The relationship of vitamin D deficiency with severity and outcome of acute stroke

REZA EBRAHIMI RAD[1*], MOHAMMADREZA ZARBAKHSH[2], SAMIRA SARABI[3]

[1] M.D., Department of Neurology, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
[2] PhD., Department of psychology, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
[3] M.D., General Physician, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

Background. There are currently conflicting results regarding the link between vitamin D deficiency and the increased risk for stroke and its poor prognosis. The present study aimed to assess the relationship between vitamin D deficiency and prognosis of acute stroke.

Methods. This bi-center cross-sectional study was performed on 140 consecutive patients who referred to two general hospitals in Iran with the diagnosis of acute stroke. The levels of 25-hydroxy vitamin D were evaluated by Electrochemiluminescence (ECL) technique. Clinical severity of stroke on admission as well as on discharge time were evaluated using the National Institutes of Health Stroke Scale (NIHSS) or Modified Rankin (mRS) tools.

Results. Mean serum level of vitamin D was 25.51 ± 18.87 ng/mL, ranging from 3.0 to 98.6 ng/ml. There was a significant difference between the two groups (with and without vitamin D deficiency) in terms of stroke severity and disability, as reflected by mRS (P=0.003) and NIHSS evaluation (14.24 ± 9.23 versus 9.73 ± 7.36, P=0.003). Also, regarding patients' clinical condition, the mean NIHSS score in those with deficient and normal levels of vitamin D was 14.24 ± 9.23 and 9.73 ± 7.36, respectively with NIHSS score > 5 in 76.1% and 61.5%, respectively (P = 0.003).

Conclusion. According to the results of study, vitamin D status can be related to the severity of stroke. However, considering the cross-sectional design of our study, it could not point out the causality between vitamin D deficiency and acute stroke and further studies are warranted. It is not possible to draw any conclusions in terms of causality. Further studies are required in order to assess the relationship between the serum vitamin D levels and stroke severity.

Key words: Vitamin D; acute stroke; prognosis; risk factors; atherosclerosis; cardiovascular disease.

INTRODUCTION

Stroke is the most common neurological condition across the world, leading to high mortality and disability as well as impaired health-related quality of life [1,2]. Its etiopathogenesis entails modifiable factors such as cardiovascular risk factors and sedentary lifestyle as well as unchangeable factors, including genetic susceptibility [3–5]. The first pathogenic pathway elicited in ischemic cerebrovascular injuries involves inflammatory responses, namely migration and infiltration of circulating immune cells, activation of astrocytes as well as dysfunction of endothelial cells [6,7]. Some of these pathways are mediated and activated by vital micronutrients such as oligoelements and vitamins [8,9]. A central role has been attributed to vitamin D deficiency in inducing endothelial dysfunction and initiating dyslipidemia and arterial hypertension [10,11]. Additionally, vitamin D deficiency might be involved in expanding the volume of ischemic infarction [12–16]. It has been demonstrated that most tissues, particularly nervous system and immune cells, display vitamin D receptors (i.e. VDR) that actively respond to 1, 25dihydroxyvitamin D [17–19]. Furthermore, vitamin D has a major role in regulation of immune cells function by inhibiting prostaglandin, mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathways as well as down regulation of pro-inflammatory cytokines, leading to inhibition of inflammation-related pathways involved in acute ischemic stroke or cardiovascular ischemic events [20–22]. Some animal and human-based studies sought to prove the relationship between acute stroke and vitamin D deficiency [23–25]. Moreover, there are conflicting results regarding the association between vitamin D deficiency and stroke prognosis [26, 27]. Considering this, we designed a study aiming to assess the relationship between vitamin

D3 deficiency and the severity and outcome of acute stroke in Iran.

MATERIALS AND METHODS

We conducted a bi-center cross-sectional study including 140 patients with acute stroke who referred to two general hospitals in Iran between May 2013 and October 2015 (Figure 1). They were first evaluated through interviewing, clinical examination and accessing prior medical records. The study was approved by the Ethics Committee at Iran University of Medical Sciences. All the patients or their families signed the informed consent in order to participate in the study. The patients included were not eligible for thrombolysis (came later than 4.5 hours after the onset of the symptoms). The diagnosis of stroke was established according to World Health Organization (WHO) criteria, based on patients' story, clinical findings and brain imaging, including Computerized Tomography (CT scan) and Magnetic Resonance Imaging(MRI);The following data were extracted from the medical records and served as study variables: **1)** baseline characteristics, including demographics, anthropometric parameters, **2)** cardiovascular risk factors, including arterial hypertension (systolic blood pressure > or = 160 or diastolic blood pressure, > or = 95 mm Hg or both, or treatment with antihypertensive drugs), **3)** diabetes mellitus (blood glucose≥ 140 mg/dl in past medical history or treatment with insulin or oral glucose-lowering drugs), **4)** atrial fibrillation (known or diagnosed during hospitalization), **5)** hypercholesterolemia (total cholesterol level ≥ 220 mg/dl in past medical history or treatment with lipid lowering drugs), **6)** tobacco consumption, **7)** myocardial infarction, **8)** peripheral vascular disease and past history of transient ischemic attack or ischemic stroke, and **9)** recent medications or therapeutic interventions were collected. Therefore, all files missing the mentioned items were excluded from our study. To measure the serum level of 25-hydroxy vitamin D within the first 48 hours of admission, Electrochemiluminescence technique was applied. To assess the clinical severity of stroke on admission, the NIHSS criteria [33] were used (a NIHSS score≤ 5 indicates a mild clinical condition, whereas a score >5 stands for a severe stroke), whereas M-Rankin Scaling tools [34] were used on discharge_ (i-a mRS score≤ 3 correlates with mild disability and m-Rankin >3suggests a rather disabling stroke).

The modified M-Rankin score was also used to assess the disease without prognosis. Score "0" means no symptom, score "1" no significant disability, "2" slight disability, "3" as moderate disability, "4" as moderately severe disability, "5" as severe disability, and "6" as dead. Vitamin D deficiency was defined as serum vitamin D level < 25.7 ng/mL. Results of the statistical analyses of the data were reported as mean ± standard deviation (SD) for the numerical variables whereas for the categorical variables the results were summarized by absolute frequencies and percentages. With Kolmogorov-Smirnoff test, analysis of normality of the data was performed; if more than 20% of cells with expected count of less than 5 were observed, Fisher's exact test or Chi-square test were applied to compare categorical variables.

Moreover, t test or Mann-Whitney U test also were used to compare the numerical variables. In this study the data were analyzed using SPSS that the version 22 for windows (SPSS Inc., Chicago, IL). P values of 0.05 or less were considered statistically significant.

RESULTS

One hundred forty patients (73 men and 67 women, average age 68.71 ± 9.92 years) were included in the present study out of which (85%) had ischemic stroke, and 21 (15%) suffered from a hemorrhagic stroke. As shown in Table 1, the most frequent risk factor related to stroke was arterial hypertension followed by diabetes mellitus, smoking and dyslipidemia. Regarding the medication history prior to stroke, anti-hypertensive and anti-platelet therapies were the most frequently used drugs. In total, 70.7% had a NIHSS score > 5.51 whereas 4% of the patients had poor prognosis according to the M-Rankin score > 3. The mean serum level of vitamin D was 25.51 ± 18.87 ng/mL ranging from 3.0 to 98.6 ng/mL. Comparing the baseline characteristics between the patients with vitamin D deficiency and those with normal level of this vitamin (Table 1), we found a lower mean age in the former group (68.71 ± 9.92 years versus 66.93 ± 9.71 years, p = 0.005); however, there was no difference between the groups in terms of gender, type of stroke (ischemic or hemorrhagic) or cardiovascular risk factors. As shown in Table 1, regarding M-Rankin score (score ≥ 3 and score< 3), there was a significant difference between the two groups with and without vitamin D deficiency (P = 0.003). The same applies to NIHSS (14.24 ± 9.23 vs. 9.73 ± 7.36, P = 0.003).

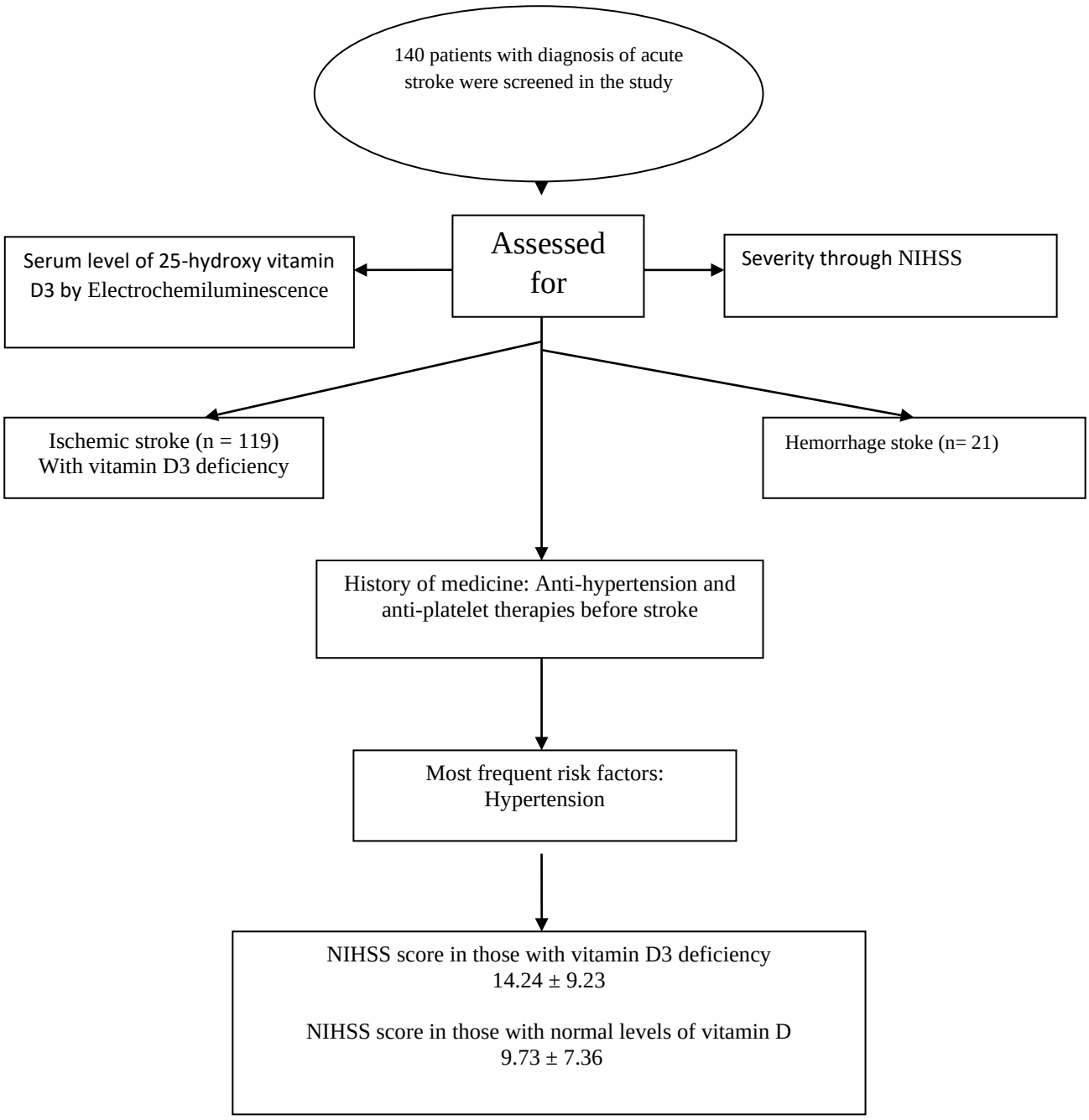
Study flow chart
140 patients with diagnosis of acute stroke were screened in the study
Assessed for
Serum level of 25-hydroxy vitamin D3 by Electrochemiluminescence
Severity through NIHSS
Ischemic stroke (n = 119) With vitamin D3 deficiency
Hemorrhage stoke (n= 21)
History of medicine: Anti-hypertension and anti-platelet therapies before stroke
Most frequent risk factors: Hypertension
NIHSS score in those with vitamin D3 deficiency 14.24 ± 9.23
NIHSS score in those with normal levels of vitamin D 9.73 ± 7.36

Table 1.
Baseline characteristics in the two groups with and without vitamin D deficiency

Item		Total N=140	25(OH)D<25.7 N=88	25(OH)D≥25.7 N=52	P-value
Age, Mean(±SD)		68.71(±9.919)	66.93(±9.714)	71.71(±9.621)	0.005
<60		29(20.7)	22(25)	7(13.5)	0.021
60-74		68(48.6)	46(52.3)	22(42.3)	
≥74		43(30.7)	20(22.7)	23(44.2)	
sex	Female	67(47.9)	42(47.7)	25(48.1)	0.553
	Male	73(52.1)	46(52.3)	27(51.9)	
M-Rankin, Mean(±SD)		3.22(±1.654)	3.57(±1.639)	2.63(±1.521)	0.001
< 3		68(48.6)	34(38.6)	34(65.4)	0.003
≥ 3		72(51.4)	54(61.4)	18(34.6)	
NIHSS, Mean(±SD)		12.56(±8.829)	14.24(±9.228)	9.73(±7.359)	0.003
≤ 5		41(29.3)	21(23.9)	20(38.5)	0.084
> 5		99(70.7)	67(76.1)	32(61.5)	
Type of Stroke	Ischemic (%)	119(85)	71(80.7)	48(92.3)	0.086
	Hemorrhagic (%)	21(15)	17(19.3)	7(7.7)	
HTN	No (%)	23(16.4)	16(18.2)	7(13.5)	0.638
DM	No (%)	54(38.6)	34(38.6)	20(38.5)	0.565
AF	No (%)	118(84.3)	73(83)	45(86.5)	0.638
Hypercholesterolemia	No (%)	96(86.6)	65(73.9)	31(59.6)	0.092
History of MI	Yes (%)	18(12.9)	11(12.5)	7(13.5)	0.532
Peripheral Vessels	No (%)	139(99.3)	87(98.9)	52(100)	0.629

Disease					
Smoking	No (%)	111(79.3)	67(76.1)	44(84.6)	0.284
History of stroke	No (%)	124(88.6)	75(85.2)	49(94.2)	0.168
Oral Anti-Coagulant	Yes (%)	139(99.3)	87(98.9)	52(100)	0.629
Anti HTN	Yes (%)	103(73.6)	63(71.6)	40(76.9)	0.555
Anti-Platelet	Yes (%)	70(50)	33(37.5)	37(71.2)	< 0.001
Statins	Yes (%)	37(26.4)	17(19.3)	20(38.5)	0.017

DISCUSSION

In this study, we emphasize the correlation between vitamin D deficiency and poor outcome in patients with stroke. Comprehensive studies suggest that reduced levels of vitamin D3 in the serum are an independent risk factor for atherosclerosis and cardiovascular disease. The association between vitamin D deficiency and large artery atherosclerosis as well as small artery disease has also been stated. A recent study showed that decreased levels of 25-hydroxyvitamin D are associated with increased intimal media thickness and arterial plaques [37]. A strong association between vitamin D deficiency and cardiovascular disease has been well described [38–40]. As shown by Giovannucci *et al.* [41], a lower level of 25-hydroxyvitamin D might increase the risk of myocardial infarction. Although it is unanimously accepted that reduced level of 25-hydroxyvitamin D can be a risk factor for atherosclerosis, coronary calcifications and some trials failed to prove the association between cardiovascular risk and vitamin D [42–45]. Further research is needed in order to fully understand the pathogenic pathway of atherosclerosis in vitamin D deficiency in both cardiovascular and cerebrovascular systems.

Li *et al.* [46] revealed that vitamin D can act like a regulator for blood pressure, by suppressing the renin-angiotensin system. Apart from its effect on blood pressure, vitamins D also seem to inhibit thrombosis and reduce arterial classification [47–49]. Moreover, reduction of the proliferation of lymphocytes and the production of cytokines can be attributed to vitamin D using some specific mechanism including 1) expressing receptors for vitamin D by smooth muscle cell and lymphocytes, and 2) converting 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D [50]. Since there is increasingly evidence of the systemic inflammatory milieu triggering atherosclerosis, vitamin D could also have a protective vascular role as an anti-inflammatory agent [51].

As important finding of our study is that vitamin D deficiency is associated with poor prognosis in patients with stroke, independently of age, sex, and underlying risk factors. This result emphasizes the potential role of vitamin D deficiency in the pathogenesis of brain ischemia by mediating post-stroke inflammatory responses leading to more severe manifestations and greater disability [52].

It seems that vitamin D functions lead to dampen cell mediated immune responses e.g. the vitamin acts on the antigen presenting cells process, also on the T cell, simultaneously leading to Th2 cell development [22]. These evidences can suggest the role of vitamin D deficiency in exacerbating cerebral inflammation and neuronal ischemic cell death. Furthermore, vitamin D can induce neuroprotection by increasing some neurotrophic factors, such as nerve growth factor (NGF), neurotrophins, and glial cell line-derived neurotrophic factor (GDNF) [53,54].

Study limitations

However, it should be noted that an important limitation was the small sample size. Also, independent factors affecting 25 (OH) D such as bone softness, osteoporosis, kidney failure, rickets, not exposing to sunlight, and the use of drugs such as phenobarbital and Phenytoin were not considered in this study. A case-control study taking into account the aforementioned issues should be performed in order to obtain more accurate data.

CONCLUSION

In conclusion, vitamin D deficiency seems to be related to more severe and disabling acute stroke. However, a causal relationship between vitamin D status and stroke prognosis could not be established. Given the cross-sectional design of our study, further studies are needed in order to elucidate this matter.

Introducere. *Datele din literatură referitoare la legătura dintre deficitul de vitamină D și riscul crescut de dezvoltare a atacului vascular cerebral (AVC) și prognosticul acestuia sunt încă neclare. Studiul și-a propus evaluarea deficitului vitaminei D și a prognosticului AVC ischemic.*

Metode. *A fost realizat un studiu bicentric transversal pe 140 de pacienți consecutiv cu diagnosticul de AVC ischemic. Nivelurile vitaminei D au fost evaluate prin ECL. Severitatea clinică a AVC-ului, la internare, precum și la externare a fost evaluat prin scalele NIHSS sau Rankin modificat.*

Rezultate. *Nivelurile serice ale vitaminei D au fost la 25.51 ± 18.87 ng/mL, de la 3.0 la 98.6 ng/mL. A fost găsită o diferență semnificativă statistic la pacienții fără deficit de vitamina D și cei cu deficit pentru vitamina D în raport cu gradul de severitate și dizabilitate AVC (scor Randkin modificat, p=0.003), scor NIHSS (14.24 ± 9.23 versus 9.73 ± 7.36, P=0.003).*

Concluzii. *Statusul vitaminei D se asociază cu severitatea AVC. Nu se poate evidenția cauzalitatea din acest tip de studiu, fiind unul transversal, fiind necesare studii viitoare.*

Correspondence to: Reza Ebrahimi Rad, M.D**,** Department of neurology, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
Email: R.Ebrahimi.R.Neurology@gmail.com and reza_er_neuro@yahoo.com,
Mobile: +98-9111318297

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