Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.188499.2729 Volume 29, Issue 6, November 2023

Manuscript ID ZUMJ-2301-2729 (R1)
DOI /10.21608ZUMJ.2023.188499.2729

ORIGINAL ARTICLE

Serum Vitamin D as a Predictor for Short-Term Outcome of Ischemic Stroke: A Prospective Cohort Study

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Submit Date 24-01-2023
Revise Date 16-02-2023
Accept Date 2023-02-22

ABSTRACT

Background: stroke is considered a major cause of disability worldwide. Vitamin D has been linked to cardiovascular health, including the reduction of stroke risk, while its role in stroke outcome has not been fully studied yet, so we aimed to find the role of vitamin D in the prediction of short-term outcomes of ischemic stroke. **Methods:** This prospective cohort study was conducted on 58 patients with their first acute ischemic stroke who underwent assessment of their serum vitamin D and their functional outcome three months later by modified Rankin scale. **Results:** serum vitamin D had a significant role in the prediction of poor short-term outcomes. The mean vitamin D level in our patients was 14.01 ± 8.94ng/ml. **Conclusions:** the poor short-term outcome of a stroke at three months can be predicted by the presence of hypovitaminosis D, so vitamin D supplementation should be taken into consideration when managing ischemic stroke patients.

Keywords: Stroke, Short term, outcome, vitamin D

INTRODUCTION

Stroke has been rated as the second most important reason for universal mortality, responsible for more than 10% or 5.7 million deaths every year, and it is expected that this number will increase in the next few years [1].

Vitamin D (VD) is a biological substance composed of fat-solvable steroids responsible primarily for calcium and phosphorous regulation besides other important roles [2]. Vitamin D insufficiency is proposed to be associated with a lesser stroke hazard, which is explained by the effect of vitamin D insufficiency on the development of hypertension, diabetes mellitus, atherosclerosis, thrombosis, and inflammation [3]. According to the American Stroke Association International Conference, 2015 hypovitaminosis D in ischemic stroke is associated with severe strokes, larger ischemic infarcts, and worse post-stroke outcomes [4].

The prevalence of vitamin D deficiency among stroke survivors is high and is estimated to be 71% [5]. It has been claimed that the severity of stroke, prognosis, and outcomes are worse with deficient vitamin D [6].

The role of vitamin D in different ischemic stroke outcomes has not been fully studied yet, especially in sunny climates like ours, so we suppose that patients with poor functional post-stroke outcomes tend to have lower vitamin D levels.

This work aimed to find the role of vitamin D levels at stroke onset and the short-term outcome in those patients.

Methods

We conducted this prospective cohort study on 58 individuals with their first acute ischemic stroke and diagnosed following the world health organization criteria (WHO) for

stroke [7]. They were 20(34.5%) males and 38(65.5%) females with their ages ranging from 50 years to 85 years and their mean age was (±SD) 64.64 ± 7.99 Table (1), the patients were admitted to the neurology intensive care unit in the era from April 2022 to July 2022. the exclusion criteria were: patients with CT scan findings of old infarctions, intracerebral hemorrhage, subarachnoid hemorrhage, and venous infarctions, those with brain tumors or other systemic malignancies, patients with metabolic disorders, patients with endocrinal diseases and those with exogenous vitamin D supplements.

Written consent was obtained from all participants after an explanation of the procedure. The Institutional Review Board, Faculty of Medicine Zagazig University approved this study (ZU-IRB #9044/11-2021). The study was done according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were exposed to a detailed clinical assessment including a detailed neurological history with special attention paid to the stroke risk factors and a comprehensive general and neurological examination including the stroke severity evaluation at admittance by the National Institutes of Health Stroke Scale (NIHSS) [8].

The short-term outcome was valued after three months of stroke occurrence via the modified Rankin Scale (mRS). This scale was interpreted as the following: a worthy outcome could be specified at mRS ≤ 2, and an unworthy outcome is specified at mRS ≥ 3 [9].

Laboratory assessment: In addition to the routine laboratory investigations, measurement of 25-hydroxyvitamin D was done using the enzyme-linked immunosorbent assay (ELISA) technique for the collected patient's serum that was drained under completely uninfected circumstances. We documented the results as sufficient vitamin D when its value is ≥30 ng/dl, insufficient at 20–29 ng/dl, and deficient when less than 20 ng /ml [10].

Statistical analysis

Statistical Package for Social Science (SPSS) version 22.0, 2013 generated by IBM, Armonk, NY, USA was used for the analysis of our data.. Numbers and percentages help in assessing the qualitative data. A description of the distribution normality was performed via the Kolmogorov-Smirnov test. Quantitative data were described in terms of range, mean, and standard deviation. The findings were considered significant at the 5% level. We used the Marginal Homogeneity Test, Paired t-test, Mann-Whitney test, and Receiver operating characteristic curve (ROC) to detect the best applicable cutoff points and Logistic Regression was used to detect factors responsible for poor outcomes.

The study was approved by the Institutional Ethics of the Faculty of medicine. Zagazig University (ZU-IRB #9044/11-2021).. Written informed consent was obtained from all the participants after explaining the details and benefits as well as risks to them.

RESULTS

As demonstrated in Table (2), hypertension was found to be the most prevalent risk factor among our patients, followed by the presence of cardiac diseases and dyslipidemia. Serum vitamin D level in our patients ranges from 5.2 – 33 ng with Mean ± SD14.01 ± 8.94 the table (3). Table (4) illustrates the short-term outcome of our patients using mRS, which ranges from 2-5 with a Mean ± SD of 3.64 ± 1.18. A significant relationship between serum vitamin D at stroke onset and the short-term outcome was measured by mRs (table 5). In the table (6) we found that the cutoff value of vitamin D that can predict a poor short-term outcome was ≤8.21 ng/ml with a sensitivity of 83.33% and a specificity of 73.91%. Table (7) showed that different factors could predict poor short-term outcomes including old age, low vitamin D level, NIHSS at admission, and large infarction size, while the multivariate model demonstrated that the stroke severity measured by NIHSS could predict the outcome at three months.

Table (1): Distribution of the studied cases according to demographic data (n = 58)

Demographic data	N.	%
Sex		
Male	20	34.5
Female	38	65.5
Age (years)		
Min. – Max.	50 – 85	
Mean ± SD.	64.64 ± 7.99	

IQR: Inter quartile range, SD: Standard deviation, Min : minimum
Max: maximum

Table (2): Distribution of the studied cases according to risk factors

Risk factors	No		Yes	
	N.	%	N.	%
DM	26	44.8	32	55.2
HPN	12	20.7	46	79.3
Smoker	33	56.9	25	43.1
Cardiac	22	37.9	36	62.1
Obesity	15	25.9	43	74.1
Dyslipidemia	20	34.5	38	65.5

DM: Diabetes mellitus, HPN: Hypertension

Table (3): Distribution of the studied cases according to Serum Vitamin D at admission

S. Vit D at admission	N	%
Deficient (<20)	38	65.5
Insufficient (20 –29)	13	22.4
Sufficient (≥30)	7	12.1
Min. – Max.	5.20 –33.0	
Mean ± SD.	14.01 ±8.94	
Median (IQR)	8.83 (7.31 –22.0)	

IQR: Inter quartile range, SD: Standard deviation, S.Vit D : serum vitamin D,
Min : minimum, Max : maximum

Table (4): Descriptive analysis of the studied cases according to outcome

	Min. –Max.	Mean ± SD.	Median (IQR)
mRS at follow up	2.0 –5.0	3.64 ±1.18	4.0 (2.0 –5.0)

IQR: Inter quartile range, SD: Standard deviation, mRS: modified rankin scale

Table (5): Relation between S. Vitamin D and functional outcome according to modified rankin score)

Functional Outcome	N	S. Vitamin D (ng/mL)		U	p
		Mean ± SD.	Median (IQR)		
mRS 0-2	15	23.79 ±8.48	22.60 (18.63 –31.15)	56.0*	<0.001*
mRS 3 -5	43	10.59 ±6.19	8.21 (6.89 –9.80)		

IQR: Inter quartile range, SD: Standard deviation, U: Mann Whitney test, p: p value for comparing between the studied categories, *: Statistically significant at $p \leq 0.05$, mRS: Modified Rankin Score

Table (6): ROC curve for initial serum vitamin D as a prognostic marker for neurological deterioration

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Initial serum vitamin D	0.805	0.001*	0.654 –0.957	≤8.21	83.33	73.91	45.5	94.4

AUC: Area Under a Curve, p value: Probability value, CI: Confidence Intervals, NPV: Negative predictive value, PPV: Positive predictive value , #Cut off was chosen according to Youden index, *: Statistically significant at p ≤ 0.05

Table (7): univariate and multivariate analysis of different predictors of the short term outcome

	Neurological deterioration		Univariate		Multivariate	
	No (n = 46)	Yes (n = 12)	P	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
Age	63.35 ±6.78	69.58 ±10.44	0.023*	1.110 (1.014 –1.215)	0.914	1.011 (0.835 – 1.223)
Female sex	30 (65.2%)	8 (66.7%)	0.925	1.067 (0.278 –4.094)		
Diabetes	23 (50.0%)	9 (75.0%)	0.132	3.00 (0.719 –12.521)		
hypertension	36 (78.3%)	10 (83.3%)	0.700	1.389 (0.261 –7.393)		
Smoking	21 (45.7%)	4 (33.3%)	0.446	0.595 (0.157 –2.258)		
Obesity	34 (73.9%)	9 (75.0%)	0.939	1.059 (0.245 –4.573)		
Dyslipidemia	29 (63.0%)	9 (75.0%)	0.441	1.759 (0.418 –7.402)		
Serum Vitamin D, ng/mL	15.31 ±9.16	9.02 ±6.03	0.024*	0.010 (0.0002 –0.539)	0.130	0.010 (0.000 – 3.841)
NIHSS Admission	12.46 ±4.55	20.83 ±1.85	0.001*	2.197 (1.402 –3.442)	0.013*	2.084 (1.167 – 3.721)
Size of infarction						
Small or medium	32 (69.6%)	1 (8.3%)		1.0		
Large infarction	14 (30.4%)	11 (91.7%)	0.003*	25.143 (2.954 –213.98)	0.451	3.698 (0.124 – 110.664)

OR: Odd`s ratio, C.I: Confidence interval, LL: Lower limit, UL: Upper Limit, #: All variables with p<0.05 was included in the multivariate, *: Statistically significant at p ≤ 0.05

DISCUSSION

Vitamin D is supposed to have both neuroprotective and vasoprotective properties as it causes slowing down the process of atherosclerosis, advancement of endothelial function, and inhibition of the renin-angiotensin system.

Vitamin D supplements in stroke survivors have been proven to deliver a beneficial role in recurrent stroke prevention [11]and are also proposed to reduce morbidity and mortality and improve stroke outcomes [12].

In this study, the presence of hypertension was found to be the most dominating risk factor among our patients, while diabetes was rated as the fifth risk factor and this was in agreement with Lewington et al. [13]. While Selim et al. [14]registered that diabetes mellitus was the most prevalent one.

A statistically significant relationship between lower serum vitamin D and poor stroke short-term outcome at three months was detected and these results are in accordance with [11, 15, 16, 17, 18]. Narasimhan and his colleague [19] assessed the severity of stroke by the Scandinavian Stroke Scale (SSS) at the onset and three months later, in case-control research, vitamin D supplementation at stroke onset to one group was done. They documented much improvement with better outcomes in those who received vitamin D . These findings may be clarified by the lack of

neuroprotective function of vitamin D which may be exerted through enhancing the detoxification paths, reduction of nitric oxide synthase activity, promoting antioxidant and anti-inflammatory pathways, regulation of neuronal calcium inflow or improving nerve conduction [20].

Different previous studies have demonstrated different cutoff values of vitamin D predicting poor outcomes. As Park et al.[12] found, vitamin D level at 20 ng/ml is linked to better outcomes, while at 17 ng/ml, worse outcomes are predicted. While Selim et al. [14] revealed that the vitamin D serum cutoff that can guess a poor stroke outcome was ≤17 ng/ml with 81.4% sensitivity and 42.7% specificity. In a similar context, Moraes et al.[21] reported a cutoff value of 12ng/ml that could predict post-stroke mortality. Our cutoff value was much lower and estimated at ≤8.21 ng/ml.

Upon evaluating the factors that may affect stroke outcome using mRS, the univariate analysis showed that older age, increased NIHSS score at the onset of stroke, a larger size of infarction, and low vitamin D levels could be linked to poor functional outcomes and this is in agreement with Tu et al. [15]. Also, Zhou et al. [22] demonstrated that each nanogram per milliliter reduction in the vitamin D quantity causes a rise in the burden of a negative outcome by 10.5.

Conclusion

Patients with poor functional post-stroke outcomes at three months tend to have lower vitamin D levels. So we recommend serial screening of vitamin D levels among people at high risk of having a stroke to diminish the possibility of having a stroke and improve the outcome if it occurs.

Disclosure of potential conflict of interest

The authors declare that they have no conflict of interest and the study was not supported by any source of funding.

REFERENCES

1) Kim AS and Johnston SC. Temporal and geographic trends in the global stroke epidemic.Stroke.2013;44:S123–5. doi: 10.1161/STROKEAHA.111.000067
2) Alkhatatbeh MJ, Abdul-Razzak KK, Khasawneh LQ, Saadeh NA. High prevalence of vitamin D deficiency and correlation of serum vitamin D with cardiovascular risk in patients with metabolic syndrome. Metab Syndr Relat Disord. 2017; 15:213–9. Doi: 10.1089/met.2017. 0003
3) Gupta A, Prabhakar S, Modi M, Bhadada SK, Lal V, Khurana D. Vitamin D status and risk of ischemic stroke in North Indian patients. Indian J Endocr Metab. 2014;18:721-5.
4) Turetsky A, Goddeau RP Jr, Henninger N. Vitamin D independently predicts cerebral infarct volume and post-stroke outcome. J Stroke Cerebrovasc Disease. 2015;24(7):1555–63.
5) Gupta A, Prabhakar S, Modi M, Bhadada SK, Kalaivani M, Lal V, et al. Effect of vitamin D and calcium supplementation on ischaemic stroke outcome: a randomized controlled open-label trial. Int J Clin Pract. 2016;70(9):764–70.
6) Yarlagadda K, Ma N and Doré S . Vitamin D and Stroke: Effects on Incidence, Severity, and Outcome and the Potential Benefits of Supplementation. Front. Neurol.2020; 11:384. doi: 10.3389/fneur.2020.00384.
7) Musuka TD, Wilton SB, Traboulsi M, Hill MD. Diagnosis and management of acute ischemic stroke: speed is critical. CMAJ. 2015 Sep 8;187(12):887-93. doi: 10.1503/cmaj.140355. Epub 2015 Aug 4. PMID: 26243819; PMCID: PMC4562827.
8) Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol.
2006;5(7):603–12.
9) Sulter G, Steen C, De Keyser J, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke. 1999;30(8):1538–41.
10) Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 dietary reference intakes for calcium and vitamin D: what dietetics practitioners need to know? J Am Diet Assoc. 2011;111(4):524–7.
11) Pilz S, Tomaschitz A, Drechsler C, Zittermann A, Dekker JM, März W. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. Curr Drug Targets. 2011 Jan;12(1):88-96. Doi: 10.2174/138945011793591563. PMID: 20795935.
12) Park KY, Chung PW, Kim YB, Moon HS, Suh BC, Won YS, et al. Serum vitamin D status as a predictor of prognosis in patients with acute ischemic stroke. Cerebrovasc Dis. 2015;40(1–2):73–80
13) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–1913.

14) Selim FO, Fahmi RM, Ali AE, Raafat N, Elsaid AF. Serum vitamin D levels in acute stroke patients. Egypt J Neurol Psychiatry Neurosurg .2019;55: 80 https://doi.org/10.1186/s41983-019-0129-0.
15) Tu WJ, Zhao SJ, Xu DJ, Chen H. Serum 25-hydroxyvitamin D predicts the short-term outcomes of Chinese patients with acute ischaemic stroke. Clin Sci. 2014;126:339.
16) Wang Y, Ji H, Tong Y, Zhang ZB. Prognostic value of serum 25-hydroxyvitamin D in patients with stroke. Neurochem Res. 2014;39(7):1332–7.
17) Xu T, Zhong C, Xu T, Peng Y, Bu X, Chen CS, et al. Serum 25-hydroxyvitamin D deficiency predicts long-term poor prognosis among ischemic stroke patients without hyperglycemia. Clin Chim Acta. 2017;471:81–5.
18) Fahmy E, Sharaf S, Helmy H, Sherif S. Vitamin D status in acute ischemic stroke: relation to initial severity and short-term outcome. Egypt J Neurol Psychiatr Neurosurg. 2019; 55: 18.
19) Narasimhan S and Balasubramanian P. Role of Vitamin D in the Outcome of Ischemic Stroke- A Randomized Controlled Trial. J Clin Diagn Res. 2017 Feb;11(2):CC06-CC10. doi: 10.7860/JCDR/2017/24299.9346. Epub 2017 Feb 1. PMID: 28384856; PMCID: PMC5376887.
20) Michos ED and Gottesman RF. Vitamin D for the prevention of stroke incidence and disability: promising but too early for prime time. Eur J Neurol. 2013 Jan;20(1):3-4. Doi: 10.1111/j.1468-1331.2012.03799.x. Epub 2012 Jul 11. PMID: 22779772; PMCID: PMC3496842.
21) Moraes RB, Friedman G, Wawrzeniak C, Marques LS, Nagel FM, Lisboa TC, et al. Vitamin D deficiency is independently associated with mortality among critically ill patients. Clinics (Sao Paulo). 2015; 70: 326.
22) Zhou R, Wang M, Huang H, Li W, Hu Y, Wu T. Lower vitamin D status is associated with an increased risk of ischemic stroke: a systematic review and meta-analysis. Nutrients. 2018;10(3):277.

To Cite:
abdelaziz, S., Elseddawy, A., ashour, W., Fathy, S. Serum Vitamin D As A Predictor For Short Term Outcome Of Ischemic Stroke : A Prospective Cohort Study. *Zagazig University Medical Journal*, 2023; (1491-1496): -. doi: 10.21608/zumj.2023.188499.2729