

Original Research Article

Is there an association between vitamin D and risk of stroke?: a North Indian study

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ABSTRACT

Background: Vitamin D deficiency is present in India in epidemic proportions despite plenty of sunshine. Reduced plasma 25(OH) D concentrations as a diagnostic marker of vitamin D deficiency have been in past decade associated with several well-established risk factors for ischaemic stroke, such as arterial hypertension, thrombosis, atherosclerosis. The aims and objectives of this study was to compare the serum 25(OH) D levels between the first ever acute stroke patients and healthy controls.

Methods: A cross-sectional, case control study was conducted in a tertiary care hospital in New Delhi situated in north India. Serum 25-hydroxyvitamin D (25(OH) D) levels in 85 patients of ischemic stroke, presenting within 7 days of onset of stroke was measured and was compared with 70 age and gender matched controls.

Results: The mean age was 61.02±11.58 years and 58.63±11.28 years in cases and controls respectively. Females constituted 37.6% of the total number of cases and 43.4% of the controls. The age and gender-distribution were comparable between the cases and controls. The median value (IQR) of serum 25(OH) vitamin D level was 7.94 ng/mL (4.59-14.00) in the cases and it was 8.82 ng/mL (5.59-14.70) in the controls. The difference between the serum 25(OH) vitamin D levels of the two groups was not found to be statistically significant.

Conclusions: There is a high prevalence of biochemical hypo-vitaminosis D in apparently healthy Indians of all age and sex groups despite adequate sunshine. There is no association between low vitamin D levels and stroke.

Keywords: 25 OH vitamin D level, Stroke, Vitamin D

INTRODUCTION

Vitamin D deficiency is present in India in epidemic proportions despite plenty of sunshine.¹ Globally every second person has a poor vitamin D status and thus is now recognized as a public health problem.² Reduced plasma 25(OH) D concentrations as a diagnostic marker of vitamin D deficiency have been associated with several well-established risk factors for ischemic stroke, such as arterial hypertension, thrombosis, atherosclerosis, and inflammation.²

A population-based study demonstrated a step-wise increased risk of ischemic stroke with step-wise decreasing serum 25(OH) D concentrations, which they substantiated with an accompanying meta-analysis, but another general population study showed no such correlation.^{3,4}

Some western cross sectional studies support the association between vitamin D deficiency and risk of ischemic stroke but the evidence is not very strong.⁵⁻⁷ In past few years, there were two Indian studies one from

north India and another from south India and they had conflicting results.^{8,9} Available literature also suggests that a poor vitamin D status may be associated with adverse health outcomes of post-stroke patients.¹⁰ Thus, the relationship between vitamin D and stroke is turning out to be a conundrum.

Furthermore, the cumulative incidence of stroke ranged from 105 to 152/100,000 persons per year and the crude prevalence of stroke ranged from 44.29 to 559/100,000 persons in different parts of the country during the past decade and these values were higher than those of high-income countries.¹¹

This study was conducted with the primary intention to compare serum 25(OH) D levels in first ever acute stroke patients and healthy subjects. The aims and objectives of this study was to comparison of serum 25-hydroxyvitamin D (25(OH) D) levels in acute stroke patients and healthy subjects.

METHODS

The study was conducted in the Department of Neurology in a Tertiary Care Hospital in New Delhi situated in north India 28.7041°N, 77.1025°E.

Sample size calculation was considered incidence of vitamin D insufficiency as 40% in Indian population after taking average of summer and winter values as documented in the study by Ramakrishnan S et al.¹²

Authors presumed that 77% of acute stroke patients would be Vitamin D deficient. This presumption was based on the study by Kendrick J et al.⁷ Establishing an alpha error of 0.05 and the power of study as 90% authors determined our significant sample size to be 70 in each limb by using power/sample size calculator.

A written informed consent was obtained from all the and study was undertaken after due approval of the hospital ethics committee.

Inclusion criteria

Patients with first-ever stroke (ischemic or hemorrhagic) within one week of onset of complaints, previously healthy and ambulatory with modified ranking scale score (MRS) <2, age >40 belonging to either sex and stroke confirmed by CT scan head or MRI.

Exclusion criteria

Patients with previous hip fracture, bone disease, steroid treatment, vitamin D/calcium supplementation and renal or liver impairment, hypothyroidism, malignancy, alcohol abuse. Previous hip fracture, bone disease, steroid treatment, vitamin D/calcium supplementation and renal or liver impairment, alcohol abuse.

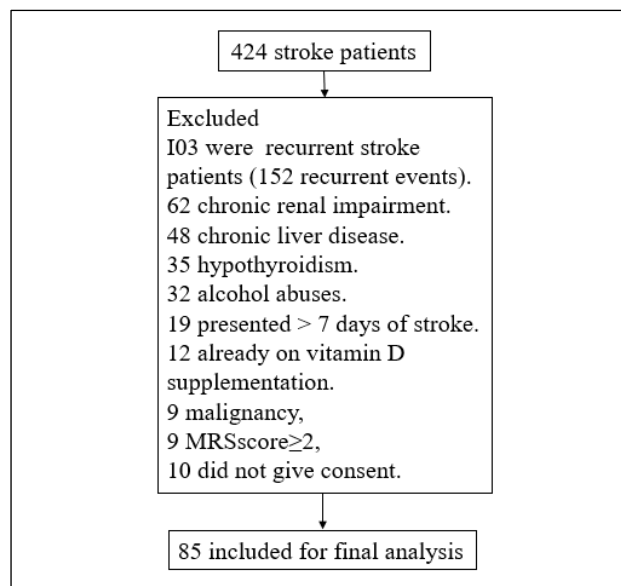


Figure 1: The inclusion and exclusion path for the stroke patients.

Data collection

Patient information was documented in the proforma including presenting complaints, present, past medical, personal and family history with details of duration of disease. All patients underwent a detailed physical and neurological examination.

NIH stroke scale at admission was recorded for every case. All cases will undergo diagnostic radiological investigations namely CT scan of brain and if required MRI brain, CT angiography. The stroke was classified according to the TOAST criteria. All patients underwent routine blood investigations including complete blood count, blood sugars, liver and renal function tests, lipid profile, urine examination, chest X-ray, ECG, 2D echo, carotid Doppler, thrombophilic profile on need to do basis.

Serum 25-hydroxyvitamin D (25OHD) levels estimation was performed for all the participants using the “DiaSorin 25-OH-D assay Radio Immunoassay (RIA)” kit in the RIA lab of the Department of Nuclear Medicine of the hospital as per the instructions in the manual provided with the kit. The length of time between stroke onset and 25(OH) D sampling in the cases was documented. Blood pressure was recorded by mercury sphygmomanometer and hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or use of antihypertensive therapy. Diabetes mellitus was diagnosed fasting blood sugar ≥126 mg% or HbA1c ≥6.5% or there was use of insulin or oral hypoglycemic agents. Criteria for diagnosing dyslipidemia was either of serum triglycerides >150 mg/dl or high-density lipoprotein cholesterol HDL <40 mg/dl in males and <50 mg/dl females or low-density lipoprotein cholesterol LDL >100 mg/dl.

Statistical analysis

Statistical analyses were performed using the SPSS version 17.0 program for Windows (SPSS Inc., Chicago, IL, USA). Authors conducted a Shaipro Wilk test to verify the distribution of the data.

All data were summarized as the mean±SD, while those with a skewed distribution were described as a median (IQR). The chi-square test was used to compare the differences in variables between the two groups. Student’s t-test was used for continuous, normal variables. The Mann-Whitney test was used to test independent relationships between the variables that did not demonstrate normality. A two-sided P value less than 0.05 was considered statistically significant.

RESULTS

The total number of cases and controls were 85 and 76 respectively. The mean age was 61.02±11.58 years and 58.63±11.28 years in cases and controls respectively. Females constituted 37.6% of the total number of cases and 43.4% of the controls. The age and gender-distribution were comparable between the cases and controls (Table 1). The mean body mass index (BMI) was 27.74±1.72 kg/m² in cases and 26.36±3.66 kg/m² in controls (Table 1).

A statistically significant difference was observed between the two with cases having a higher BMI than the controls (p=0.003). The most common risk factor was hypertension that was seen in 82.4% of the cases,

followed by dyslipidemia (63.5%), diabetes mellitus (48.2%), ischemic heart disease (16.5%), left ventricular systolic dysfunction (9.4%) and arrhythmia (8.2%) in that order. Among controls, 20% had hypertension and 14% had diabetes. The percentage of smokers in cases and controls was 30 % and 14% respectively.

The median value of serum 25(OH) vitamin D level was 7.94 ng/mL in the cases with an IQR of 4.59-14.00 ng/mL and it was 8.82 ng/ml in the controls with an IQR of 5.59-14.70 ng/ml (Table 2).

Table 1: Comparison of age, gender distribution, BMI, percentage having hypertensive, percentage having diabetes among cases and controls.

Parameter	Cases (N=85)	Controls (N=76)	P-value
Age (years)	61.02±11.58	58.63±11.28	0.187
Male	53 (62.4%)	43 (56.6%)	0.456
Female	32 (37.6%)	33 (43.4%)	
BMI (kg/m ²)	27.74±1.72	26.36±3.66	0.003
Hypertension	70 (82.4%)	25(32%)	<0.0001
Diabetes	41 (48.2%)	15 (20%)	<0.001
Smokers	25 (30%)	11 (14%)	<0.05

The difference between the serum 25(OH) vitamin D levels of the two groups was not found to be statistically significant. On doing sub group analysis, there was no statistical difference between the vitamin D level in the age-group of 40-65 years or in the age group of >65 years (Table 2).

Table 2: Comparison of serum 25(OH) vitamin D levels between cases and controls. age-group wise in first two rows and all subjects in the lowest row.

25(OH) vitamin D levels (ng/ml)							
Age	Cases			Controls			P-value
	Number	Median	IQR	Number	Median	IQR	
40-65 years	56	8.02	4.60-14.05	53	9.1	5.84-15.49	0.195
>65 years	29	7.94	4.58-17.31	23	7.46	4.88-14.62	0.934
All subjects	85	7.94	4.59-14.00	76	8.82	5.59-14.70	0.267

Table 3: Comparison of 25(OH) vitamin d levels between ischaemic and haemorrhagic stroke subtypes.

25(OH) Vitamin D Levels (ng/mL)	Ischaemic (n=76)		Haemorrhagic (n=9)		p-value
	Median	IQR	Median	IQR	
	8.17	4.63-13.75	5.8	4.17-22.03	0.774

The median value (IQR) of serum 25(OH) vitamin D level in the ischemic stroke subtype (n=76) was 8.17 ng/mL (4.63-13.75 ng/mL) and it was 5.8 ng/mL (4.17-22.03 ng/mL) in the hemorrhagic stroke subtype (n=9) shown in Table 3. The difference between the serum

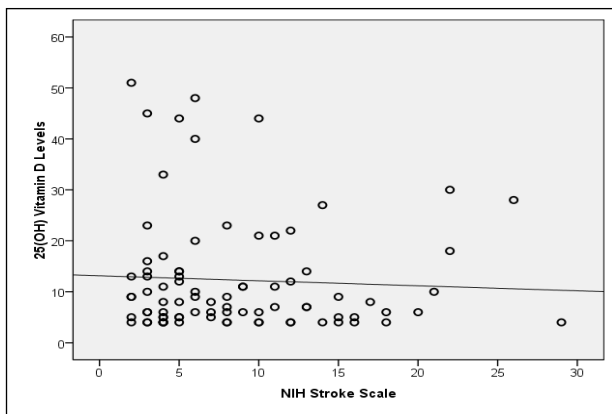
25(OH) vitamin D levels of the two groups was not found to be statistically significant (p=0.774) according the NIH stroke scale at admission. After applying the NIH stroke scale among the 85 cases of first ever stroke, the median NIH stroke scale was 7 with IQR of 4-12.

Minor stroke was seen in 31.77% of the cases, moderate in 55.29%, moderate to severe in 7.06% and severe stroke in 5.88% of cases. The serum 25(OH) D levels were

inversely related to the NIH stroke scale, however, the correlation between the two was not statistically significant ($p = 0.618$) as shown in the Figure 2.

Table 4: Distribution of TOAST subclass among ischemic stroke patients and comparison of 25(OH) vitamin D levels among these TOAST subclasses.

TOAST class	Cases (n=76)				p-value
	N	Percent	Median	IQR	
Large-artery atherosclerosis (embolus/thrombosis) (L)	50	65.78	7.59	4.29-12.13	0.370
Cardio-embolism (high-risk/medium-risk) (C)	3	3.95	5.87	4.62-12.80	
Small-vessel occlusion (lacune) (S)	8	10.53	15.11	6.19-22.68	
Stroke of other determined etiology (O)	0	0	-	-	
Stroke of undetermined etiology (U)	15	19.74	10.7	4.73-14.31	



R=-0.055; N=85; P=0.618.

Figure 2: Correlation between NIH strokes scale and 25(OH) vitamin D levels.

Among the 76 cases of ischemic stroke, the most common TOAST class was large-artery atherosclerosis (65.78%), followed by stroke of undetermined etiology (19.74%), small-vessel occlusion (10.53%), and cardio-embolism (3.95%) as shown in Table 4. None had stroke of other determined etiology.

DISCUSSION

This study intended to look at the serum 25(OH) D in acute stroke, which is a relatively novel field of interest as more and more data is coming up to look into a role of vitamin D deficiency in stroke. In present study, the mean age, sex ratio of cases and controls is comparable similar studies, from India.^{8,9} Indian collaborative acute stroke study (ICASS) also showed similar age demographics in Indian stroke patients.¹³ The cases and controls differed with respect to body mass index (BMI). Cases had a statistically significant higher BMI than the controls ($p = 0.003$). BMI, though not a criterion for metabolic syndrome, is a marker of obesity, which is considered to

be an important risk factor for cardiovascular disease CVD. Similarly, hypertension, diabetes, smoking was seen more in cases.

The most common risk factor observed in present study was hypertension, seen in 82.4 percent of the cases, followed by dyslipidemia (63.5%), diabetes mellitus (48.2%), ischemic heart disease (16.5%), left ventricular systolic dysfunction (9.4%), and arrhythmia (8.2%) in that order. This study was conducted at a tertiary care centre in Northern India and included both ischemic as well as hemorrhagic strokes. Out of the total of 85 majority were ischemic (89.4%) that corroborates with the usual trend.¹⁴ ICASS, reported a lower proportion of ischemic strokes (77%) than present study.¹³ Poole et al, also included both the varieties of stroke and the proportion of hemorrhagic strokes in their study was higher (18.18%) than present study.⁵ The difference in the proportions may be explained by the institutional referral bias.

According the NIH stroke scale at admission, among the total of 85 cases of first ever acute stroke, the median NIH stroke scale was 7 with an IQR of 4-12. Using the inter-conversion of the NIH Stroke Scale and Scandinavian Stroke Scale in acute stroke as developed and validated by Gray et al, the cases had much less median NIH stroke scale as compared to the Poole KE et al.^{5,15}

Majority of the cases had a moderate (55.29%) or a minor stroke (31.77%) at admission according to the NIH stroke scale. Authors did see severe stroke in 5.88 percent of cases and moderate to severe in 7.06 percent. This may be then explained by the fact that majority of the cases of severe stroke had one or the other exclusion criterion especially the co-morbidities, or they had suffered a recurrent stroke.

Among our 76 cases of ischemic stroke, the most common TOAST class was large-artery atherosclerosis (65.78%), followed by stroke of undetermined etiology (19.74%), small-vessel occlusion (10.53%) and cardioembolic (3.95%). Present findings are consistent with Kaul et al with large artery stroke being the most common TOAST class followed by stroke of undetermined etiology.¹⁶

Authors found no association between vitamin D deficiency and the stroke risk. Though in the present study, the median value of serum 25(OH) vitamin D level was lower in the cases (n =85) suffering with first ever acute stroke than the controls (n =76) (7.94 ng/mL (IQR= 4.59-14.00 ng/mL) as compared to cases 8.82 ng/mL (IQR = 5.59-14.70 ng/mL)). However, the difference between the serum 25(OH) vitamin D levels of the two groups did not reach statistical significance (p=0.267). These observations are not consistent with those of Poole et al, who although had a similar type of study population, found reduced vitamin D in the majority of patients with acute stroke throughout the year and they suggested that this might have preceded the stroke.⁵ Considering that the in-vivo half-life of 25(OH) D as 3 weeks, present study used more stringent criteria for inclusion of acute stroke patients, and sampling was done within one week of symptom onset. In contrast in study done by Poole et al the sampling was done within 30 days of stroke, mean (IQR) day of sampling from onset of stroke was 14.4 (10.0-22.8), together with the inclusion criteria of hemiplegia involving lower limb and inability to walk after one week of stroke the cohort of stroke patients in study done by Poole KE et al, was at risk of having vitamin deficiency at the time of sampling.⁵ Present study also does not support the findings of a recently published population-based study by Brondum-Jacobsen et al, and Kojima G et al, that demonstrated increased risk of ischemic stroke with decreasing serum 25(OH) D concentrations, which they substantiated with an accompanying meta-analysis.^{3,17} However, it is noteworthy that although Kojima and Brondum-Jacobsen et al, adjusted for low physical activity, smoking, and obesity etc. in their multivariate adjusted cox regression model regarding reverse causation/confounding; it is well known from epidemiological studies that low 25(OH) D concentrations are seen in such individuals and these are also risk factors for ischemic stroke, low 25(OH) D concentrations may merely be a proxy for these risk factor.^{3,17} Also, the results of this study and meta-analysis were not reproduced in a more recent large population study by Skaaby T et al, that found no association between vitamin D status and incidence of stroke.⁴ Moreover, it has been observed that models treating vitamin D as continuous variable as in present study suggested no significant associations.¹⁸ Another cross-sectional analysis data from Nhanes III showed an association between 25(OH) D deficiency with prevalent cardiovascular disease (CVD). But the outcome was based on self-report. No information about the date of

onset CVD or any subsequent life style changes, which could have occurred long before the patients' participation in the study.⁷ In a study on Vitamin D status, hypertension and ischemic stroke Majumdar V et al, found that high blood pressure partly explains the association between low 25(OH)D levels and ischemic stroke.¹⁹ They found that a pronounced association between low 25(OH)D and risk of ischemic stroke in hypertensives, OR=13.54, 95% CI=1.94-94.43 as compared with no association in non-hypertensives.

Similarly, in a German study by Kühn T et al, no clear linear inverse relationships between 25(OH)D and stroke/myocardial infarction risk was detected.²⁰ Further there was attenuation of the associations between 25(OH)D and stroke/myocardial infarction risks by adjustment for classical cardiovascular risk factors in their study. This supports the notion that 25(OH)D is not an independent causal factor in cardiovascular etiology. They could not show associations between genetic vitamin D status determinants (single nucleotide polymorphisms SNPs) and cardiovascular disease risks and therefore led to the conclusion that low vitamin D levels and cardiovascular disease risk may be due to uncontrolled confounding or reverse causation.

In present study, a similar trend of statistical insignificant difference in serum 25(OH) D levels was seen with age-wise subgroup analysis, where no statistically significant difference was observed for both 40-65 years and >65 years age-group.

Furthermore, no statistically significant difference was found for the serum 25 (OH) D levels between the ischemic and the hemorrhagic stroke subtype; among the various stroke subgroups as per the NIH stroke scale at admission; and among the various TOAST ischemic stroke classes.

Also, no statistically significant correlation existed between the NIH stroke scales as a continuous variable, the TOAST ischemic stroke class. There was no correlation between the day of sampling from the onset of complaints and the serum 25(OH) vitamin D levels. Likewise, no correlation was found by Poole et al, in 25OHD level and the length of time between stroke and 25OHD.

CONCLUSION

There is a high prevalence of biochemical hypovitaminosis D in apparently healthy Indians of all age and sex groups despite adequate sunshine. There is no association between low vitamin d levels and stroke.

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