

Correlation between vitamin D levels and cognitive impairment on 90 days post ischemic stroke patients

Rizaldy Taslim Pinzon^{1,2}, Nindya Stephanie Christina¹, Oey Yedida Stephanie Sugianto¹,
Tillandsia Filli Folia Primastuti¹

¹Duta Wacana Christian University School of Medicine, Yogyakarta, Indonesia

²Neurology Department Bethesda Hospital, Yogyakarta, Indonesia

ABSTRACT

The prevalence of ischemic stroke based on the American Heart Association (AHA) data in 2019 reached 77.2 million people. As much as 72% of post ischemic stroke patients got cognitive impairment. Vitamin D deficiency is often found in post-stroke patients and causes functional decline. This study aims to assess the relationship between vitamin D levels and cognitive impairment in 90 days post ischemic stroke patients. This study is a cross-sectional study using secondary data from medical records at Bethesda Hospital Yogyakarta taken from January to March 2021. Cognitive impairment in 90 days post ischemic stroke patients were assessed using MMSE (Mini-Mental State Examination) and CDT (Clock Drawing Test). This study was analyzed through univariate tests and bivariate tests using Spearman correlation. This proves a correlation between vitamin D levels and cognitive impairment which is formulated by the value of MMSE ($p=0.000$) and CDT ($p=0.031$). The mean of vitamin D levels was 13.53 ± 3.625 . The proportion of hypovitaminosis D was divided into 5.7% of insufficiency patients and 94.3% patients stated as deficiency. The lower the vitamin D levels, the lower the MMSE and CDT values accordingly. In conclusion, there is a relationship between vitamin D levels and cognitive impairment in 90 days post ischemic stroke patients. Low levels of vitamin D result in more frequent and more severe cognitive impairments.

Keywords: Vitamin D, cognitive impairment, ischemic stroke

INTRODUCTION

Vitamin D is a fat-soluble steroid vitamin that plays a role in many body systems such as endocrine system, nervous system, cardiovascular system, as well as in bone health and strength. It is known that vitamin D also affects the increase of NGF (nerve growth factor) which plays a role in brain health and function, modulation of cell growth, neurogenesis, neuroprotection, immune function, detoxification, and reduction of inflammation [1,2].

Low vitamin D levels have become a common condition in the world. Data were obtained from the population of children and adults in the United States, Europe, New Zealand, and Asia that 30-50% got vitamin D deficiencies [3]. In post-stroke pa-

tients, vitamin D deficiency has the potential to cause body functional decline such as the likelihood of a person's cognitive decline (memory, orientation, and executive function) [4,5]. The World Stroke Organization in 2019 stated that worldwide there are 12,2 million new stroke cases per year every 3 seconds and there are 101 million cases worldwide and this number has almost doubled over the last 30 years. This brought up the case of the importance of preventing and treating post-stroke cognitive impairment [6].

Vitamin D deficiency is also known to be an independent risk factor for stroke and suggests that vitamin D supplementation may serve as a potential therapy for stroke patients [7]. Previous studies have shown the association between vitamin D insufficiency with chronic disease like diabetes, cardi-

Corresponding author:

Rizaldy Taslim Pinzon

E-mail: drpinzon17@gmail.com

Article history:

Received: 5 August 2022

Accepted: 18 August 2022

ovascular disease, autoimmune disease, metabolic disorders, and malignancies [2]. A study also proved a relationship between vitamin D insufficiency to impaired parathormone excess, insulin resistance, pancreatic beta cell dysfunction, hypertension, and the occurrence of dyslipidemia [8]. This study aims to assess the correlation between vitamin D levels in the body of the level of cognitive impairment of a person after an ischemic stroke which was measured for 90 days.

METHODS

This study is a cross-sectional study using secondary data from medical records taken at Bethesda Hospital Yogyakarta in March 2021. The independent variable of this study is vitamin D levels, while the dependent variable is cognitive impairment. The presence of cognitive impairment was assessed by MMSE (Mini-Mental State Examination) score <24 and CDT (Clock Drawing Test) score <2. Sampling was done by consecutive sampling method and obtained a total sample of 53 subjects who met the inclusion and exclusion criteria. The inclusion criteria were subjects >18 years old diagnosed with ischemic stroke by a clinician with neurological and radiological examinations. Exclusion criteria in this study were patients whose vitamin D levels were not measured, patients with chronic liver disease, patients with chronic kidney disease, patients with periodic vitamin D and calcium supplementation, and patients with aphasia or other serious conditions. The analysis used in this study is the Spearman correlation test because the data normality test is not evenly distributed.

RESULTS

A total of 53 post-ischemic stroke patients were the subjects of this study. The mean age of the research subjects was 69.58 ± 7.407 with 27 men and 26 women. Comorbid diseases suffered by the patient were hypertension (32.1%), diabetes (35.8%), and dyslipidemia (69.8%). Infarct location was not visible (16 persons), parietal lobe (20.8%), temporal lobe (7.5%), and multiple (41.5%). The medication received by the patient was antiplatelet, statin, and donepezil. The mean level of vitamin D in post-stroke patients was 13.53 ± 3.625 where 5.7% had insufficiency and 94.3% had deficiency. When measured by MMSE, 83% of post-stroke patients experienced cognitive impairment and 17% of post-stroke patients did not experience cognitive impairment with a mean MMSE value of 18.47 ± 4.308 . This is different when measured by CDT where 60.4% have cognitive impairment and 39.6% have no cognitive impairment with a mean CDT value of 1.58 ± 1.420 (Table 1).

TABLE 1. Clinical characteristics of post-stroke patients

Characteristics	n=53	%
Age (year) (mean±SD)	69.58±7.407	
Sex,	n	(%)
Male	27	50.9
Female	26	49.1
Comorbidities		
Hypertension	17	32.1
Diabetes	19	35.8
Dyslipidemia	37	69.8
History of Smoking		
Yes	13	24.5
No	40	75.5
Infarct location		
Not visible	16	30.2
Frontal lobe	0	0
Parietal lobe	11	20.8
Temporal lobe	4	7.5
Multiple locations	22	41.5
Medication		
Anti-platelet	14	26.4
Antiplatelet, statin	29	54.7
Anti-platelet, statin, donepezil	8	15.1
Antiplatelet, donepezil	2	3.8
Vitamin D levels (mean±SD)	13.53±3.625	
Sufficient (≥30ng/ml)	0	0
Insufficiency (<30ng/ml)	3	5.7
Deficiency (<20ng/ml)	50	94.3
MMSE Score (mean±SD)	18.47±4.308	
≥24 (normal)	9	17
<24 (cognitive impairment)	44	83
Nilai CDT (Rerata±SD)	1.58±1.420	
>2 (normal)	21	39.6
≤2 (cognitive impairment)	32	60.4

According to the MMSE examination on vitamin D levels in the body (Table 2), the mean of vitamin D levels in cognitively impaired patients was 13.18 ± 3.787 ng/ml, which was lower than that in cognitively normal patients (15.22 ± 2.108 ng/ml). Correspondingly, on CDT examination, patients with cognitive impairment had lower vitamin D levels than patients without cognitive impairment. The p-value of both types of examination was <0.05, which means that there was a correlation between vitamin D levels and cognitive impairment in patients 90 days after the ischemic stroke.

Based on the analysis of the MMSE value, diabetes had a significant correlation with cognitive impairment ($p=0.019$) while CDT value stated a correlation between hypertension and cognitive impairment ($p=0.024$) (table 3).

There was a significant positive correlation (table 2) between vitamin D levels and MMSE values ($p=0.000$) and a significant positive correlation with CDT values ($p=0.031$). Distribution of Vitamin D levels on MMSE and CDT may be seen in figure 1&2.

TABLE 2. Comparison of Vitamin D levels and cognitive performance on MMSE and CDT

Examination Type	Vitamin D levels (ng/ml)				P value
	Cognitive Impairment	CI 95%	Normal	CI 95%	
MMSE	13.18±3.787	12.03-14.33	15.22±2.108	13.60-16.84	0.000
CDT	13.09±4.138	11.60-14.59	14.19±2.620	13.00-15.38	0.031

TABLE 3. Confounding variables for cognitive impairment as assessed by MMSE and CDT

Confounding variables	P value	
	MMSE	CDT
Sex	0.142	0.311
Hypertension	0.445	0.024
Diabetes	0.019	0.235
Dyslipidemia	1.000	1.000
Smoking	0.199	1.000
Location	0.163	0.109
Comedication	0.316	0.066

DISCUSSION

Stroke is one of the main causes of disability in the world and post-stroke cognitive impairment is a frequent occurrence in stroke patients. Cognitive disorders are disorders related to memory and attention deficits that cause problems in executive function which ultimately causes a person to have difficulty taking care of himself, difficulty organizing and planning things [9]. Studies show that *vitamin D receptors (VDR)* and other enzymes that are also needed to activate vitamin D are found in areas of the brain for cognitive function. In this study, it was shown that patients with cognitive impairment had lower levels of vitamin D compared to patients without cognitive impairment.

Stroke, which has become one of vascular cognitive impairment and dementia (VCID) risk factors, showed a higher incidence in men than in women which didn't reach statistical significance for the risk [10]. This grows in line with this study which stated that the results were not significantly related to gender differences with cognitive impairment.

The research of Wei et al. (2018) shows that the correlation between hypertension and cognition is age-dependent. People aged 45-59 years may be able to compensate for neurological deficits caused by hypertension. The presence of increased systolic blood pressure might become a risk factor of cognitive decline. Similar conditions in 75 year-old people might predict the presence of degenerative cognition [11]. Hypertension disrupts the structural and functional integrity of cerebral microcirculation, thinning of small blood vessels, cerebrovascular and neurovascular endothelial dysfunction, which in turn disrupts blood supply to the brain and disrupts the blood-brain barrier which triggers neuroinflammation and exacerbation of amyloid accumulation at once. Aging itself is characterized by dysfunctional homeostasis and impaired cellular stress resistance, which exacerbates the effects of hypertension on blood vessels in the brain. The risk of cognitive impairment in hypertensive patients increased 4.3-fold in patients who did not receive anti-

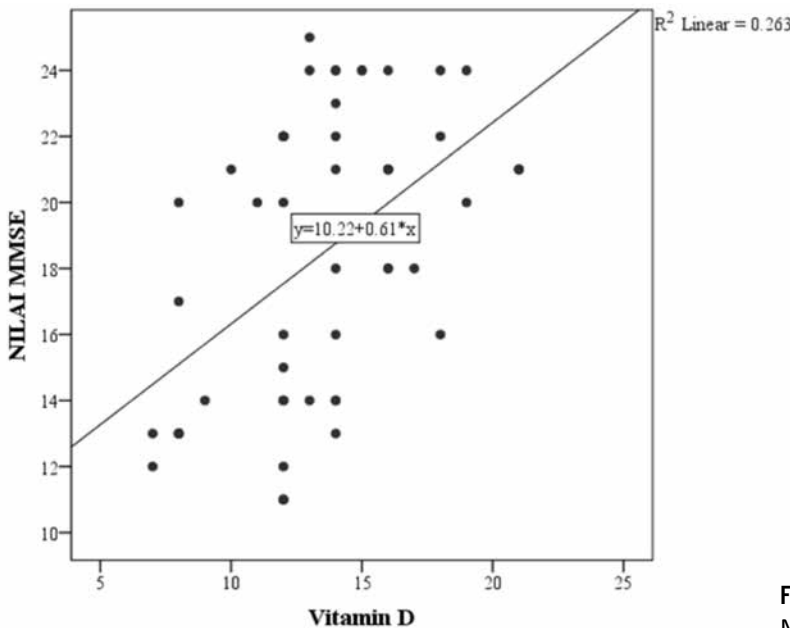


FIGURE 1. Distribution of vitamin D levels to MMSE values

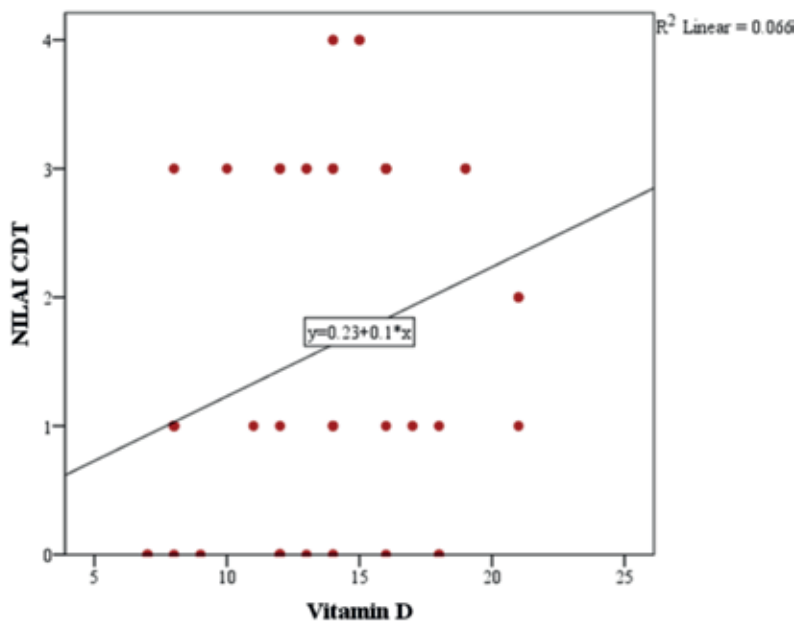


FIGURE 2. Distribution of vitamin D levels to CDT values

hypertensive therapy, whereas in patients who had antihypertensive control the risk increased 1.9-fold for cognitive impairment [12-14].

Vitamin D as a natural drug is able to regulate the homeostasis of calcium and phosphate. Many studies have shown that vitamin D plays a role in autoimmunity, inflammation, and angiogenesis as well as vascular cell activity. Vitamin D receptors are widely distributed in vascular endothelium, vascular smooth muscle cells and cardiomyocytes. This case is supported by data that show the association between vitamin D deficiency with the risk of cardiovascular disease in hypertension [15].

Diabetes has proved to improve the risk and severity of cognitive impairment caused by processes such as chronic hyperglycemia or hypoglycemia, insulin resistance or hyperinsulinemia, oxidative stress and accumulation of beta-amyloid in the brain. Pathological cerebrovascular remodeling has been postulated to contribute to poor neuronal repair and worsened cognitive deficits in diabetes patients [16,17].

A meta-analysis consisting of some RCT done by Barbarawi et al. (2020) concluded that vitamin D supplementation at moderate to high doses (≥ 1000 IU/day) in prediabetes patients significantly reduced the incidence risk of type 2 diabetes [18]. Vitamin D acts as control of both gene transcription and cell signaling pathways for decreasing insulin resistance especially in adipose tissue [19].

Cigarette smoking is independently associated with mild cognitive impairment, duration of smoking links to cognitive function [20], it is different with our research, smoking has unspecific correlation with cognitive impairment based on MMSE and

CDT data. Ischemic stroke location can predict cognitive outcome at 3 months, it is in line with current knowledge on anatomic-functional role on brain structure [21]. Based on the results obtained, there was no significant relationship between dyslipidemia and cognitive impairment. These results are in accordance with research conducted by Fu et al. in 2021 which stated that there was no relationship between high triglyceride and cholesterol levels with the cognitive domain [22].

Cognitive status measurement by MMSE (Mini-Mental State Examination) and CDT (Clock Drawing Test) proposed a slope of function in ischemic stroke patients with low levels of vitamin D. These results are consistent with previous studies which showed that patients with cognitive impairment had lower levels of vitamin D compared to cognitively normal patients.

CONCLUSION

In summary, there is a relationship between vitamin D levels and cognitive impairment in 90 days post ischemic stroke. Patients with low levels of vitamin D result in more frequent and more severe cognitive impairments. Diabetes and hypertension also had correlation with cognitive impairment based on MMSE and CDT values.

Acknowledgements

Authors have no conflict of interest to divulge, including personal relationships, financial, or otherwise. This research was personally funded by the authors.

Conflict of interest: none declared

Financial support: none declared

REFERENCES

- Sultan S, Taimuri U, Basnan SA, Ai-Orabi WK, Awadallah A, Almwald F, et al. Low Vitamin D and Its Association with Cognitive Impairment and Dementia. *J Aging Res.* 2020;2020.
- Lee DH, Chon J, Kim Y, Seo YK, Park EJ, Won CW, et al. Association between Vitamin D deficiency and cognitive function in the elderly Korean population: A Korean frailty and aging cohort study. *Med (United States).* 2020;99(8).
- Chen H, Liu Y, Huang G, Zhu J, Feng W, He J. Association between vitamin D status and cognitive impairment in acute ischemic stroke patients: A prospective cohort study. *Clin Interv Aging.* 2018;13:2503–9.
- Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: Present status and future perspectives. *Int J Mol Sci.* 2020;21(20):1–24.
- Balbaloglu O, Tanik N. The effect of vitamin D on cognitive functions in young female patients: A prospective controlled study using the montreal cognitive assessment. *Arq Neuropsiquiatr.* 2019;77(1):19–24.
- World Stroke Organization. *Global Stroke Fact Sheet 2022 Purpose : Data sources : 2022;1–14.*
- Ashouri R, Fangman M, Briellaier J, Fields ZA, Campo N, Doré S. Nutritional Supplementation of Naturally Occurring Vitamin D to Improve Hemorrhagic Stroke Outcomes. *Front Neurol.* 2021;12(July):1–9.
- Wajda J, Świat M, Owczarek AJ, Brzozowska A, Olszanecka-Glinianowicz M, Chudek J. Severity of Vitamin D deficiency predicts mortality in ischemic stroke patients. *Dis Markers.* 2019;2019.
- Aam S, Einstad MS, Munthe-Kaas R, Lydersen S, Ihle-Hansen H, Knapkog AB, et al. Post-stroke Cognitive Impairment—Impact of Follow-Up Time and Stroke Subtype on Severity and Cognitive Profile: The Nor-COAST Study. *Front Neurol.* 2020;11(July):1–10.
- Gannon OJ, Robison LS, Custozzo AJ, Zuloaga KL. Sex differences in risk factors for vascular contributions to cognitive impairment & dementia. *Neurochem Int* [Internet]. 2019;127:38–55. Available from: <https://doi.org/10.1016/j.neuint.2018.11.014>
- Wei J, Yin X, Liu Q, Tan L, Jia C. Association between hypertension and cognitive function: A cross-sectional study in people over 45 years old in China. *J Clin Hypertens.* 2018;20(11):1575–83.
- Aronow WS. Treatment of hypertensive emergencies. *Ann Transl Med.* 2017;5(8):1–4.
- Liu Y, Dong YH, Lyu PY, Chen WH, Li R. Hypertension-Induced Cerebral Small Vessel Disease Leading to Cognitive Impairment. *Chin Med J (Engl).* 2018;131(5):615–9.
- Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, et al. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol* [Internet]. 2021;17(10):639–54. Available from: <http://dx.doi.org/10.1038/s41581-021-00430-6>
- Lin L, Zhang L, Li C, Gai Z, Li Y. Vitamin D and Vitamin D Receptor: New Insights in the Treatment of Hypertension. *Curr Protein Pept Sci.* 2019;20(10):984–95.
- Ward R, Valenzuela JP, Li W, Dong G, Fagan SC, Ergul A. Poststroke cognitive impairment and hippocampal neurovascular remodeling: The impact of diabetes and sex. *Am J Physiol - Hear Circ Physiol.* 2018;315(5):H1402–13.
- Świątoniowska-Lonc N, Polański J, Tański W, Jankowska-Polańska B. Impact of cognitive impairment on adherence to treatment and self-care in patients with type 2 diabetes mellitus. *Diabetes, Metab Syndr Obes Targets Ther.* 2021;14:193–203.
- Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, Gakhal I, et al. Effect of Vitamin D Supplementation on the Incidence of Diabetes Mellitus. *J Clin Endocrinol Metab.* 2020;105(8):2857–68.
- Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J.* 2017; 474(8):1321–32.
- Hu M, Yin H, Shu X, Jia Y, Leng M, Chen L. Multi-angles of smoking and mild cognitive impairment: is the association mediated by sleep duration? *Neurol Sci.* 2019;40(5):1019–27.
- Sagnier S, Munsch F, Bigourdan A, Debruxelles S, Poli M, Renou P, et al. The Influence of Stroke Location on Cognitive and Mood Impairment. A Voxel-Based Lesion-Symptom Mapping Study. *J Stroke Cerebrovasc Dis.* 2019;28(5):1236–42.
- Fu M, Bakulski KM, Higgins C, Ware EB. Mendelian Randomization of Dyslipidemia on Cognitive Impairment Among Older Americans. *Front Neurol.* 2021;12(June).