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Correlation between serum vitamin D3 levels and infarct volume in acute ischemic stroke patients: A cross sectional study

M S Siddiqui[1], Dr. Tushar Tyagi[2]
[1] Professor, Department of Medicine, Era's Lucknow Medical College, Era University, Lucknow, Uttar Pradesh, India
[2] Department of Medicine, Era's Lucknow Medical College, Era University, Lucknow, Uttar Pradesh, India

Abstract
Background: Vitamin D3 levels have been shown to have an association with severity, outcome, and infarct size in acute ischemic stroke patients. The association of vitamin D3 levels with infarct size and prognostic significance of vitamin D3 levels as a surrogate prognostic marker of outcome in acute ischemic stroke patients needs to be evaluated further, especially in Indian patients.
Methodology: The study was a cross sectional study conducted at the Department of Medicine, Era's Lucknow Medical College & Hospital, Lucknow on 65 admitted patients with acute ischemic stroke. Infarct volume was measured and laboratory parameters like vitamin D3 levels, lipid profile and glycaemic parameters were assessed on the first day of admission.
Results: The mean age of the patients was 58.82±12.47 (Range - 23-82) years. There was a male preponderance (66.20%) and most of the patients were overweight or obese. Hypertension (72.30%) and diabetes (53.80%) were the most common comorbidities. The mean vitamin D3 levels were 37.81±25.00 nmol/L with a range of 7.5-150 nmol/L. Most of the patients were either Vit D3 deficient (28, 43.10%) or severely deficient (20, 30.80%). Most of the infarcts were ≤10 cc (41.50%) or >30 cc (32.30%) in volume with a mean volume of 51.71±81.66 cc. Volume of stroke and Vitamin D3 level were found to be inversely correlated with a Pearson's corelation coefficient of -0.201. A higher vitamin D3 level was observed among patients with lower infarct volume and a higher infarct size was observed among severe vitamin D3 deficient patients. None of the trends were significant statistically (P>0.05). The only significant variable between the groups based on vitamin D3 status was in terms of positive family history of cerebrovascular disease.
Conclusion: Vitamin D3 deficiency was highly prevalent in stroke patients yet was unrelated with major clinical and demographic variables including the infarct size.

Keywords: acute ischemic stroke, vitamin D3, infarct volume

Introduction

Stroke is a major global health hazard and cause of serious long-term disability and the third most common cause of death in developed countries [1]. Stroke is one of the leading causes of death and disability in India. The estimated adjusted prevalence rate of stroke range, 84-262/100,000 in rural and 334-424/100,000 in urban areas.

Vitamin D3 deficiency is a new emerging cardiovascular risk factors identified to be associated with atherosclerosis. Vitamin D3, both directly and indirectly, in involved in the atherogenic process. It directly influences the endothelial function through autocrine/intracrine modulatory actions of vitamin D3 [9]. Indirectly, it participates in promotion of atherogenesis by influencing insulin resistance, dyslipidemia, the renin-angiotensin-aldosterone system (RAAS), and consequent hypertension [2].

Vitamin D3 levels have been shown to have an association with severity, outcome and infarct size in acute ischemic stroke patients as shown by a number of previous studies [3]. The severity and outcome of acute ischemic stroke has reportedly been shown to be affected by the size of the infarct [4].

Methodology

The present study was a Cross sectional study conducted over a period of 24 months on 65 consecutive patients of acute ischemic stroke admitted in Neurology Clinic, Emergency and Medicine wards at Department of Medicine, Era's Lucknow Medical College & Hospital, Lucknow after clearance was obtained from the Institutional Ethical Committee.

The following *inclusion exclusion criteria* were used -

1. Inclusion criteria - All admitted patients with onset of acute ischemic infarct.
2. Exclusion criteria –

a. Recurrent stroke.
b. Renal insufficiency (Creatinine >1.5 mg/dl)
c. Patients who have received calcium or Vitamin D3 therapy in the past 3 months.

The sample size came out to be n=65.

Method of Serum Vitamin D3 Measurement - chemiluminescence technique on Vitros 5600 integrated system Analyzer of Ortho Clinical Diagnostics (a division of Johnson & Johnson)

Reference range of vitamin D (5) -

Deficient	:	<20 ng/ml or <50 nmol/L
Insufficient	:	20-30 ng/m or 50-75 nmol/L
Sufficient	:	30-100 ng/ml or 75-250 nmol/L
Potential toxicity	:	>100 ng/ml or >250 nmol/L

Stroke Size and Volume Measurement

Infarct volumes indicated by DWI (Diffusion weighted imaging) were measured on MRI (HITACHI 0.4 Tesla, open magnet; model APERTO) at Era's Lucknow Medical College with MIPAV software (Medical Image Processing, Analysis, and Visualization, version 3.0; NIH, Bethesda, MD). Infarct volume was measured using the standard radiological techniques.

Statistical Analysis

The data was compiled and analyzed using MS Excel (R) office 365, Graph Pad prism 8.4.2 and SPSS version 21. Descriptive statistics were presented in the form of proportions/percentages for categorical variables and mean & standard deviation for continuous data variables. Fisher Exact test/Chi square test was used for the comparison of proportions (Categorical variables). Continuous variables were analyzed using the Mann Whitney test/student T test (Independent group/Unpaired data) and Wilcoxon sign rank test/Paired T test (for paired data) based on the normality of the data. Multigroup comparison was done using Two-way ANOVA assuming normal distribution of data. P value of <0.05 was considered significant.

Results

Sixty-five patients of acute ischemic stroke with mean age of 58.82±12.47 (Range - 23-82) years were included in the analysis. There was a male preponderance (66.20%). More than 50% of the patients were overweight or obese. Hypertension (72.30%) and diabetes (53.80%) were the most common comorbidities seen in the study. A summary of the baseline lipid profile and glycemic parameters have been shown in Table 1. The mean vitamin D3 levels in the study were 37.81±25.00 nmol/L with a range of 7.5-150 nmol/L. Most of the patients were either deficient (28, 43.10%) or severely deficient (20, 30.80%) in vitamin D3 levels. A summary of the overall baseline parameters has been given in Table 1.

Volume of stroke and Vitamin D3 level were found to be inversely correlated with a Pearson's corelation coefficient of -0.201. The extent of correlation was weak and statistically non-significant (P=0.109) (Figure 1).

A higher vitamin D3 level was observed among patients with lower infarct volume i.e.,

<10 cc (42.31±30.96 nmol/L) and 10-20 cc (43.30±26.08 nmol/L) as compared to those having higher infarct volume i.e., 20-30 cc (37.50±17.59 nmol/L) and >30 cc (30.34±17.71 nmol/L). The difference was not significant statistically (P=0.385) (Table 2).

A higher infarct size was observed among severe vitamin D3 deficient and deficient of vitamin D (60.69±78.85 & 67.44±99.82 cc respectively) as compared to vitamin D3 insufficient (16.63±25.84 cc) and having Normal vitamin D3 levels (11.82±16.21 cc), but this association was not found to be significant statistically (P=0.197) (Table 3).

A comparison of the clinico-demographic variables was done for the stroke patients based on the vitamin D3 status. It was observed that the only significant variable between the two groups was a positive family history of cerebrovascular disease. There was no significant difference between the two groups in terms of other parameters (Table 4).

Discussion

Li *et al.* [6] in their study reported the median age of patients as 64 years (IQR 56-75 Years) and a dominance of females (53.2%), Wang *et al.* [7] reported the median age as 65 (IQR 56-75 Years) and a dominance of males (60.4%). Huang *et al.* [8] on the other hand reported the median age to be even higher at 68 years (IQR 54-76) years and reported a dominance of males (59.2%). Median age of patients reported by Nie *et al.* [9] was 59 years (IQR 46-66 Years) and proportion of males as 53%. Ji *et al.* [10] reported the median age as 65 Years (IQR 56-75 Years) and proportion of males as 59.9%. Most of these studies have been done on Chinese patients which can introduce a bias due to population level differences.

Li *et al.* [6] showed the prevalence of hypertension, diabetes, smokers, and other risk factors at 68.5%, 26.4%, 13.6% and 48.2% respectively. Wang *et al.* [7] in their study reported hypertension, diabetes, hypercholesterolemia, coronary heart disease, atrial fibrillation, and family history in 72.1%, 39.9%, 42%, 20.2%, 28.2% and 34.8% patients respectively. The infarct volume ranged from 0.84 to 320 cc with a mean infarct volume of 51.71±81.66 cc. In the study by Huang *et al.* [8] the median infarct volume was reported to be 32 ml (IQR 10-49 ml). Median infarct volume was reported to be 28 ml (IQR 24.2-27.3) by Nie *et al.* [9] in their study while Ji *et al.* [10] reported it to be 26 ml (IQR 8-42 ml). Infarct size estimation with variable accuracy is a possible reason for the heterogeneity across studies.

Park *et al.* [11] in their study reported the vitamin D3 deficiency in 68.8% of ischemic stroke patients in their study and found only 13.6% patients with optimum vitamin D levels.

Our study showed a weak negative corelation between the two parameters (r= -0.201) which was similar to the findings of Turetsky *et al* (r= -0.228, P=0.034) (12). One possible explanation for the significance in Turetsky *et al* [12] was the presence of relatively higher proportion of patients with normal vitamin D3 levels. There was an element of skewness in terms of the infarct volume (as suggested by the fact that 67.7% patients had stroke volume smaller than the mean value) which may have impacted the corelation trends. Wang *et al* [7] showed similar negative corelation between the two parameters in 326 cases and the strength of correlation was only -0.355.

In present study, we also evaluated a relationship of vitamin D3 with other variables and did not find a significant association with any of these variables except family history of cerebrovascular diseases which were significantly higher in vitamin D3 deficient as compared to patients with vitamin D3 sufficiency/insufficiency. Turetsky [12] conducted a similar analysis and found a significant association with age, atrial fibrillation, tobacco, and alcohol abuse only.

Table 1: Baseline parameters

Parameter	Value
Age (Mean±S.D) (in years)	58.82±12.47
Range	23-82
Gender n (%)	
Male	43 (66.20)
Female	22 (33.80)
BMI (Mean±S.D) (in kg/m2)	25.14±4.55
BMI category	
Underweight	4 (6.20)
Normal weight	28 (43.10)
Overweight	25 (38.50)
Obese	8 (12.30)
Comorbidity	
Diabetes n (%)	35 (53.80)
Hypertension	47 (72.30)
Other risk factors	14 (21.50)
Family history of CVDs	15 (23.10)
Smoking	39 (60)
Hemodynamic parameters	
Systolic BP (mmHg)	152.46±29.95
Diastolic BP (mmHg)	90.31±16.30
Pulse rate (per min)	88.14±12.20
Lipid profile	
Total cholesterol (mg/dl)	159.72±46.28
Triglyceride (mg/dl)	155.48±80.43
HDL (mg/dl)	35.05±9.33
LDL (mg/dl)	95.45±40.56
VLDL (mg/dl)	30.58±13.44
Glycaemic profile	
FBS (mg/dl)	164.32±80.53
HbA1c (%)	7.27±2.11
Infarct Volume (in cc)	
≤10	27 (41.50)
10.1-20	7 (10.80)
20.1-30	10 (15.40)
>30	21 (32.30)
NIHSS category	
Mild (<5)	9 (13.80)
Moderate (5-15)	40 (61.50)
Severe (>15)	16 (24.60)
Vitamin D levels	
Severe deficiency (<25 nmol/L)	20 (30.80)
Deficiency (25-49.9 nmol/L)	28 (43.10)
Insufficiency (50.0-75.0 nmol/L)	12 (18.50)
Normal (>75 nmol/L)	5 (7.7)

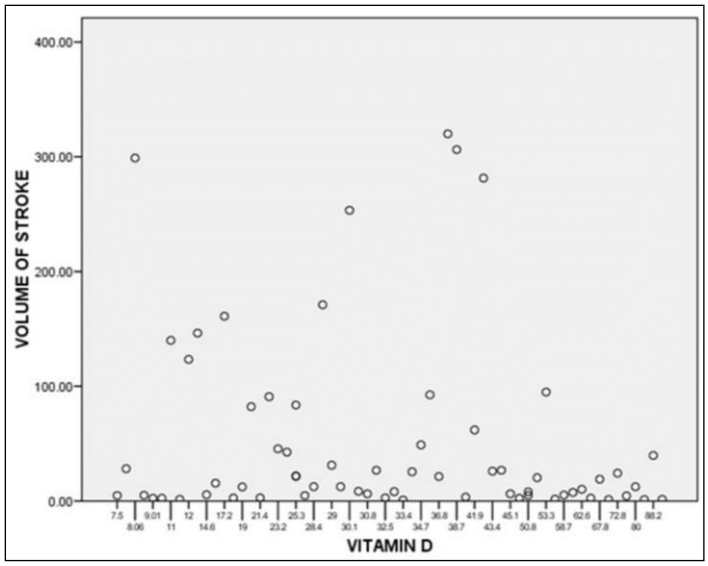

Fig 1: Infarct volume and Vitamin D levels

Table 2: Mean Vitamin D level and Infarct Volume

Infarct Volume	Number of patients	Vitamin D (nmol/L)	P value	F statistic
<10 cc	27	42.31±30.96	0.385	1.032
10-20 cc	7	43.30±26.08		
20-30 cc	10	37.50±17.59		
>30 cc	21	30.34±17.71		

Table 3: Vitamin D status and Infarct volume

Vitamin D status	Number of patients	Infarct volume	P value	F statistic
Severe deficiency	20	60.69±78.85	0.197	1.607
Deficiency	28	67.44±99.82		
Insufficiency	12	16.63±25.84		
Normal	5	11.82±16.21		

Table 4: Association of Vitamin D deficiency in stroke patients with different clinicodemographic variables

Characteristic	Vitamin D Deficiency (n=48)		Normal+ Insufficiency (n=17)		'p' value	
	Mean	SD	Mean	SD	't'	'p'
Age (years)	58.61	10.56	63.59	15.27	-1.382	0.173
Volume of stroke (cc)	48.43	80.96	15.22	23.02	1.652	0.105
NIHSS score	11.08	5.87	9.18	4.73	1.170	0.248
TC (mg/dl)	147.78	38.74	141.12	27.16	0.637	0.527
TG (mg/dl)	121.33	39.11	122.00	34.94	-0.060	0.953
HDL (mg/dl)	37.08	9.80	39.47	6.27	-0.917	0.364
LDL (mg/dl)	83.64	30.26	73.41	20.72	1.258	0.214
VLDL (mg/dl)	24.27	7.82	24.40	6.99	-0.060	0.953
Fasting blood sugar (mg/dl)	165.25	71.21	168.35	95.84	-0.132	0.895
HbA1c (%)	7.03	1.87	6.54	1.83	0.887	0.379
SBP (mmHg)	147.78	30.06	151.18	30.39	-0.383	0.703
DBP (mmHg)	89.17	17.46	88.24	16.29	0.185	0.854
Heart rate (bpm)	88.44	11.66	89.53	12.89	-0.306	0.761
BMI (kg/m2)	25.03	4.99	23.18	2.72	1.423	0.161
	No.	%	No.	%	□2	'p'
Female sex	14	29.2	8	47.1	1.795	0.180
Smoking	31	64.6	8	47.1	1.606	0.205
Diabetes	27	56.3	8	47.1	0.427	0.514
Hypertension	33	68.8	14	82.4	1.160	0.281
Other risk factors	9	18.8	5	29.4	0.844	0.358
Family history	15	31.3	0	0.0	6.906	0.009

Conclusion

We concluded that vitamin D3 deficiency was highly prevalent in stroke patients, yet it was unrelated with any of the clinical and demographic variables including the infarct size. An inverse correlation between infarct size and vitamin D3 levels was observed but the level of correlation was weak and statistically non-significant. The findings corroborated with the published literature in this domain and needs larger studies for further validating the findings.

Acknowledgement
Conflict of interests
Financial declaration
Ethical clearance

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