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SERUM VITAMIN D3 (CHOLECALCIFEROL) LEVEL AND ITS CORRELATION WITH ACUTE ISCHEMIC STROKE: A HOSPITAL BASED CROSS-SECTIONAL STUDY

Internal Medicine

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KEYWORDS

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INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide, posing a significant challenge to public health systems, especially in low- and middle-income countries (LMICs). The World Health Organization (WHO) defines stroke as the rapid onset of focal or global neurological dysfunction resulting from a disturbance in cerebral blood supply that persists for more than 24 hours or leads to death, with no apparent cause other than vascular origin(1). Stroke is commonly referred to as a cerebrovascular accident (CVA) and constitutes a major non-communicable disease (NCD) burden, ranking as the second leading cause of death and the third leading cause of disability globally.(2) It is also one of the major contributors to long-term complications such as dementia and depression, creating both direct and indirect socioeconomic consequences. The scale of the problem is enormous. Annually, approximately 15 million people worldwide experience a stroke, of whom about 5 million die and another 5 million live with permanent disabilities that severely compromise their independence and productivity This makes stroke not only a neurological condition but also a global socioeconomic challenge affecting patients, caregivers, and national health systems alike. Importantly, while stroke is often considered a disease of the elderly, cases in younger adults—particularly in LMICs—are not uncommon, and the risk factors in these populations may differ significantly from those in high-income countries(2).

Epidemiological Trends

The global burden of stroke has seen a striking increase over the past three decades. Between 1990 and 2019, the absolute number of stroke cases rose dramatically: incident strokes increased by 70%, deaths due to stroke rose by 43%, prevalence more than doubled (102%), and disability-adjusted life years (DALYs) lost increased by 143%. These figures highlight that, despite advances in medical technology and acute care, stroke prevention remains suboptimal. The burden is disproportionately higher in LMICs, where almost 86% of stroke deaths and 89% of DALYs lost occur(2). This is largely attributed to limited healthcare infrastructure, inadequate primary prevention, poor control of hypertension and diabetes, delayed recognition of symptoms, and insufficient access to acute care services. Countries such as India are witnessing a rapid epidemiological transition, with stroke incidence rising as a result of urbanization, lifestyle changes, and aging of the population.

Stroke Subtypes and Pathophysiology

Stroke is broadly classified into two major categories: ischemic stroke and hemorrhagic stroke.

1. **Ischemic Stroke** (≈80–85% of cases) Caused by obstruction of cerebral blood flow, usually due to thrombosis or embolism. Subtypes include, large artery atherosclerosis (thrombotic or embolic events), Cardioembolic stroke (e.g., due to atrial fibrillation), Small vessel occlusion (lacunar infarcts), Stroke due to other determined causes (e.g., vasculitis, arterial dissection), Stroke of undetermined causes.
2. **Hemorrhagic Stroke** (≈15–20% of cases) Caused by rupture of intracerebral or subarachnoid vessels, leading to bleeding within brain parenchyma or surrounding spaces.

Emerging Risk Factors

Vitamin D3 Deficiency While the classical risk factors have been extensively studied, increasing attention has been paid in recent years to emerging, potentially modifiable risk factors, such as Vitamin D3 deficiency. Vitamin D3 (cholecalciferol) is a fat-soluble vitamin synthesized endogenously in the skin upon exposure to ultraviolet-B radiation. It is also obtained in smaller amounts from dietary sources such as fatty fish, fortified foods, and supplements(3). The biologically active form, 1,25-dihydroxy vitamin D3 [1,25$(OH)_2$D], is derived from its precursor 25-hydroxy vitamin D [25(OH)D] in the kidney. Serum 25(OH)D concentration is considered the best indicator of Vitamin D3 status. The widely accepted cutoffs are:

- Deficiency: <25 nmol/L
- Insufficiency: 25–74 nmol/L
- Sufficiency: ≥75 nmol/L.(4)

Global Burden of Vitamin D3 Deficiency Vitamin D3 deficiency is recognized as a global public health problem. Studies estimate that over 1 billion people worldwide have inadequate levels of Vitamin D3, with prevalence varying according to geography, lifestyle, skin pigmentation, and dietary patterns(5). The deficiency is common not only in colder climates but also in sunny countries like India, due to cultural practices limiting sun exposure, pollution reducing UV-B penetration, and poor dietary intake(5). While traditionally linked to calcium-phosphate metabolism and bone health, Vitamin D3 has been increasingly implicated in the pathophysiology of multiple chronic conditions, including Systemic hypertension, Coronary artery disease, Diabetes mellitus, Heart failure, Metabolic syndrome, Cancer, Autoimmune disorders, Peripheral vascular disease(6).

Biological Basis Linking Vitamin D3 and Stroke

The link between Vitamin D3 deficiency and stroke has gained increasing recognition. The discovery of Vitamin D3 receptors (VDRs) and 1-α hydroxylase in endothelial cells, vascular smooth muscle, and neurons has provided biological plausibility(7). Several mechanisms have been proposed to explain this relationship.

1. Blood Pressure Regulation: Vitamin D3 suppresses the renin–angiotensin– aldosterone system, reducing arterial stiffness and blood pressure.
2. Endothelial Function: Vitamin D3 enhances nitric oxide production and improves vascular reactivity.
3. Anti-inflammatory Effects: It downregulates pro-inflammatory cytokines such as IL-6 and TNF-α.
4. Neuroprotection: Vitamin D3 promotes neurotrophic factors and reduces excitotoxicity.
5. Antioxidant Properties: It inhibits reactive oxygen species, preventing vascular and neuronal injury(7) (8).

Deficiency of Vitamin D3 has been associated with higher risk of ischemic stroke, increased stroke severity, and poorer functional outcomes Genetic variations in VDR may further influence susceptibility to stroke, pointing to a gene– environment interaction(9).

Indian Scenario

India bears a dual burden:

1. High and rising incidence of stroke — estimated at 119–145 per 100,000 population annually, with considerable regional variation [10].

2. Widespread Vitamin D3 deficiency — prevalent in both rural and urban settings, across socioeconomic strata, and affecting all age groups(4) (5).

Despite this overlap, there is limited research from India directly investigating the association between Vitamin D3 deficiency and acute ischemic stroke, especially in semi-urban and rural areas like Shahjahanpur, Uttar Pradesh. Given that Vitamin D3 deficiency is both easily measurable and correctable, studying this relationship could have profound implications for primary and secondary stroke prevention.

Case Study:

RESULT

Table 1: Baseline Characteristics of the Study Population (N=96)

Characteristic	Category	Number (n)	Percentage (%)
Age (Years), Mean ± SD	61.4 ± 11.2		
30-50	31	32.3	
51-70	49	51.0	
>70	16	16.7	
Gender	Male	58	60.4
	Female	38	39.6
Residence	Rural	67	69.8
	Urban	29	30.2

The above table illustrates that out of a total of 96 study participants with acute ischemic stroke, the mean age was 61.4 ± 11.2 years, with 31 patients (32.3%) belonging to the 30–50-year age group, 49 patients (51.0%) in the 51–70-year age group, and 16 patients (16.7%) aged more than 70 years. Males constituted 58 cases (60.4%) while females accounted for 38 cases (39.6%). A majority of patients were from rural areas comprising 67 cases (69.8%), whereas 29 patients (30.2%) were from urban areas. According to TOAST classification, large artery atherosclerosis was the most common subtype seen in 42 patients (43.8%), followed by small vessel occlusion in 29 patients (30.2%), cardioembolic stroke in 18 patients (18.8%), and other or undetermined causes in 7 patients (7.3%). The median baseline NIHSS score was 12 with an interquartile range of 8–17.

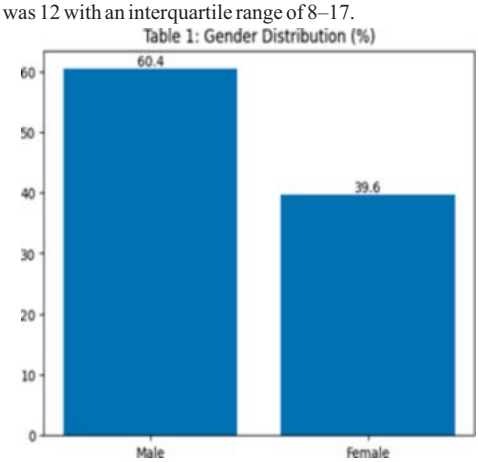


Table 2: Overall Prevalence of Vitamin D3 Status Among Acute Ischemic Stroke Patients (N=96)

Vitamin D3 Status	Serum 25(OH)D (nmol/L)	Number (n)	Percentage (%)
Severe Deficiency	< 25	52	54.2
Deficiency	25 - 49	28	29.2
Insufficiency	50 - 74	12	12.5
Adequacy	≥ 75	4	4.2
Total Vitamin D3 Deficiency	< 50	80	83.3
Descriptive Statistics. The overall mean serum Vitamin D3 level was 29.8 ± 16.1 nmol/L.			

The above table illustrates that out of the total 96 acute ischemic stroke patients, severe vitamin D3 deficiency (<25 nmol/L) was observed in 52 patients (54.2%), deficiency (25–49 nmol/L) in 28 patients (29.2%), insufficiency (50–74 nmol/L) in 12 patients (12.5%), and adequate vitamin D3 levels (≥75 nmol/L) in only 4 patients (4.2%). Overall vitamin D3 deficiency defined as serum levels below 50 nmol/L was present in 80 patients, accounting for 83.3% of the study population, with an overall mean serum vitamin D3 level of 29.8 ± 16.1 nmol/L.

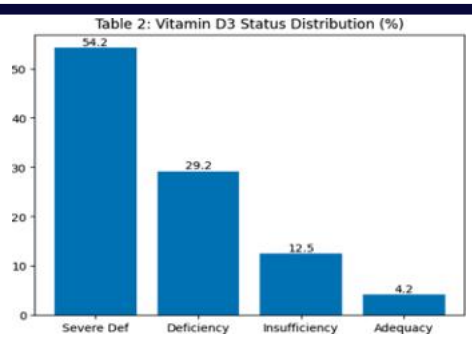


Table 3: Association Between Serum Vitamin D3 Levels and Clinical Severity at Admission (NIHSS Score)

Vitamin D3 Status	n (%)	Median NIHSS Score (IQR)	p-value
Severe Deficiency (<25 nmol/L)	52 (54.2)	15 (11-19)	<0.001
Deficiency (25-49 nmol/L)	28 (29.2)	10 (7-14)	
Insufficiency (50-74 nmol/L)	12 (12.5)	7 (5-10)	
Adequacy (≥75 nmol/L)	4 (4.2)	5 (3-7)	
*Statistical Test: Kruskal-Wallis Test. Post-hoc analysis (Dunn's test) showed a statistically significant difference between the Severe Deficiency and Adequacy groups (p<0.001) and between Severe Deficiency and Insufficiency groups (p=0.009). *			

The above table illustrates that among the 96 study participants, patients with severe vitamin D3 deficiency (<25 nmol/L), constituting 52 cases (54.2%), had a median NIHSS score of 15 with an interquartile range of 11–19. Patients with vitamin D3 deficiency (25–49 nmol/L), comprising 28 cases (29.2%), had a median NIHSS score of 10 (IQR 7–14), while those with insufficiency (50–74 nmol/L), 12 cases (12.5%), had a median NIHSS score of 7 (IQR 5–10). Patients with adequate vitamin D3 levels (≥75 nmol/L), 4 cases (4.2%), had the lowest median NIHSS score of 5 (IQR 3–7), with a statistically significant association observed (p<0.001).

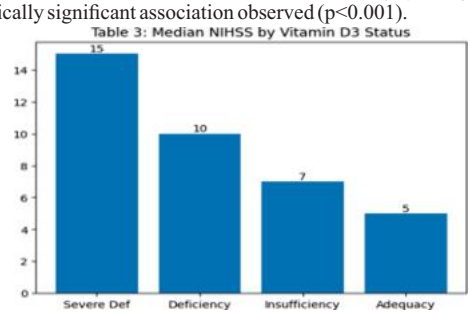
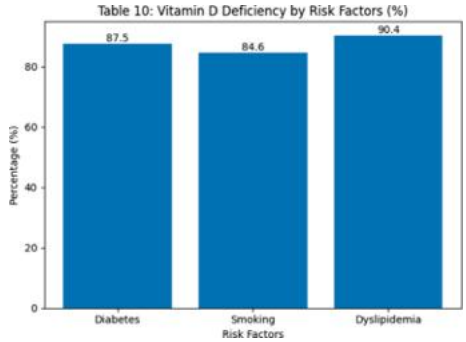


Table 10: Association of Other Modifiable Risk Factors with Vitamin D3 Deficiency (<50 nmol/L)

Risk Factor	Present	Deficient n/N (%)	p-value
Diabetes Mellitus	48	42/48 (87.5%)	0.283
Current Smoking	39	33/39 (84.6%)	0.782
Dyslipidemia	52	47/52 (90.4%)	0.041
Statistical Test: Chi-square test.			

The above table illustrates that vitamin D3 deficiency (<50 nmol/L) was present in 42 out of 48 patients with diabetes mellitus (87.5%), in 33 out of 39 current smokers (84.6%), and in 47 out of 52 patients with dyslipidemia (90.4%), with dyslipidemia showing a statistically significant association with vitamin D3 deficiency (p=0.041).



CONCLUSION

1. Out of the total 96 acute ischemic stroke patients studied, the mean age was 61.4 ± 11.2 years, with the majority belonging to the 51–70 years age group (51.0%), followed by 30–50 years (32.3%) and >70 years (16.7%); males constituted 60.4% and females 39.6%, with rural residence in 69.8% and large artery atherosclerosis being the most common stroke subtype (43.8%), and a median NIHSS score of 12 (IQR 8–17).
2. Vitamin D3 deficiency (60 years (87.8%), females (89.5%), rural residents (92.5%), and those belonging to lower socioeconomic classes IV and V (91.8%), with statistically significant associations for rural residence (p=0.002) and lower socio-economic status (p=0.006).
3. A statistically significant inverse relationship was observed between serum vitamin D3 levels and stroke severity, with median NIHSS scores of 15 in severe deficiency, 10 in deficiency, 7 in insufficiency, and 5 in adequate vitamin D groups (p=0.006).
4. Vitamin D3 deficiency was more prevalent among patients aged >60 years (87.8%), females (89.5%), rural residents (92.5%), and those belonging to lower socioeconomic classes IV and V (91.8%), with statistically significant associations for rural residence (p=0.002) and lower socioeconomic status (p=0.006).
5. Mean serum vitamin D3 levels were lowest among newly diagnosed hypertensive patients (23.1 ± 10.3 nmol/L), followed by known hypertensives on treatment (28.4 ± 14.7 nmol/L), and highest among normotensive patients (43.8 ± 18.4 nmol/L), with a statistically significant difference (p<0.001).
6. Among known hypertensive patients, vitamin D3 deficiency was more frequent in non-adherent patients (91.3%) compared to adherent patients (74.2%), though the association was not statistically significant (p=0.184).
7. Median serum vitamin D3 levels varied significantly across ischemic stroke subtypes, being lowest in large artery atherosclerosis (24.5 nmol/L), 50 followed by small vessel occlusion (28.0 nmol/L), cardioembolic stroke (38.5 nmol/L), and highest in other/undetermined causes (49.0 nmol/L), with statistical significance (p=0.008).
8. Female patients practicing purdah or burka had significantly lower median serum vitamin D3 levels (21.0 nmol/L) compared to those not practicing purdah (31.0 nmol/L), with a statistically significant association (p=0.003).
9. Poor functional outcome at discharge (mRS 3–6) was observed in 65.0% of vitamin D3 deficient patients compared to 37.5% among non-deficient patients, showing a statistically significant association between vitamin D3 deficiency and adverse functional outcome (p=0.018).
10. The combined presence of hypertension and severe vitamin D3 deficiency(<25nmol/Lit) was associated with a markedly increased adjusted odds ratio of 14.67 for stroke risk (95% CI: 3.55–60.61, p<0.001), compared to normotensive patients without severe deficiency.
11. Vitamin D3 deficiency was observed in 87.5% of diabetic patients, 84.6% of current smokers, and 90.4% of patients with dyslipidemia, with dyslipidemia showing a statistically significant association with deficiency (p=0.041).
12. On multivariable analysis, rural residence (aOR 4.12, p=0.008), lower socioeconomic class IV and V (aOR 3.05, p=0.021), and severe stroke defined by NIHSS >10 (aOR 2.88, p=0.016) were identified as independent predictors of severe vitamin D3 deficiency, while age >60 years and female sex with purdah practice were not statistically significant predictors.

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