Original Article

Low Serum Vitamin D is Independently Associated with Acute Ischemic Stroke

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Abstract

Low serum vitamin D levels have been associated with various vascular diseases. Very little is known its association with acute stroke in Bangladeshi population. We therefore sought to assess whether low serum 25-hydroxyvitamin D, a marker of vitamin D status is associated with acute stroke. We performed a prospective study in Comilla Medical Collage, Comilla, from November 2016 to November 2017. All the patients diagnosed as acute ischemic stroke on the basis of CT scan or MRI of brain. Patients were eligible for inclusion if they were admitted with onset of symptoms within 24 hours. Estimation of 25(OH)D level was done at presentation. The patients were stratified by vitamin D status, >30 as vitamin D sufficient, vitamin D 20-20.9 as insufficient and finally vitamin D<20 as deficient. Multivariate logistic regression analysis revealed that out of the desired 7 variables, smoking, hypertension and low serum vitamin D were found independent predictors for acute stroke with ORs being 1.44, 4.23 and 2.39 respectively. Vitamin D deficiency represents an important risk factor for acute stroke and it might play a causal role in the development adverse events associated with stroke.

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Introduction

Stroke is the second leading cause of disability in Europe and sixth leading cause worldwide[1]. Women have a higher lifetime risk of stroke than men. It is estimated that about one in five women (20% to 21%) and one in six men (14% to 17%) will suffer from a stroke in their lifetime[1]. Low serum 25 hydroxy vitamin D [25(OH)D] is independently associated with larger infarct volume, which may partially explain worse outcomes in ischemic stroke patients[2]. This poor stroke outcome possibly due to inhibition of thrombogenic influences and mitigation of endothelial dysfunctionin vitamin deficiency[3]. It also triggers secondary hyperparathyroidism which promotes myocyte hypertrophy, vascular remodeling and has pro-inflammatory effects[4-5].

Body vitamin D status is measured by estimation of serum 25(OH)D because of its long half life[6]. Early reports shows link between vitamin D deficiency and easily treatable cardiovascular risk factor such as hypertension, diabetes mellitus, obesity, metabolic syndrome, left ventricular hypertrophy, heart failure, coronary heart disease and renal disease[7-8]. Despite evidence suggesting that vitamin D deficiency may lead to elevated cardiovascular disease risk but the association of 25(OH) D levels with ischemic stroke risk is inconclusive. Recent reports of the association of hypovitaminosis D with multiple cardiovascular (CV) conditions have been of great interest suggesting the need for prospective validation and extended observations. We conducted a prospective study to examine the relationship between plasma 25(OH)D levels and risk of stroke.

Materials and Methods

We performed a prospective study in Comilla Medical Collage on the patients presented with acute stroke from November 2016 to November 2017. Patients were eligible for inclusion if they were admitted to the emergency department with onset of symptom within 24 hours[9].

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Acute ischemic stroke was diagnosed by with computed tomography (CT) and/or magnetic resonance imaging. Estimation of 25(OH)D level was done at presentation. A single vitamin D level provides an estimate of long-term vitamin D status[10-11]. Patients suffering from malignant tumor, renal insufficiency (creatinine>1.5 mg/dl), febrile disorders, acute or chronic inflammatory disease at study enrolment and autoimmune diseases were excluded from this study. The patients who used vitamin and/or calcium supplementation before stroke onset were also excluded. All the laboratory data, comorbidities, preadmission medications and stroke etiology after completion of diagnostic evaluation were collected. Written informed consent was obtained from all subjects. This study was reviewed and approved by our institutional review board. Serum levels of 25(OH)D were analyzed using 25-hydroxy chemiluminescent immunoassay. We trichotomized vitamin D status as sufficient (≥30 ng/mL [75 nmol/L]), insufficient (20-29.9 ng/mL [50-75 nmol/L]), and deficient (□20 ng/ mL [50 nmol/L]) according to the Endocrine Society criteria[9]. In addition, we dichotomized vitamin D status as 25(OH)D concentration of 30 ng/mL or more versus less than 30 ng/mL and 20 ng/mL or more versus less than 20 ng/mL, respectively.

During Statistical analysis continuous variables are reported as mean ± standard deviation or median (interquartile range), and categorical variables are reported as proportions. Between-group comparisons for continuous variables were performed using Student's t test, ANOVA analysisas appropriate. Categorical variables were compared using the chi-square test or the Fisher exact test. Univariable regression models were constructed to examine associations of serum 25(OH)D concentrations and acute stroke. The following prespecified variables were included in the multivariable linear regression model with backward elimination to identify independent predictors for a final acute stroke model as they have been associated with acute stroke: age, sex, smoking, diabetes mellitus, hypertension and dyslipidaemia[7]. All statistical analyses were performed using SPSS statistics version 16 Windows 2007. All the authors vouch for the completeness and accuracy of data and analyses presented.

Results

The study patients were stratified by vitamin D status>30 as vitamin D sufficient, vitamin D 20-20.9 as insufficient and finally vitamin D<20 as deficient. Patients having vitamin D deficient were more older than vitamin D insufficient and sufficient respectively with statistically significant difference (p=0.04) by ANOVA test. Male patients were higher in vitamin D sufficient than that of vitamin D insufficient and deficient with statistically significant difference (p=0.04). Female patients were found higher in vitamin D deficient than that of vitamin insufficient and sufficient with statistically significant difference (p=0.04). Smoking habit was found higher in vitamin D deficient patients than that of vitamin insufficient and sufficient with statistically significant difference (p=0.04).

Hypertension was found higher in vitamin D deficient patients than that of vitamin insufficient and sufficient with statistically significant difference (p=0.04).The remaining factors such as diabetes mellitus, IHD, dyslipidaemia and obesity were observed more in vitamin D deficient patients but did not reach the level of significance (p>0.05) (Table - I).

Table- I: Participants baseline clinical characteristics of the study patients as stratified by vitamin D status (n=116).

Variables	Total patients (n=116)	Vitamin D sufficient (n=26)	Vitamin D insufficient (n=42)	Vitamin D deficient (n=48)	P value
Age, years	61.7±11.3	58.1±12.8	60.6±12.1	64.7±9.0	0.04[s]
Sex (Male)	70 (60.3%)	20 (76.9)	27 (64.3%)	23 (47.9)	0.04[s]
Sex (Female)	46 (39.7%)	6 (23.1%)	15 (35.7%)	25 (52.1%)	0.04[s]
Smoker	57 (49.1%)	11 (42.3%)	17 (40.5%)	29 (60.4%)	0.03[s]
Diabetes mellitus	38 (32.8%)	5 (19.2%)	13 (31.0%)	20 (41.7%)	0.09[ns]
Hypertension	52 (44.8%)	8 (30.8%)	17 (40.5%)	27 (56.2%)	0.04[s]
IHD	37 (31.9%)	7 (26.9%)	12 (28.6%)	18 (37.5%)	0.54[ns]
Dyslipidaemia	35 (30.2%)	6 (23.1%)	10 (23.8%)	19 (39.6%)	0.17[ns]
Obesity	15 (12.9%)	3 (11.5%)	4 (9.5%)	8 (16.7%)	0.58[ns]

Data were expressed as mean±SD. p:probability value reached from Chi Square test for qualitative data and ANOVA test for quantitative data. Ns = Not significant (p>0.05), Bold indicates significant (p<0.05).

Vitamin D status of patients in percentage with smoking habit, diabetes mellitus, hypertension, IHD, dyslipidaemia and obesity are plotted in bar diagram in figure-1.

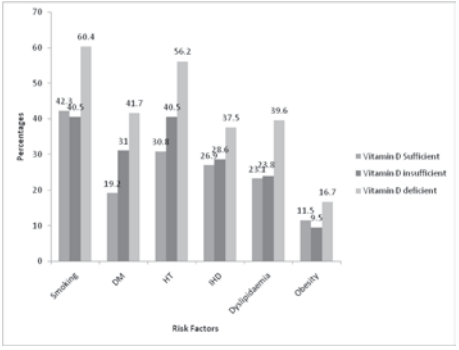

Figure-1: Bar diagram showing risks factors of the study patients according to Vitamin D status.

The following table displays the binary logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely for having stroke. Multivariate analysis revealed that out of the desired 7 variables smoking, hypertension and low serum vitamin D were found to be the independently significant predictors for having stroke with ORs being 1.44, 4.23 and 2.39 respectively. The table revealed that smoking habit, hypertension and low

serum vitamin D is associated more than 1 time, 4 times and 2 times for having stroke than non smoker, normotensive and raised serum vitamin D≥ 20 ng/ml (Table- II).

Table-II: Multivariate binary logistic regression analysis of having stroke by low serum vitamin D and other variables (n=116).

Variables of interest	Multivariate	
	OR (95% CI)	P value
Advance age>55	0. 98 (0.689 - 4.274)	0.12^{ns}
Sex (female)	0. 92 (0.409 - 5.274)	0.15^{ns}
Smoking	1.44 (1.241 - 6.101)	0.03^{s}
Hypertension	4.23 (1.247- 14.210)	0.02^{s}
Dyslipidemia	1.11 (0.241 - 6.222)	0.19^{ns}
Diabetes mellitus	1.20 (1.189 - 13.112)	0.008^{s}
Low serum Vitamin D (<20 ng/ml)	2.39 (1.101-6.201)	0.03^{s}

s = Significant (p<0.05), ns = Not significant (p>0.05)

OR= odds ratio p: probability value, n= number of the subjects

Discussion

In the present prospective observational study, we assessed serum levels of 25(OH)D with regard to their accuracy to predict acute stroke. A large body of evidence from epidemiological studies indicates that vitamin D deficiency is associated with an increased risk of stroke[12], and Stepwise decrease in plasma 25(OH)D concentrations were associated with stepwise increasing risk of ischemic stroke[1]. To the best of our knowledge, no previous work has focused on the association between 25(OH)D and acute stroke in Bangladeshi population. In the present study, we found that serum levels of 25(OH)D were substantially lower in patients with acute stroke. Vitamin D deficiency and insufficiency (77.5%) was very common in our patients. Median baseline 25(OH)D levels 14.03ng/ml in our patients were similar compared with other studies 15.2ng/ml[14] and 14.1 ng/ml[15]. Pathophysiological mechanisms remain speculative, but several possible biological mechanisms might explain the association of low 25(OH)D with poor outcome[16]. Low 25(OH)D levels may contribute to pro-atherosclerotic changes of vascular smooth muscle cells, endothelial dysfunction and increased macrophage to foam cell formation[17]. High dose oral vitamin D supplementation produced short-term improvement in endothelial function in stroke patients with well controlled baseline blood pressure[14]. Finally, low 25(OH)D levels are known to influence macrophage and lymphocyte activity in atherosclerotic plaques and to promote chronic inflammation in the artery wall[18]. Various studies suggest that vitamin D may exert anti-inflammatory effects. Reduced 25(OH)D levels might be associated with overall increased inflammatory activity[19].

Low level of vitamin D has been associated with an increased future risk of stroke and acute myocardial infarction during 10 years of follow-up[20] and was independently predictive for fatal stroke in patients who were referred for coronary angiography at baseline[19]. In a prospective population-based cohort study, individuals with severe 25(OH)D deficiency (<20 nmol/l) had higher risk of ischemic stroke (hazard ratio 1.36, 95% CI 1.09-1.70) compared with individuals with optimal 25(OH)D level (>75 nmol/l) during 21 years of follow- up[20]. Daubail et al found that the mean 25(OH)D level was lower in ischemic stroke patients[14]. In our study, we found that circulating serum 25(OH)D levels were deficient and insufficient in 77.5 % of patients with acute stroke. Another study in Chinese patients also found that vitamin D deficiency (78.6 %) was very common[15]. Tu et al also suggested that 25(OH)D was an independent predictor of major disability and death within 90 days after onset of ischemic stroke with ORs (95% CIs) of 0.79 (0.73-0.85) and 0.70 (0.50-0.98) respectively[16]. Strengths of the present study relate to the extensive measurement of covariates and rigorous adjustment for variables that have been associated with acute stroke. There are some limitations relate to the retrospective study design like. Uncontrolled or unknown factors that may affect the incidence of stroke. For example, we did not collect information on nutritional habits. However, surrogate markers for the nutritional status were not associated with stroke incidence or vitamin D status in our study. This may assuage concerns that the noted association of vitamin D with acute stroke was a spurious finding related to overall poor nutritional health. Nevertheless, careful assessment of the nutritional status should be done in future studies assessing these associations. Although our data show a significant association between 25(OH)D and acute stroke, a causal relationship remains to be established. Large scale prospective studies in tertiary level hospital in different region of this country is necessary to establish this relationship.

Conclusion

In the context of our observations, vitamin D deficiency represents an important risk factor for acute stroke and it might play a causal role in the development adverse events associated with stroke.

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