



## Association between Vitamin- D Deficiency and Stroke - A Comparative Study

Author

**Dr Kumar Jee Kaul MD**

General Medicine, Junior Resident Department of General Medicine, KIMS Hospital

Add- Kempegowda Institute of Medical Sciences, K.R Road, V.V. Puram Bangalore-560004 Karnataka  
India

Contact No: +919731914489, Email: [kumarkaul388@gmail.com](mailto:kumarkaul388@gmail.com)

### Abstract

**Objective:** To determine the serum levels of 25-OH Vitamin-D in both ischemic as well as hemorrhagic stroke patients and to determine the magnitude of Vitamin-D deficiency in the study group. To compare Vitamin-D deficiency in the control group with the study group.

**Materials and Methods:** 100 adults above 18 yrs, fulfilling the inclusion and exclusion criteria were admitted in KIMS Hospital Bangalore between December 2014 to June 2016 and serum levels of 25-OH Vitamin-D in both ischemic as well as hemorrhagic stroke patients were compared.

**Results:** Statistically significant ( $p < 0.05$ ) values were obtained for low serum vitamin D levels and risk of both ischemic and hemorrhagic stroke, 57.60% and 52.90% respectively.

**Conclusion** This study shows that a single serum measurement of vitamin D could be a useful marker in predicting future outcomes in respect to stroke. So early identification and correction of vitamin D deficiency can be an important tool to reduce the incidence of Stroke.

**Keywords** - Vitamin D, Ischemic Stroke, Hemorrhagic Stroke.

### Introduction

Vitamin D is a fat soluble vitamin. It is a steroid hormone that is essential for calcium and phosphate metabolism. It is naturally present in very few foods. It is produced endogenously by ultraviolet light which strikes the skin and gives vitamin D thus making it unique among all vitamins<sup>(1)</sup>. This combined with its ability to act on specific target tissues and receptors makes its classification as a steroid hormone more appropriate.

Stroke is a sudden onset of focal neurological deficit, a major cause of morbidity and mortality

and the second leading cause of death worldwide<sup>(2)</sup>. Stroke has a heterogeneous etiology, caused by modifiable and un-modifiable risk factors.

Recent studies have strongly suggested an association of deficiency of 25-hydroxyvitamin D with ischemic stroke<sup>(3,4)</sup> and cardiovascular disease<sup>(5,6)</sup>. Most common forms of Vitamin D in humans are vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol)<sup>(3)</sup>.

Vitamin D is essential for the human body to maintain a balance between calcium and phosphorus. Inadequate vitamin D can cause weakness, reduced bone mineralization, increased

bone loss and hip fracture<sup>(7)</sup> and its prevalence is high in both hemispheric populations<sup>(8)</sup>. Serum 25-hydroxyvitamin D is the circulating form of vitamin D with a half life of 2 to 3 weeks and is converted to the active form -1,25-dihydroxy vitamin D<sub>3</sub> in the kidneys<sup>(9)</sup>. 25-hydroxyvitamin D is a marker of vitamin D status in the human body<sup>(10,11)</sup>. Some population based studies have shown that 40% - 45% of Indians have 25-hydroxyvitamin D deficiency in India<sup>(12)</sup>. The study aim to investigate the association between serum 25-hydroxyvitamin D deficiency in ischemic as well as hemorrhagic stroke patients.

### Vitamin D and Role in CNS

Several vitamin D metabolites are present in the CNS especially in substantia nigra and hypothalamus. Examples of these metabolites include 23 OH vitamin D<sub>3</sub>, 1, 25 Di OH D<sub>3</sub>; 24, 25 Di OH D<sub>3</sub>. It is suggested that vitamin D is a substrate for the synthesis of these substances at the above sites. Vitamin D receptors in the brain are found in cerebellum basal ganglia and hippocampus<sup>(15)</sup>. Substantia nigra has the highest density of vitamin D receptors

### Materials and Methods

Patients fulfilling the inclusion and exclusion criteria admitted in KIMS Hospital Bangalore between December 2014 to June 2016 were taken up for the study.

#### Inclusion criteria

Patients willing to participate in the study and diagnosed to have ischemic or hemorrhagic stroke based on clinical history, physical examination and CT/MRI imaging.

Both sexes above 18yrs of age diagnosed to have ischemic or hemorrhagic stroke.

#### Exclusion criteria

Significant renal or hepatic dysfunction defined as serum creatinine of >2.5mg/dl or aspartate aminotransferase >2.5 times normal. Malabsorption including history of inflammatory bowel disease or small bowel or gastric surgery.

Diseases associated with altered bone metabolism (hyperthyroidism) and patients already on vitamin D supplements.

The diagnosis of stroke was established based on clinical history, physical examination and CT/MRI imaging. • Early morning blood sample was collected after an overnight fast. Blood samples was collected via venipuncture. Serum 25(OH)D level was measured using DiaSorin LIAISON 25(OH)D TOTAL CLIA. The LIAISON 25(OH) Vitamin D TOTAL Assay is a direct competitive chemiluminescence immunoassay for human serum or plasma intended for use on the DiaSorin LIAISON automated analyzer. The assay uses magnetic particles (solid phase) coated with antibody against 25(OH) D and 25(OH)D conjugated to an isoluminol derivative (tracer). During the first incubation phase (10 min), 25(OH)D is dissociated from binding protein by buffer containing 10% ethanol and then binds to the anti-25(OH)D antibody on the solid phase. After a second 10 min incubation with the tracer, the unbound material is washed off and starter reagents are added to generate a flash chemiluminescent signal which is concentration levels following an overnite fast using DiaSorin LIAISON 25(OH)D TOTAL CLIA: Normal /sufficient levels of vitaminD -  $\geq 30$ ng/m Relative insufficient levels of vitaminD - 21-29ng/ml Deficient levels of vitamin d -  $< 20$ ng/ml.

### Methods of Statistical Analysis

Data tabulation and analysis using tests such as unpaired t test for the parametric data and chi square test and Mann Whitney U test for non parametric data, along with other statistical tests will be applied based on the need, based on these to draw appropriate conclusions and graph recommendation merited.

### Results

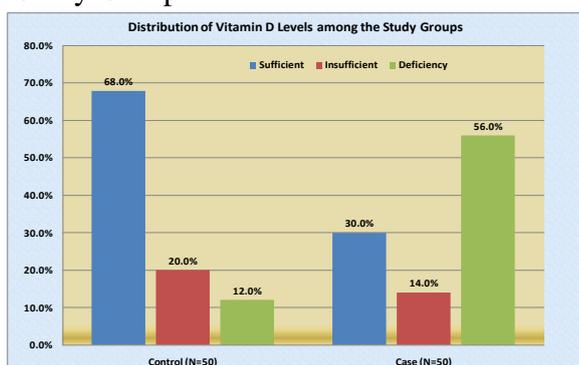
This study included 100 patients , of which 50 cases were stroke cases (ischemic and

hemorrhagic) and 50 were controls, admitted in Department of General Medicine, Kempegowda Institute of Medical Sciences, Bangalore between December 2014 to June 2016.

The mean age of controls was 61.5 years and that of cases was 63.8 years. The number of males and females in the control group was 30 and 20 respectively, whereas in the case group there were 28 males and 22 females. Among the controls and cases, the prevalence of vitamin D deficiency among stroke patients (cases) was 56% while 14% patients were found to have insufficient levels of vitamin D and 30% were found to have sufficient vitamin D levels. Vitamin D deficiency among controls was 12% while 20% controls were found to have insufficient levels of vitamin D and 68% were found to have sufficient levels of vitamin D. The prevalence of vitamin D deficiency in ischemic stroke was 57.60% as compared to hemorrhagic stroke where it was 52.90%.

The prevalence of vitamin D deficiency in our study was found to be statistically significant in stroke patients ( $p < 0.001$ ) vs the controls with an chi square value of 12.960. This corroborates the fact that vitamin D deficiency is an independent risk factor for both ischemic as well as hemorrhagic stroke.

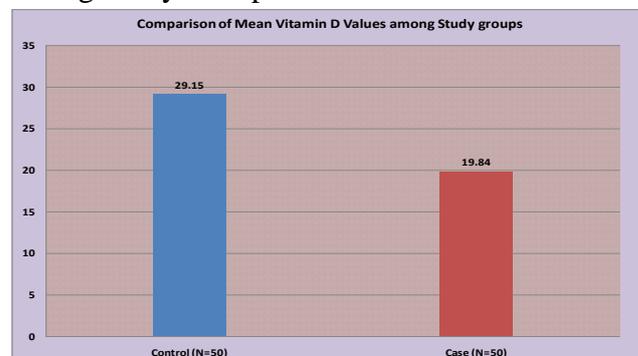
**Graph 1** Distribution of Vitamin D Levels among the Study Group



This Graph shows distribution of vitamin D levels among the study groups. In the controls group, 68% had vitamin D sufficient levels, 20% had vitamin D insufficient levels and 12% had vitamin D deficiency.

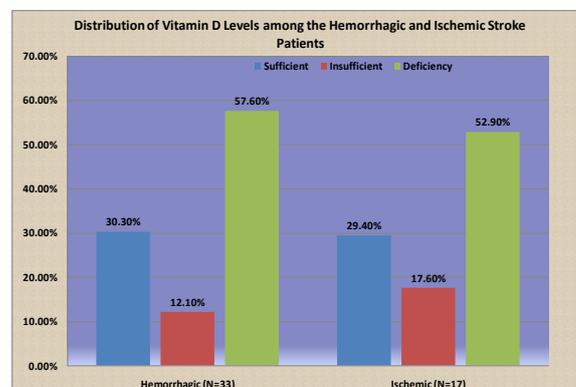
In case group, 30% had vitamin D sufficient levels, 14% had vitamin D insufficient levels and 56% had vitamin D deficiency.

**Graph 2-** Comparison of Mean Vitamin D Values among Study Group



This graph compares mean vitamin D value among control group and case group. In control group, mean vitamin D value was 29.15ng/ml and in case group mean vitamin D value was 19.84ng/ml.

**Graph 3-** Distribution of Vitamin D Levels among Hemorrhagic and Ischemic Stroke Patients.



In this graph, out of 33 ischemic stroke cases, 30.30% patients had vitamin D sufficient levels, 12.10% patients had vitamin D insufficient levels and 57.60% patients had vitamin D deficiency. Out of 17 hemorrhagic stroke cases, 29.40% patients had vitamin D sufficient levels, 17.60% patients had vitamin D insufficient levels and 52.90% patients had vitamin D deficiency.

## Discussion

The present study included 100 patients, of which 50 cases were stroke cases (ischemic or hemorrhagic) and 50 were controls. The mean age of controls was 61.5 years and that of cases was 63.8 years. There was male preponderance in both controls (60%) and cases (56%). Among the controls and cases, the prevalence of vitamin D deficiency among stroke patients was 56% while 14% patients were found to have insufficient levels of vitamin D. The prevalence of vitamin D deficiency in ischemic stroke was 57.60% as compared to hemorrhagic stroke where it was 52.90%.

The prevalence of vitamin D deficiency in our study was found to be statistically significant in stroke patients ( $p < 0.001$ ) vs the controls with an chi square value of 12.960. This corroborates the fact that vitamin D deficiency is an independent risk factor for both ischemic as well as hemorrhagic stroke. Our results are in tune with other studies which have been conducted in India as well as other parts of the world.

A similar study was conducted by Jaydeep Ray Choudhary et al (2014) on Indian patients attending the department of Neurology at Yashoda hospital Hyderabad. Out of 250 stroke patients, 190 (76%) were men and mean age was  $58.4 \pm 11.1$  years (age range-26-89 years). 25-hydroxyvitamin D deficiency was observed in 122 (48.8%) stroke patients and 79 (31.6%) controls ( $P = 0.001$ ). Among stroke patients, serum 25-hydroxyvitamin D deficiency was found in 54.9% (50/91) of patients with large artery atherosclerosis, 54% (20/37) in cardio-embolic stroke, 44.4% (20/45) in small artery diseases, 42.8% (15/35) in stroke of other determined etiology and 40.4% (17/42) in stroke of un-determined aetiology. Multiple logistic regression analysis showed an independent association of 25-hydroxyvitamin D deficiency with ischemic stroke (odds ratio: 1.6; 95% CI 1.2-2.8). The association was strongest with large artery atherosclerosis (odds ratio: 2.4; 95% CI 1.6-3.5) and cardioembolic stroke (odds ratio: 2.0; 95% CI 1.0-3.2). They found that 25-

hydroxyvitamin D deficiency had an independent association with ischemic stroke. Though our results are further supported by the a forementioned studies, the prevalence of vitamin D deficiency in our study was more in case of haemorrhagic stroke (57.60% vs 42.8% in the above study)<sup>(13)</sup>.

In a study conducted by An Pan et al. (2012) entitled 25-hydroxyvitamin D levels and risk of stroke: A prospective study and meta-analysis. The study measured 25(OH)D levels among 464 women who developed ischemic stroke and an equal number of controls who were free of stroke through 2006 in the Nurses' Health Study (NHS). The study searched MEDLINE and EMBASE for articles published through March 2011 that prospectively evaluated 25(OH)D levels in relation to stroke. After multivariable adjustment for lifestyle and dietary covariates, lower 25(OH)D levels were associated with an elevated risk of ischemic stroke in the NHS: the odds ratio (95% CI) comparing women in the lowest vs. highest tertiles was 1.49 (1.01, 2.18;  $P_{trend} = 0.04$ ). We found 6 other prospective studies that examined 25 (OH)D in relation to stroke outcomes. After pooling our results with these prospective studies that included 1,214 stroke cases in total, low 25(OH)D levels were associated with increased risk of developing stroke outcomes in comparison to high levels: the pooled relative risk (95% CI) was 1.52 (1.20, 1.85;  $I^2 = 0.0\%$ ,  $P_{heterogeneity} = 0.63$ ). In two studies that explicitly examined ischemic stroke, this association was 1.59 (1.07, 2.12;  $I^2 = 0.0\%$ ,  $P_{heterogeneity} = 0.80$ ).

In this study these data provide evidence that low vitamin D levels are modestly associated with risk of stroke. Maintaining adequate vitamin D status may lower risk of stroke in women<sup>(14)</sup>.

## Conclusion

It was found that there was a significant association between low serum vitamin D levels and risk of both ischemic as well as hemorrhagic stroke. The prevalence of vitamin D deficiency in

ischemic stroke was 57.60% as compared to hemorrhagic stroke where it was 52.90%.

In control group, mean vitamin d value was 29.15ng/ml and in case group mean vitamin d value was 19.84ng/ml. A single serum measurement of vitamin D could be a useful marker in predicting future outcomes in respect to stroke. So early identification and correction of vitamin D deficiency can be an important tool to reduce the incidence of Stroke.

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