Original Research Article

International Journal of Neurology and Neurosurgery
Volume 12 Number 1, January – March 2020
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.12120.6

Association of Serum 25-hydroxyvitamin-D Levels with Severity of Acute Arterial Stroke in South-Indian Population

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Received on 02.01.2019, **Accepted on** 11.01.2020

How to cite this article:

Anil Kumar Kasukurthy, Naveen Prasad SV, Nataraja P et al. Association of Serum 25-hydroxyvitamin-D Levels with Severity of Acute Arterial Stroke in South-Indian Population. Int J Neurol Neurosurg. 2020;12(1):41–47.

Abstract

Background and Purpose: Vitamin-D deficiency is common across all age groups and may contribute to cardiovascular diseases. Serum 25-hydroxyvitamin-D deficiency causing acute arterial stroke has been documented in recent reports. *Aim:* To investigate the levels of serum 25-hydroxyvitamin-D in acute arterial stroke and association of 25-hydroxyvitamin-D deficiency with severity of acute arterial stroke at presentation. *Methods:* A total of 344 consecutive acute arterial stroke patients and 87 controls attending the Department of Neurology, at Sri Venkateswara Institute of Medical Sciences, Tirupati, India, from April 2015 to October 2016 were enrolled into the study. Stroke severity was assessed at admission by using the National Institutes of Health Stroke Scale (NIHSS) score and ICH score. 25-hydroxyvitamin-D levels were measured by chemiluminescence test. Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone were also measured in both cases and controls. *Results:* Out of 344 stroke patients, 218 (63.4%) were men and mean age was 58.01 ± 13.8 years (age range: 15–90 years). 25-hydroxyvitamin-D deficiency was observed in 156 (45.3%) stroke patients and 31 (35.6%) controls ($p < 0.0001$). Among stroke patients, 25-hydroxyvitamin-D deficiency in ischemic stroke patients were 109/251 (43.4%) and haemorrhagic stroke patients were 47/93 (50.5%) respectively. Among stroke patients, serum 25-hydroxyvitamin-D levels reduced with increasing severity of stroke as defined by the NIHSS score and ICH score. *Conclusions:* We found that 25-hydroxyvitamin-D deficiency had an independent association with acute arterial stroke. Increasing severity of stroke showing low Serum 25-hydroxyvitamin-D levels.

Keywords: Acute arterial stroke; 25-hydroxyvitamin-D; Stroke; South-India.

Introduction

Acute arterial stroke is a most common debilitating neurological disease. As per the World Health Organization (WHO), 15 million people suffer stroke worldwide each year.[1] Of these 15 million stroke patients, 5 million die and 5 million are permanently disabled. Without intervention, the global number of deaths from stroke is expected to rise 7.8 million by 2030.[2]

Stroke has heterogeneousan etiology, caused by modifiable and non-modifiable risk factors. The role of serum 25-hydroxyvitamin-D in bone metabolism and calcium homeostasis is well known. There is

an evidence that serum 25-hydroxyvitamin-D deficiency is associated with many conditions including hypertension, insulin resistance, diabetes mellitus, cancer, infections, autoimmune diseases, heart failure, cardiovascular diseases, and stroke.[4–6] Serum 25-hydroxyvitamin-D deficiency is highly prevalent due to lifestyle and environmental factors which limit sunlight-induced vitamin-D production in the skin.[7] A meta-analysis on 25-hydroxyvitamin-D and symptomatic ischemic stroke has found stepwise increasing risk of symptomatic ischemic stroke with decreasing concentration of serum 25-hydroxyvitamin-D.[8]

There are few studies in India which studied association of serum 25-hydroxyvitamin-D deficiency in acute arterial stroke patients. In a study from South India Chaudhuri et al. found 25-hydroxyvitamin-D deficiency had an independent association with ischemic stroke. The association was established in large artery arthrosclerosis and cardioembolic stroke.[9]In present study, association of serum 25-hydroxyvitamin-D with acute arterial (ischemic and hemorrhagic) stroke is studied.

Materials and Methods

All patients diagnosed with acute stroke and admitted in the Neurology intensive care unit, Medical intensive care unit, Neurology and Medicine wards at Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, between April 2015 and October 2016 were prospectively studied.

Cases: Patients admitted with first episode of acute arterial stroke within 7 days of onset were taken as cases.

Controls: Controls were recruited from healthy volunteers with no prior history of stroke or transient ischemic attacks from OPD. Controls and cases were taken in 1:4 ratio.

Exclusion criteria for cases: (i) Patients with recurrent stroke (ii) Patients with venous stroke (iii) Patients who are on vitamin D supplements. (iv) Patients who are not willing to participate in the study.

Exclusion criteria for controls: (i) Who are on vitamin D supplements, (ii) who are not willing to participate in the study.

This study was approved by the Research Approval Committee and as well by the Institutional Ethical Committee of our institute.

Study Procedures

The patients with clinical diagnosis of stroke, confirmed with neuroimaging studies, were considered for inclusion into the study. Patients were enrolled into the study after obtaining a written informed consent from the patient or from their legally accepted representative in case of patient was in unconscious.

Patient history on risk factors of stroke was captured. All the participants were subjected to a detailed physical examination, consisting of general physical examination, detailed neurological examination and examination of other systems.

All patients were subjected to CT scan of the brain (plain) (Siemens Somatom Emotion Spiral CT Scanner, Muenchen, Germany). The patients with acute ischemic stroke were confirmed with Magnetic Resonance Imaging (MRI) of the brain [T2-weighted (T2W) and diffusion weighted (DWI) images] and magnetic resonance angiogram (MRA) (Siemens Symphony Maestro Class MRI Scanner, Muenchen, Germany).

National Institutes of Health Stroke Scale (NIHSS) score was documented in all patients with acute ischemic stroke.[10] Ischemic stroke subtypes were classified as per TOAST (trial of ORG 10172 in acute stroke treatment) classification.[11] Intracerebral Hemorrhage (ICH) score[12] was documented in all patients with acute hemorrhagic stroke. All the patients were assessed for functional status at the end of their hospital stay using modified Rankin Scale (mRS)[13] which were classified as— complete recovery (score 0 – 1), partial recovery and independent (score 2), partial recovery and dependent (score 3 – 5), and death (score 6). The mRS 3–6 was considered as poor outcome.

Three ml of whole blood was collected in ice from cases and controls. 25-hydroxy vitamin D levels were measured by radioimmune assay (RIA) after extraction with Acetonitrile with a commercial kit (Diasorin kit, USA). Normal range of vitamin D is 30–100 ng/ml. Parathyroid hormone (PTH) was measured in plasma on the same day by a commercial kit on Beckmann access 2 chemiluminescence autoanalyzer. Normal range of PTH was taken as 12–88 pg/ml. Serum calcium, serum phosphorous and serum alkaline phosphatase were measured in all patients.

In case of young patients with stroke (ageless than 45 years), the following additional laboratory tests were carried out: rheumatoid factor, anti-nuclear antibody, anti-double-stranded deoxy-ribonucleic acid (anti-ds DNA) antibody, protein

C and S, antithrombin III, serum homocysteine, anticardiolipin antibody, serology for venereal disease research laboratory testing, human immunodeficiency virus infection.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (IBM Corp. Chicago, IL, USA). Continuous variables are expressed as Mean ± SD. Student´s test was applied to test the differences in continuous variables and chi-square test was applied to study the association in proportions. ODDs ratio was calculated with 95% confidence interval. Multiple logistic regression was performed before and after adjustment for potential confounders. All tests were two sided and p value < 0.05 was considered statistically significant.

Results

Three hundred sixty-five patients diagnosed with acute stroke in the Neurology intensive care unit, Medical intensive care unit, Neurology and Medicine wards at Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, between April 2015 and October 2016 were recruited into the study. Out of these, 21 patients were excluded from the study because of the reasons shown in Fig. 1. Patients satisfying the inclusion criteria were studied and followed-up till the time of discharge from hospital or death. Eighty-seven controls were recruited for 344 patients (in 1:4 ratio) from healthy volunteers with no prior history of stroke or transient ischemic attacks. The mean age of patients presented with stroke was 58.01 ± 13.8 years (Age ranges 15–90 years). Majority (27.9%) of patients were in the fifth decade. There were 218/344 (63.4%) males. The patients with stroke in young (ageless than 45 years) were 62/344 (18%). In the present study, majority of patients had ischemic stroke (73%) than hemorrhagic stroke (27%). The large artery atherosclerosis (thrombosis/embolus) in 182 (72.5%), cardioembolic stroke in 28 (11.1%), small vessel occlusion in 39 (15.5%), stroke of undetermined etiology in 2 (0.8%) patients were seen.

The patients with minor stroke were 14 (5.6%), moderate stroke were 174 (69.3%), moderate to severe stroke were 41 (16.3%), severe stroke 22 (8.7%). Out of 93 hemorrhagic, 35 (37.6%) patients showed score one, 31 (33.3%) patients showed score two, 19 (20.4%) patients showed score three, 2 (2.1%) patients showed score four. No patient has presented with score five and six.

The frequency of various risk factors found in this study were hypertension (74.4%), diabetes (33.7%), old age i.e., >65 years (35.1%), smoking (36.3%), alcohol intake (30.5%), dyslipidemia (34%), coronary arterial disease (6.6%), arrhythmias (5.5%), hyperhomocysteine (4%), antiphospholipid antibody (1.1%), obesity (1.1), polycythemia (1.7%), Takayasu's arteritis (0.29%), drugs (0.3%).

In the present study 25-hydroxyvitamin-D deficiency was more prevalent in cases 156 (45.3%) than in controls 31 (35.6%), which was statistically significant (p = 0.000). Among cases 25-hydroxyvitamin D deficiency was more prevalent in hemorrhagic stroke patients 47 (50.5%) than in ischemic stroke patients 109 (43.4%). There was no statistically significant difference (p = 0.241) in 25-hydroxyvitamin-D levels between hemorrhagic and ischemic stroke patients.

There was no significant difference in mean serum total calcium, mean serum phosphorous,mean serum parathyroid hormone and mean serum alkaline phosphatase as per their 25-hydroxy-vitamin D status. There was no statistically significant (p = 0.894) difference among stroke subtypes and 25-hydroxyvitamin-D levels. There was no statistically significant (p = 0.209) difference among mild, moderate, moderate to severe and severe ischemic stroke patients in their 25-hydroxyvitamin-D levels as shown in Table 1.

There was no statistically significant (p = 0.160) difference between stroke severity based on ICH score[12] and their 25-hydroxyvitamin-D levels. There was no statistically significant difference in the 25-hydroxyvitamin-D levels between complete recovery and disability (p = 0.018) as shown in Table 2.

Table 1: Ischemic stroke severity and 25-hydroxyvitamin-D levels.

Stroke severity*	Ischemic stroke patients (n = 251)	Serum 25 (OH) D levels <20 ng/ml	Serum 25 (OH) D levels >20.1 ng/ml	p-valve
Mild	14 (5.6%)	8 (57.1%)	6 (42.9%)	
Moderate	174 (69.3%)	68 (39.1%)	106 (60.9%)	
Moderate to severe	41 (16.3%)	21(51.2%)	20 (48.8%)	
Severe	22 (8.7%)	12 (54.5%)	10 (45.5%)	0.209

*As per NIHSS (National Institute of Health Stroke Scale)[10]

Table 2: 25-hydroxyvitamin-D levels in Hemorrhagic stroke patients categorized severity

ICH score	Hemorrhagic stroke patients (n=93)	Serum 25(OH) D levels <20 ng/ml	Serum 25 (OH) D levels >20.1ng/ml	p- valve
0	6	0	6 (100%)	
1	35	15 (42.9%)	20 (57.1%)	
2	31	20 (64.5%)	11 (35.5%)	
3	19	10 (52.6%)	9 (47.4%)	
4	2	2 (100%)	0	0.160

Table 3: Mean biochemical parameters of cases and controls

Variables	Cases (n = 344)	Controls (n = 87)	p-valve
Mean Serum total Calcium	9.2 ± 0.5	10.2 ± 8.6	0.691
Mean Serum Phosphorous	3.6 ± 2.3	3.6 ± 0.6	0.291
Mean Serum Parathyroid hormone	32.9 ± 21.6	32.9 ± 23.2	0.742
Mean Serum Alkaline Phosphatase	95.1 ± 62.0	89.3 ± 34.3	0.012
Mean Serum 25- hydroxyvitamin D	26.8 ± 21.4	29.0 ± 11.5	0.000

Table 4: Risk factors of cases based on 25-hydroxyvitamin-D levels

Variables	No. of patients	Serum 25(OH) D levels <20 ng/ml	Serum 25 (OH) D levels >20 ng/ml	p-valve
Mean age years		57.8±13.5	58.2±14.1	NS
Male	218	91 (41.7%)	127 (58.2%)	0.780
Hypertension	256	117 (45.7%)	139 (54.3%)	0.901
Diabetes	116	54(46.5%)	62 (53.4%)	0.819
Dyslipidemia	118	53 (44.9%)	64 (54.2%)	1.000
Smoking	125	51 (40.8%)	74 (59.2%)	0.217
Alcohol	105	45 (42.8%)	60 (57.1%)	0.310
Old age (>65 years)	121	53 (43.8%)	68 (56.2%)	0.734
Ischemic heart disease	23	8 (34.9%)	15 (65.2%)	0.387
Arrhythymias	19	7 (36.8%)	12 (63.1%)	0.486
Homocysteine (>15 micro mol/L)	14	8 (57.1%)	6(42.8%)	0.419
Polycythemia (>20 g/dl)	6	2(33.3%)	4(6.7%)	0.693

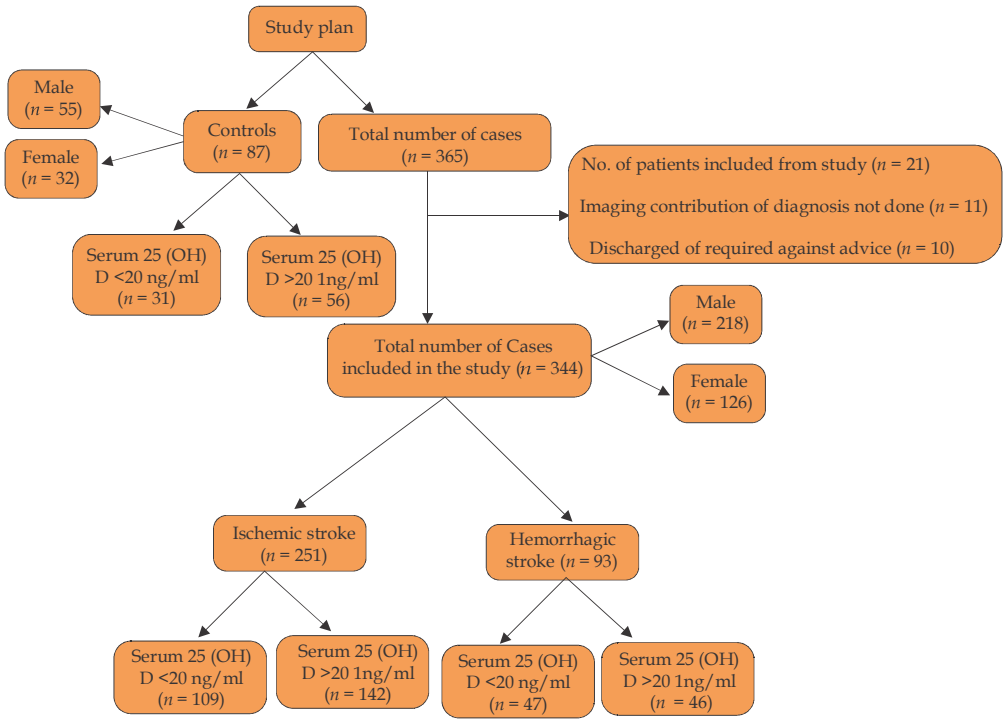

Fig. 1: Schematic representation of study design.

The mean serum 25-hydroxyvitamin-D levels of cases and controls were 26.8 ± 21.4 and 29.0 ± 11.5 ng/ml respectively, and is statistically significant (p = 0.000). There was no statistically significant difference among case and controls in mean serum total calcium, mean serum phosphorous, mean serum alkaline phosphatise, mean serum parathyroid hormone levels (Table 3).

No statistical significance was observed either in the prevalence sex hypertension, diabetes, dyslipidemia, smoking, alcohol, old age, ischemic heart disease, arrhythmias, homocysteine, polycythemia as per vitamin-D status among cases as shown in Table 4.

Discussion

In our study, we found a significant association between 25-hydroxyvitamin-D deficiency and ischemic stroke and established an independent association. These results are in accordance with Chaudhuri et al.,[9] Majumdar et al.,[14] Poole et al.[15]

In the present study deficiency of 25-hydroxyvitamin-D deficiency with large artery atherosclerosis and with small artery disease was in 82 (45.1%) and 20(51.3%) patients respectively. In Chaudhuri et al.,[9] large artery atherosclerosis and small artery disease patients showing vitamin D deficiency were 54.9% and 44.4% respectively. In Yan Wang et al.[16] small artery disease subtype patients deficiency of 25-hydroxyvitamin-D was 38.1%. A reason for this was shown in the recent study that low serum 25-hydroxyvitamin-D was significantly associated with increasing intima medial thickness and carotid plaques in individuals.[17]Another study demonstrated vascular effects of serum 25-hydroxyvitamin-D with inhibition of thrombosis[18] and reduction in arterial calcification.[19] Sun et al.[20] found stronger association for small artery disease and vitamin D deficiency. The effects of serum 25-hydroxyvitamin-D on hypertension and diabetes may explain this stronger association.

In the present study serum 25-hydroxyvitamin-D deficiency in moderately severe stroke patients and severe stroke patients based on NIHSS[10] at admission were 51.2% and 54.5% respectively. Present study showed that severity of stroke is higher in patients with serum 25-hydroxyvitamin -D deficiency when compared to patients with normal serum 25-hydroxyvitamin-D levels. Yang et al.,[16] found that the serum 25-hydroxyvitamin-D levels at admission had inversely correlated with infarct volume and admission neurological deficit assessed by NIHSS.[10] Daubail et al.[21] reported low serum 25-hydroxyvitamin-D level is a predictor of severity of stroke. It has been suggested that serum 25-hydroxyvitamin-D has neuroprotective properties[22] and supplementation could contribute to reduce volume of cerebral infarct in animal models of stroke.[23] Reduced serum 25-hydroxyvitamin-D might be associated with overall increased inflammatory activity. In the present study 57.1% patients with ICH score two and 52.6% patients with ICH score[12] three at admission presented with serum 25-hydroxyvitamin-D deficiency. It might be due association between vitamin D and hypertension.

Based on mRS score[13] patients partially recovered but dependent at discharge and those who died, serum 25-hydroxyvitamin-D deficiency were 44.9% and 70.6% respectively. Park. et al.,[24] showed serum 25-hydroxyvitamin D levels were significantly lower in patients with unfavourable outcomes. TuWj et al.[7] suggested low serum 25-hydroxyvitamin-D as an independent predictor of functional outcome at 90 days in acute stroke.

The possible pathophysiological mechanisms underlying the association between low serum 25-hydroxyvitamin-D and outcome could be the larger infarct volume in low serum 25-hydroxyvitamin-D levels. Vitamin D may exert anti-inflammatory effects, and post-stroke inflammatory response might be augmented in patients with vitamin D deficiency.[25]

Leukoareosis is associated with poor functional outcome after ischemic and hemorrhagic stroke.[26,27] A recent study showed that the severity of chronic small vessel disease, including Leukoareosis, is inversely associated with the 25-hydroxyvitamin D level in patients with ischemic stroke.[28] Therefore, underlying small vessel disease might affect the outcome status in patients with low vitamin D level. Vitamin D deficiency–induced derangement of bone metabolism is another potential mechanism of poor outcome in post-stroke patients.[29]

Limitations of the Study

The participants in this study were recruited from patients attending tertiary level health services and results cannot be generalized to a community dwelling population. We only measured baseline 25(OH)D levels, and a single measure may not represent long-term levels.

Conclusion

The study established association of acute stroke and serum 25-hydroxyvitamin-D deficiency. Serum 25-hydroxyvitamin-D deficiency patients presented with severe stroke and had poor functional outcome at the time of discharge. Based on the results of this study and other epidemiological studies, vitamin D supplementation may be beneficial for stroke prevention and improve functional outcome in patients with acute stroke.

Acknowledgments: We would like to thank Dr. Latheef, Research Officer at Santhiram Medical College and General Hospital for his help in manuscript editing.

Conflict of interest: None

Source of funding: None

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