there was no difference. The exact underlying mechanism is unknown, increased exposure to endogenous estradiol especially in women with post-menopausal diabetes is thought to carry a higher risk of dementia.[34] The study by Espeland et al concluded that only the carrier status of the apoE-epsilon 4 gene influenced the degree of sex-related differences.[33] More in-depth research including assessment of the menopausal phase, lifestyle, and genetic factors still needed to evaluate the role of gender in the diabetics' cognitive function.

This study has some strengths and limitations. Vitamin D examination is highly available and applicable nowadays in many healthcare facilities at relatively affordable prices. The new limit value for vitamin D deficiency obtained from this study is expected to enrich the literature and provide a basis for further research on the prevention of cognitive impairment in T2DM patients. The limitation of this study is there were some confounding factors that could not be adjusted by design in this study since the research was carried out in a center referral hospital with a high complexity of cases. In addition, the sample size is limited, so it cannot be used to characterize the population as a whole.

In conclusion, vitamin D deficiency in T2DM patients is one of factors associated with cognitive impairment based on our study. Future research with a cohort design is needed to assess the causality relationship between vitamin D deficiency and cognitive impairment in diabetic patients.

Conflicts of interest

The authors have no potential conflicts of interest to disclose.

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