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ORIGINAL ARTICLE

ASSOCIATION OF VITAMIN-D STATUS WITH ISCHEMIC STROKE AND IT'S RISK FACTORS IN BANGLADESHI PATIENTS: A CASE-CONTROL STUDY

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Abstract:

Background: *Vitamin D (VD) shortage and inadequacy are serious global health issues affecting people of all ages. Several studies have shown a link between VD insufficiency and ischemic stroke. Unfortunately, VD is rarely measured, diagnosed, or treated, especially in patients with severe neurological disorders like stroke in our context. The study aimed to explore the association between VD and the risk of acute ischemic stroke along with its risk factors in Bangladeshi patients.* ***Methods:*** *Forty-four patients with ischemic stroke and 44 age and sex-matched healthy subjects were included in this study from Chittagong Medical College Hospital. Demographic and clinical data were collected with a structured interview questionnaire. Fasting 25(OH) VD, calcium, lipid profile, and blood sugar were measured. VD levels classified the individuals in sufficient (VDSe"30.0 ng/mL), insufficient (VDI: 20.0–29.9 ng/mL), and deficient (VDD<20.0 ng/mL) status.* ***Results:*** *Out of 44 stroke patients, 27 (61.4%) were men, and the mean age was 54.6±11.0 years (age range: 18-70 years). The frequency of hypertension, diabetes mellitus, obesity, and dyslipidemia were 68.2%, 31.8%, 52.3%, and 81%, respectively, among stroke cases. VDD and VDI was observed in 29 (65.9%), 9 (20.5%) stroke patients and 5 (11.4%), 12 (27.3%) controls respectively. Multiple logistic regression analysis showed an independent association of 25(OH)D deficiency or insufficiency with ischemic stroke (odds ratio: 10.71, 95% confidence interval: 2.21-51.88, p=0.003).* ***Conclusions:*** *This study shows that low VD levels may be associated with an increased risk of ischemic stroke.*

Keywords: *Ischemic stroke, Vitamin D, Chattogram, Bangladesh.*

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Introduction:

Data from the World Health Organization in 2021 indicates that stroke is at the top of the list of 'leading causes of death in Bangladesh,' which ranks mortality due to stroke in Bangladesh as number 41 in the world.[1] Increasing burden of stroke in Bangladesh is primarily driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors.[2] Without the urgent implementation of effective primary prevention strategies, the stroke burden will probably continue to grow across the world, particularly in low to middle-income countries like Bangladesh.[3]

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Hypertension, diabetes mellitus, dyslipidemia, sedentary lifestyle, obesity, smoking are the common risk factors of stroke.[4] However, plenty of epidemiological studies are being done to spot novel emerging risk factors and their role in reducing the incidence of stroke and their exact nature of association with stroke.[5] In the recent past, researchers have given much emphasis to one such risk factor i.e., VD deficiency (VDD), but the results were inconclusive and conflicting. While some studies reported an association between low levels of VD and stroke,[6-13] as well as its relationship with outcome and prognosis,[7,9,11,13,14] but some studies failed to establish such association.[15-18]

VD is an organic compound consisting of fat-soluble secosteroids mainly responsible for regulation of calcium and phosphorous levels, among other physiological functions.[19,20] VD is measured by levels of a metabolically inactive precursor, 25-hydroxyvitamin D3hydroxy VD [25(OH)D3] since the serum concentration of 1,25(OH)2D3 is significantly lower than 25(OH)D3.[21] 25(OH)D3 deficiency can cause bone demineralization and is associated with obesity, diabetes, hypertension, and cancer.[19,20,22] 25(OH)D3 levels have been associated with regulating cardiac myocyte, systolic blood pressures, glycemic control, vascular function, high- density cholesterol, and metabolic syndrome, which all influence cerebrovascular and cardiovascular events.[19,20,22-24]

Given these discrepancies and biological plausibility, the current study was undertaken to assess the association between VD status and risk of ischemic stroke based on a population from southeastern Bangladesh.

Methods:

We conducted a case control study over a period of one year (January 2018 to December 2018). The study was conducted at Chittagong Medical College Hospital, Chattogram, Bangladesh and subjects were recruited from medicine and neurology wards.

A total of 44 patients with acute ischemic stroke were chosen in the study. An equal number of age- and sex-matched healthy controls were taken from normal healthy individuals. Sample size was calculated with reference to a previous study, where the proportion of VD deficiency was 43% and 5% respectively in stroke cases and controls.[18] By using above reference values, sample size was calculated by formula for calculating sample size for case-control study by comparing two proportion at 95% confidence interval and 80% power, 5% level of significance.[25]

Clinically and Radiologically (C.T scan of Head/MRI of brain) documented new case of Ischaemic stroke, duration of stroke within 7 days, and ages 18 to 70 years were included in the study. Known case of other comorbid conditions like, chronic liver disease, chronic hepatitis, chronic kidney disease, severe sepsis, malabsorption syndrome, systemic sclerosis, chronic obstructive pulmonary disease, bronchial asthma, nephrotic syndrome, bone diseases including fracture were excluded. Patients with ongoing drug history of steroid, oral contraceptive pill, Bisphosphonate antiepileptic and calcium & vitamin-D supplements were also excluded.

All relevant demographic and clinical data were collected using structured case record form. After keeping fasting for 8-12 hours, with all aseptic precaution 8cc venous blood was collected from median cubital vein at morning. Then blood was taken into two sealed sterile red tube, each of 4cc and immediately sent to the laboratory with proper care. For fasting lipid profile and serum calcium, blood samples were centrifuged at 3000 RPM for 5 minutes. Separated serum samples for mentioned investigations, were analyzed by auto analyzer (SIEMENS-Dimension® EXL^{TM}-200). VD levels were classified as sufficient (VDSe"30.0 ng/mL), insufficient (VDI: 20.0–29.9 ng/mL), and deficient (VDD<20.0 ng/mL) status.[26]

Data were analyzed by using SPSS version 23. Categorical variables were expressed as frequency and percentage and continuous data were either in mean (±SD) or median (Interquartile range) as appropriate according to their distribution. To see the association of demographics, laboratory parameters and risk factors of ischemic stroke between case and control groups Fisher's exact or Chi-square test were used for categorical variables and independent sample t test or Mann-Whitney U test for quantitative variables. Logistic regression model was used to estimate adjusted effect of VD and to determine the independent predictors of ischemic stroke. Additionally, binary logistic regression analysis done for same purpose and also the odds ratios (ORs) with 95% confidence interval for OR to see the association between risk factors of stroke with VD status by dividing the all-study subjects (n-88) by VD level e"30ng/dl versus <30ng/dl. P <0.05 was considered statistically significant.

Results:

The mean age of the stroke patients was 54.6 (±11.0) years and 61.4% were male. Most prevalent risk factor in stroke patients was dyslipidemia (80%), followed by hypertension (68.2%), obesity (52%), smoking (38%) and diabetes (32%).

Table I

Clinical characteristics of the participants

Variables		Stroke patients (n=44)	Control subjects (n=44)	P value
Age, in years	Mean ±SD	54.6±11.0	54.6±11.1	0.992#
Sex	Male	27 (61.4%)	27 (61.4%)	1.0*
	Female	17 (38.6%)	17 (38.6%)	
	Hypertension	30 (68.2)	16 (36.0)	0.003*
Comorbidity	Diabetes	14 (32.0)	7 (16.0)	0.080*
	Obesity	23 (52.0)	23 (52.0)	1.0*
	Dyslipidemia	35 (80.0)	29 (89.0)	0.151*
Smoking	Current	17 (38.0)	9 (20.0)	0.062*

Data are expressed as frequency and percentage if not otherwise mentioned. #Independent sample t test; *Chi-square test

Different laboratory parameters are compared between two groups in Table II. Except serum triglyceride and 25(OH)D all other laboratory parameters (total cholesterol, HDL, LDL, FBS and serum calcium) are similar in both groups. Serum 25(OH) D and triglyceride level are significantly less among stroke patients than age-sex matched controls.

Table II

Laboratory parameters of the participants

Variables	Stroke patients (n=44)	Control subjects (n=44)	P value
25(OH)D, ng/ml	19.00±7.79	31.05±8.46	<0.001#
Total cholesterol, mg/dl	204.39±48.99	204.68±40.82	0.976#
LDL, mg/dl	128.59±37.54	123.73±29.46	0.501#
HDL, mg/dl	42.57±6.29	41.89±5.66	0.594#
Triglyceride, mg/dl	118 (97-187)	155 (110-212)	<0.001**
FBS, mmol/L	7.13±2.79	6.66±2.05	0.42#
Calcium, mg/dl	8.77±0.59	8.64±0.52	0.604#

Data are expressed as mean ±SD or median (interquartile range). LDL-Low density lipoprotein; HDL-High density lipoprotein; FBS: Fasting Blood Sugar; * Mann-Whitney U test; # Independent sample t test

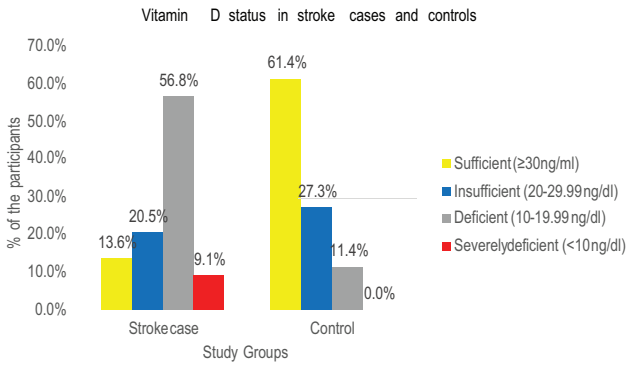

Fig.-1: *Distribution of the cases and controls according to their VD status.*

Study subjects were categorized according to their vitamin D level as vitamin D sufficient (VDD), insufficient (VDI), deficient (VDD) and severely deficient. Majority of the stroke patients (56.8%) are vitamin D deficient whereas majority of the control (61.4%) have sufficient vitamin D. Deficient & severely deficient vitamin-D status are significantly different between cases & controls.

Finally, to determine the independent predictive factor for stroke a binary logistic regression analysis is done, vitamin D level <30 ng/ml is remained as an independent factor associated with acute ischemic stroke (OR 10.71, 95% CI: 2.21–51.88; p=0.003). Relation with smoking also significant (OR 5.43, 95% CI: 1.135-25.989; p=0.034) (Table III).

Table III

Odds ratio (95%CI) for the predicting effect of the contributing factors of ischemic stroke

Variables	P value	Odds ratio (OR)	95% CI for OR	
			Lower	Upper
Vitamin D (e"30 vs. <30 ng/ml)	**0.003**	10.71	2.21	51.88
Age, in years	0.210	0.95	0.89	1.02
Sex, (male vs. female)	0.394	0.49	0.10	2.47
Smoking (Never/Ex vs. current)	0.034	5.43	1.13	25.98
Hypertension (Absent vs. present)	0.143	3.21	0.67	15.32
Diabetes (Absent vs. present)	0.440	1.78	0.40	7.83
Obesity (Absent vs. present)	0.136	0.34	0.08	1.39
Dyslipidemia (Absent vs. present)	0.408	0.46	0.07	2.85

CI: Confidence interval

All of the study subjects (both case and control) are classified according to their vitamin D status (e"30 ng/ml and <30ng/ml) and association with the risk factors of stroke are observed in Table IV. Among them hypertension is significantly associated with vitamin D status ((OR 4.73, 95% CI: 1.86-12.0; p=0.003).

Table IV

Association of the risk factors of ischemic stroke with vitamin D status (n=88)

Variables		Vitamin D status		Odds ratio (95% CI)	P value
		Sufficient (≥30ng/ml) (n=33)	Deficient (<30ng/ml) (n=55)		
Hypertension	Absent	23 (69.7%)	18 (32.7%)	4.73(1.86-12.01)	**0.003***
	Present	10 (30.3%)	37 (67.3%)		
DM	Absent	28 (84.8%)	39 (70.9%)	2.29(0.75-7.1)	0.137*
	Present	5 (15.2%)	16 (29.1%)		
Obesity	Absent	19 (57.6%)	23 (41.8%)	1.88(0.18-2.17)	0.452*
	Present	14 (42.4%)	32 (58.2%)		
Dyslipidemia	Absent	4 (12.1%)	10 (18.2%)	0.62(0.18-2.17)	0.452*
	Present	29 (87.9%)	45 (81.8%)		
Smoking	Never/Ex	23 (69.7%)	39 (70.9%)	0.94(0.37-2.42)	0.904*
	Current	10 (30.3%)	16 (29.1%)		

Data are expressed as frequency and percentage. * Chi-square test

Discussion:

In this study, we investigated whether vitamin D status was associated with ischemic stroke in Bangladeshi patients admitted to a tertiary level hospital. The study demonstrated that VDD may be considered an independent factor associated with acute ischemic stroke and here individual with vitamin D level <30ng/dl was 10.71 times more likely to have acute ischemic stroke when compared to those with vitamin D level ≥30ng/dl.

A large body of evidence from epidemiological studies indicates that VDD is associated with an increased risk of stroke, and stepwise decrease in plasma 25(OH)D concentrations were associated with stepwise increasing risk of ischemic stroke.[8,12-14] To the best of our knowledge, the present study is one of the few published reports that has focused on the association between 25(OH)D and acute stroke in Bangladeshi population.[6] Majumder et al.[6] first reported from their cross-sectional study that VDD is an important risk factor for ischemic stroke in a group of Bangladeshi patients. The present study affirms this association with a superior study (case control study) design.

In our study, the mean of serum 25(OH)D level in the 88 adult subjects examined was 25.03 (±10.1) ng/dl, the VDI (<30ng/dl) was as high as 62.5%. The results indicated that inadequacy of VD was prevalent in Chattogram as in other areas of Bangladesh and other countries.[6, 27, 28] We found signiûcantly higher rates of VDI, and VDD in the stroke patients than control group. The serum 25(OH)D levels of stroke cases were even lower than controls 19.0 (±7.79) ng/mL versus 31.05 (±8.46) ng/mL. Similar ûndings have been shown in previous observational studies on ischemic stroke.[19, 30]

In the present study, most prevalent risk factor in stroke patients was dyslipidemia (80%), followed by hypertension (68.2%), obesity (52%) and DM (32%). The corresponding figures in the study of Majumder et al.[8] was hypertension (44.8%), obesity (12.9%) and DM (32.8%) and dyslipidemia (30.2%). Among the modifiable risk factors of ischemic stroke, only hypertension was found statistically significant (p=0.005). It agrees with others, [10,12,16,19] where a significant association between hypertension and VDD were reported. On the contrary, though previous studies, [10, 12, 19] found associations between VDD, and other modifiable risk factors including DM were not found to be associated with VDD in the present study. This insignificant association of risk factors of stroke might be due to mechanism other than VD status or small sample size. As hypertension is established modifiable risk factors of stroke and that regulate RAAS and as it was found more prevalent among VDD groups, so maintenance of optimal VD level is crucial. Moreover, both hypertension and VDD are controllable and treatable parameter; worldwide stroke burden can be reduced by effective health care program.

Conclusion:

The current study shows that ischemic stroke patients are more common of VDD than age-sex matched control. Among the risk factors of ischemic stroke, hypertension might have association with VDD. In the context of our observations, VDD may be a risk factor for acute ischemic stroke.

Limitations:

Small sample size and selection of the cases from a tertiary level hospital might limit the generalizability of the study results. More sensitive method for vitamin-D estimation by HPLC could not be used in this study due to unavailability of laboratory support in our context.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

This research received no external funding.

Ethical consideration:

The study was approved by the Ethical Review Committee of Chittagong Medical College. Informed consent was obtained from each participant or caregivers of the patients.

Author Contributions:

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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