

ASSOCIATION BETWEEN VITAMIN D AND STROKE: A CASE- CONTROL STUDY

Dr. Chandan Sharma¹ and Dr. Ashima Badyal^{2*}¹Physician, Department of Medicine, GMC Jammu.^{2*}Department of Biochemistry, GMC Jammu.

*Corresponding Author: Dr. Ashima Badyal

Department of Biochemistry, GMC Jammu.

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ABSTRACT

Background: Globally every second person has a poor vitamin D status, which a public health problem of real concern. Reduced plasma 25(OH) D concentrations as a diagnostic marker of vitamin D deficiency have been associated with risk factors for ischemic stroke. The aim of this study was to compare serum 25- hydroxyvitamin D (25(OH) D) levels in acute stroke patients and healthy subjects. **Method:** A Case-Control Study was conducted in the Department of Medicine, GMC Jammu, during a period of one year, on 70 patients with stroke incidence and 70 age and gender matched healthy controls. **Results:** The mean age was 60.55 ± 12.46 years and 60.37 ± 12.02 years in cases and controls respectively. A statistically significant difference was observed in the mean body mass index (BMI), between cases and controls. The most common risk factor was found to be hypertension with 81.43% of cases. The median value of serum 25(OH) Vitamin D level was 9.06 ng/mL in the cases and 10.89 ng/mL in controls. The difference between the serum 25(OH) vitamin D levels of the two groups, even in sub group analysis, was not statistically significant; however, patients more than 65 years of age showed the lowest levels of 25(OH) Vitamin D amongst all with a median value of 8.03 ng/mL and IQR of 4.45-16.16 ng/mL. **Conclusion:** No significant association was found between low Vitamin D levels and cases of ischemic or haemorrhagic stroke, but the beneficial effects of Vitamin D supplementation can't be ignored.

KEYWORDS: Vitamin D, 25(OH)D, ischemic stroke, haemorrhagic stroke.

INTRODUCTION

Globally every second person has a poor vitamin D status, which a public health problem of real concern. Reduced plasma 25(OH) D concentrations as a diagnostic marker of vitamin D deficiency have been associated with risk factors for ischemic stroke, such as arterial hypertension, thrombosis, atherosclerosis, and inflammation.^[1] Poor vitamin D status may be associated with adverse health outcomes of post- stroke patients.^[2] Vitamin D may play a role in neuroprotection, perhaps through detoxification pathways, inhibition of inducible nitric oxide synthase, neuronal calcium regulation antioxidant or anti-inflammatory mechanisms or enhanced nerve conduction.^[3]

This study was conducted with the primary intention to compare serum 25(OH) D levels in first ever acute stroke patients and healthy subjects. Such a study has never been conducted in geographical location defined by Jammu region. Therefore, the aim of this study was to compare serum 25- hydroxyvitamin D (25(OH) D) levels in acute stroke patients and healthy subjects.

METHODS

An observational Case-Control Study was conducted in the Department of Medicine, GMC Jammu, during a

period of one year. Simple Random Sampling technique was used to select cases and controls. 70 patients with stroke incidence and 70 age and gender matched healthy controls were selected for the study. Considering the incidence of vitamin D insufficiency at 40% in general population of India, as documented by Ramakrishnan S et al,^[4] and assuming >75% stroke patients to be Vitamin D deficient, the sample size was calculated to be 70 each for cases and controls; with margin of error at 5% and power of study at 90%.

Inclusion criteria

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

Exclusion criteria

- Patients with previous hip fracture, bone disease, steroid treatment, vitamin D/calcium supplementation and renal or liver impairment, hypothyroidism,

malignancy, alcohol abuse.

NIH stroke scale at admission was recorded for every case. The stroke was classified according to the TOAST criteria. All patients underwent routine blood investigations including complete blood count, blood sugars, liver function tests, renal function tests, lipid profile, urine examination, chest X-ray, ECG, 2D echo, carotid Doppler and thrombophilic profile. Serum 25-hydroxyvitamin D (25OHD) levels estimation was performed on Siemens Kit in the department of Biochemistry, GMC Jammu. The length of time between stroke onset and 25(OH) D sampling in the cases was documented. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Diabetes mellitus was diagnosed fasting blood sugar ≥ 126 mg% or HbA1c $\geq 6.5\%$. Dyslipidemia was defined by either serum triglycerides >150 mg/dl or high-density lipoprotein, HDL <40 mg/dl in males or low-density lipoprotein, LDL >100 mg/dl.

Ethical approval was obtained from Institutional Ethical

Committee, and written informed consent was obtained from all the study participants. Statistical analyses were performed using Microsoft Excel 2010 software. All data were summarized as the mean \pm SD. The chi-square test was used to compare the differences in variables between the two groups, and p value <0.05 was considered significant.

RESULTS

The mean age was 60.55 ± 12.46 years and 60.37 ± 12.02 years in cases and controls respectively. The age and gender- distribution were comparable with females constituting 38.57% of the total number of cases and 34.29% of the controls. A statistically significant difference was observed in the mean body mass index (BMI), which was 28.01 ± 1.88 kg/m² in cases and 25.53 ± 2.52 kg/m² in controls. The most common risk factor was found to be hypertension with 81.43% of cases being hypertensive as against only 30% among controls. The percentage of smokers in cases and controls was 28.57% and 12.86% respectively. (Table 1).

Table 1: Comparison of characteristics among cases and controls.

Parameter	Cases (N=70)	Controls (N=70)	P-value
Age (years)	60.55 ± 12.46	60.37 ± 12.02	0.224
Male	43 (61.43%)	46 (65.71%)	0.525
Female	27 (38.57%)	24 (34.29%)	
BMI (kg/m ²)	28.01 ± 1.88	25.53 ± 2.52	0.010*
Hypertension	57 (81.43%)	21 (30.00%)	$<0.001^*$
Diabetes	33 (47.14%)	11 (15.71%)	$<0.001^*$
Smokers	20 (28.57%)	9 (12.86%)	$<0.05^*$

The median value of serum 25(OH) Vitamin D level was 9.06 ng/mL in the cases and 10.89 ng/mL among controls. The difference between the serum 25(OH) vitamin D levels of the two groups, even in sub group

analysis, was not statistically significant; however, aged patients showed the lowest levels of 25(OH) Vitamin D amongst all with a median value of 8.03 ng/mL and IQR of 4.45-16.16 ng/mL.(Table 2)

Table 2: Serum 25(OH) vitamin D levels (ng/mL) among cases and controls.

Age Group	Cases		Controls		P-value
	N	Median (IQR)	N	Median (IQR)	
40-65 years	46	9.37 (6.33-19.24)	49	11.44 (6.88-20.95)	0.405
>65 years	24	8.03 (4.45-16.16)	21	9.71 (5.86-19.72)	0.440
All above 40	70	9.06 (5.08-18.63)	70	10.89 (6.43-19.57)	0.198

The difference between the serum 25(OH) vitamin D levels of Ischaemic Stroke patients and Haemorrhagic Stroke patients was not found to be statistically

significant (p=0.208) according to the NIH stroke scale at admission. (Table 3)

Table 3: Serum 25(OH) Vitamin D levels in ischaemic and haemorrhagic stroke patients.

	Ischaemic (n=55)	Haemorrhagic (n=15)	P-value
	Median (IQR)	Median (IQR)	
25(OH) Vitamin D (ng/mL)	9.17 (5.08-16.05)	7.1 (4.45-16.16)	0.208

DISCUSSION

This study intended to look at the serum 25(OH) D in acute stroke, which could be field of interest as more and more data is coming up to look into various aspects of deficiency of vitamin D. In present study, cases had a

statistically significant higher BMI than the controls (p = 0.01). BMI is a marker of obesity, which is considered to be an important risk factor for cardiovascular disease CVD. The most common risk factor, however was hypertension, seen in 81.43% of the cases, 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 (78.57%) which is similar to the value found by Feigin *et al*^[5] and even ICASS, reported a similar proportion of ischemic strokes (77%).^[6]

The present study found no statistically significant association between Vitamin D deficiency and the stroke risk, but a consistently lower median values of serum 25(OH) vitamin D level were found in cases in each subgroup (40-65 year and >65 years) when compared to the corresponding values among controls. Poole *et al*^[7] had found similar, but statistically significant association between the two. This could be attributed to the more stringent criteria adopted in the present study, where sampling was done within one week of symptom onset. 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.^[8]

In a study by Majumdar *V et al*, on Vitamin D status, hypertension and ischemic stroke, found that high blood pressure partly explained the association between low 25(OH)D levels and ischemic stroke.^[9] They found that a pronounced association between low 25(OH)D and risk of ischemic stroke in hypertensives, which was quite near to the observations made in our study.

25(OH)D is thus not found to be an independent causal factor in cardiovascular etiology, but, low vitamin D levels and cardiovascular disease risk may be due to uncontrolled confounding or reverse causation. Pilz *et al*^[10] and Witham *et. al*,^[11] have suggested that 25(OH)D can cross blood brain barrier, suggesting that Vitamin D receptors activation may exert some neuro-protective effects beneficial to stroke patients. Besides, studies have shown that high dose of oral Vitamin D supplementation produced short-term improvement in endothelial function in stroke patients.

Elderly persons with a low intake of Vitamin D and low serum concentration of 1, 25(OH)2D were at higher risk of future strokes. In present study, a similar trend is observed when compared, with serum 25(OH) D levels and seen lower in higher age subgroup, while no statistically significant difference was observed for both 40-65 years and >65 years age-group.

CONCLUSION

However, there was no statistical significant association between low levels of vitamin D levels and stroke, but consequent to the high prevalence of Vitamin D deficiency among Indian population, hypertensive patients may be at a higher risks leading to stroke. Further research on effects of Vitamin D supplementation to stroke patients may reveal important findings.

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