ORIGINAL ARTICLE

ASSESSMENT OF VITAMIN D LEVEL IN CEREBRO-VASCULAR ACCIDENT PATIENTS IN EASTERN INDIA

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ABSTRACT

Aims and objectives: Vitamin D in addition to its effect on bone- mineral homeostasis has many extra-skeletal effects. Recently its association with cardiovascular disease, diabetes, hypertension are well described. In our study we have tried to find out any of its association with cerebrovascular accident (CVA) patients.

Material and Methods: In a cross sectional study serum 25 OH vitamin D_3, parathormone, calcium and phosphate were estimated in 38 CVA patients and 46 age and sex matched controls.

Results: Vitamin D level was found to be low in CVA patients [mean 20.01(±7.13) ng/ml] irrespective of their sex, residence, diabetes and hypertension. However there was no significant difference with control population [mean 20.37(±5.74) ng/ml; P= 0.79].

Conclusion: There is no significant difference in vitamin D level between CVA patients or non-CVA population. So the role of vitamin D deficiency in the causation of CVA needs reevaluation, especially in Indian patients.

Key Words: 25 hydroxy vitamin D_3; Parathormone; Cerebrovascular accident.

INTRODUCTION

Ever since its discovery vitamin D has been associated with mineral homeostasis and musculoskeletal health[1,2,3,4] through its actions on intestine, bone and kidney[3,5,6]. However after 1990 many researchers have described the extra-skeletal effects of the vitamin[3,7,8,9,10]. Recent literatures describes the association between low level of vitamin D and cardiovascular disease[11,12,33], peripheral vascular disease[13,27], diabetes[14,15], hypertension[16,31,32], multiple sclerosis[17], various cancers [17] etc. Cerebrovascular disease[30,34] (CVA), which has a similar pathophysiology like other macrovascular diseases, is an important cause of mortality and morbidity all over the world[18-23]. Although various modifiable and non-modifiable factors are described to be etiologically related to CVA, little is known about the effect(s) of vitamin D on CVA. To expand our knowledge on the effects of vitamin D on CVA a cross-sectional study was undertaken to assess the level of vitamin D in CVA patients and compare with suitable control.

MATERIALS AND METHODS

The study was done between January 2011 and December 2011, in Medical College, Kolkata. Patients admitted under the department of General Medicine with rapidly developing signs of focal or global disturbances of cerebral function lasting more than 24 hrs with no apparent cause other than vascular origin were clinically labeled as CVA and subjected to non-contrast CT scan of brain. Only neuroimaging confirmed CVA patients were included in the study. Purposive method of sampling was used. Patients with known valvular heart disease, atrial fibrillation, hypercoagulable state, vasculitis, blood dyscrasia, known patients of cerebral arterio-venous malformation, diabetic nephropathy, and chronic kidney disease, chronic liver disease were excluded. Patients with any other co-morbid diseases were also excluded from the study. None of the patients were on vitamin D supplementation.

Blood samples were collected in every CVA patients and analysed for serum 25 OH vitamin D_3 (by chemiluminiscent assay using automated instrument LAISION from Diasorin Company); parathormone (by chemiluminiscent assay using automated instrument CENTAUR from Siemens Company); calcium; and phosphate (automated instrument RXN from Siemens Company). To assess the risk factors of CVA, along with detailed history and clinical examination, complete hemogram, fasting and post prandial blood sugar and lipid profile were done. Electrocardiography (ECG), Echocardiography, Prothrombin time, APTT, Antinuclear antibody (ANA) and vasculitis profile, MRI brain, MR angiography was done to find out rarer risk factors wherever indicated.

Control population was selected from General Medicine out-patient department through purposive sampling. They were matched for age, sex and two important risk factors, diabetes and hypertension. Control population was apparently healthy with no history of CVA, cardiovascular disease (CVD), peripheral vascular disease (PVD). They were investigated for serum vitamin D, calcium and phosphate level. Normal range for important study parameters are described in table 1. In absence of any standard guideline on the normal level of vitamin D in Indian population we selected the normal range described in table 1 for our study.

All the patients or their relatives (where patient was unable to give consent) and controls gave written informed consent. The study was approved by the ethical committee of Medical College, Kolkata.

Statistical Analysis: All the variables were expressed as mean (± SD). Numerical variables were compared using student unpaired 't' test. Categorical variables were compared using Chi square test. Pearson test was used for correlation. Microsoft Excel 2010 and SPSS 17 software for windows were used for statistical analysis. P value of <0.05 was considered significant.

Table-1: Normal value of important parameters

Parameter	Normal range
25-OH Vitamin D_3(ng/ml)[1]	sufficient >30 insufficient 20-30 deficient <20
Parathormone (pg/ml) (ADVIA Centaur assay manual)	9.5-75 [age<70yrs] 4.7-114 [age>70yrs]
Calcium(mg/dl)	8.7-10.2
Phosphate(mg/dl)	2.5-4.3

RESULT

A total 38 CVA patients and 46 controls were included. Mean age of the CVA patients were (60.55± 12.28 yrs) comparable to that of controls (60.07±7.39 yrs, P=0.82). Both groups had comparable sex distribution (CVA patients male:female 27:11, control male:female 32:14, P=0.53). CVA patients were divided into subgroups based on CT findings, namely, infarction, intracerebral haemorrhage (ICH) and sub-arachnoid haemorrhage; based on residence as rural (non-corporation area) and urban (corporation area); and 4 subgroups based on the history whether they were hypertensive and/or diabetic [**Table 2**].

Table 2: Basic demographic parameters of the study and control

	CVA patients	Control	P Value
Total number of patients	38	46	
Age	60.73(12.40) yrs	60.06(7.39) yrs	0.82
Male	27(71.05%)	32(69.6%)	0.88
Female	11(28.94)	14(30.4%)	0.88
Residence			
Rural	14(36.84%)	15(32.6%)	0.68
Urban	24(63.15%)	31(67.4%)	0.68
Type of CVA		Not Applicable	
ICH	20(52.63%)		
Infarct	16(42.10%)		
SAH	2(5.26%)		
Non HTN, Non DM	12(31.57%)	15(32.60%)	0.91
Only hypertensive	16(42.10%)	19(41.30%)	0.94
Only diabetic	5(13.15%)	6(13.04%)	0.98
Both HTN & DM	5(13.15%)	6(13.04%)	0.98

CVA- Cerebrovascular accident, ICH-Intracranial Hemorrhage, SAH- Sub-arachnoid Hemorrhage, HTN- Hypertension, DM-Diabetes

Table 3: Vitamin D, Calcium level results in CVA patients

	Vitamin D Mean±SD	P value	Calcium Mean±SD	P value
Gender				
Male	21.85±6.65	**0.01**	8.71±0.64	0.35
Female	15.48±6.47		8.5±0.58	
Area				
Rural	20.24±6.60	0.88	8.70±0.69	0.75
Urban	19.87±7.56		8.63±0.59	
NHT				
Non HTN	19.62±8.08	0.76	8.70±0.46	0.71
HTN	20.32±6.46		8.62±0.74	
DM				
Non DM	20.68±7.46	0.33	8.59±0.65	0.31
DM	18.12±6.09		8.83±0.52	
Type of CVA				
ICH	21.69±7.68	0.16	8.86±0.62	0.082
Infarct	18.31±6.09		8.50±0.55	

CVA- Cerebrovascular accident, ICH-Intracranial Hemorrhage, SAH-Sub-arachnoid Hemorrhage, HTN- Hypertension, DM- Diabetes

Levels of vitamin D and calcium level in CVA patients are shown in **Table 3**.Mean vitamin D level of the CVA patient's was 20.01(±7.13) ng/ml, parathormone 45.02(±28.28) pg/ml, calcium 8.65(±0.62) mg/dl, phosphate 3.39(±0.94) mg/dl. For control it was vitamin D 20.37(±5.74) ng/ml, calcium 8.63(±0.44) mg/dl, phosphate 3.20 (±0.64) mg/dl. Serum 25 OH vitamin D levels were compared between case and control but the difference was not significant (p=0.79). Similar comparisons were done for serum calcium and phosphate as well, which too were insignificant (p=0.87 for Calcium, p= 0.30 for phosphate). Based on the normal level mentioned in table 1 around 95% (36 of 38) of the study population were not vitamin D sufficient, 50% had low calcium, whereas only 10% had low phosphate and 84% had normal PTH.

Table 4: Result of epidemiological & biochemical data in case & control, mean (SD)

		Age (yrs)	Vitamin D(ng/ml)	PTH(pg/ml)	Calcium(mg/dl)	Phosphate(mg/dl)
Population	Case(38)	60.55(12.3)	20.01(7.13)	45.02(28.3)	8.65(0.62)	3.39(0.94)
	Control(46)	60.07(7.39)	20.37(5.74)		8.63(0.44)	3.20(0.64)
	P Value	0.83	0.79		0.87	0.30
Male	Case(27)	60.48(12.4)	21.85(6.65)	46.91(31.1)	8.71(0.64)	3.24(0.75)
	Control(32)	59.31(7.82)	20.55(6.31)		8.66(0.42)	3.18(0.64)
	P Value	0.67	0.44		0.69	0.71
Female	Case(11)	60.73(12.5)	15.48(6.47)	40.38(20.1)	8.50(0.58)	3.75(1.28)
	Control(14)	61.79(6.22)	19.97(4.35)		8.58(0.5)	3.26(0.66)
	P Value	0.80	**0.05**		0.72	0.26
Rural	Case(14)	62.64(13.1)	20.24(6.60)	34.45(16.7)	8.70(0.69)	3.35(0.91)
	Control(15)	58.73(5.44)	19.99(5.75)		8.47(0.46)	3.19(0.56)
	P Value	0.31	0.91		0.30	0.57
Urban	Case(24)	59.33(11.9)	19.87(7.56)	51.18(31.9)	8.63(0.59)	3.41(0.98)
	Control(31)	60.71(8.18)	20.56(5.82)		8.71(0.42)	3.21(0.68)
	P Value	0.61	0.70		0.53	0.36
NonHTN/DM	Case(12)	62.17(16.2)	20.55(8.30)	44.48(29.2)	8.63(0.47)	3.20(0.79)
	Control(15)	60(7.69)	20.85(5.51)		8.72(0.26)	3.36(0.74)
	P Value	0.67	0.91		0.51	0.59
Only HTN	Case(16)	60.06(10)	20.78(7.03)	44.31(25.5)	8.56(0.78)	3.64(1.14)
	Control(19)	60.05(7.82)	20.92(5.84)		8.42(0.53)	3.12(0.54)
	P Value	0.99	0.94		0.52	0.11
Only Diabetic	Case(5)	60.20(16.0)	17.38(7.89)	27.06(17.4)	8.86(0.42)	3.66(0.80)
	Control(6)	57.67(6.21)	18.73(5.34)		9.01(0.24)	3.11(0.73)
	P Value	0.72	0.74		0.47	0.27
Both	Case(5)	58.60(4.93)	18.86(4.44)	66.55(36.2)	8.80(0.66)	2.80(0.255)
	Control(6)	62.67(7.28)	19.11(7.30)		8.72(0.37)	3.16(0.64)
	P Value	0.31	0.94		0.81	0.26

CVA- Cerebrovascular accident, ICH-Intracranial Hemorrhage, SAH- Sub-arachnoid Hemorrhage, HTN- Hypertension

Detailed subgroup analysis of CVA patients [**Table 4**] revealed vitamin D (in ng/ml) was significantly lower in females 15.48 (6.47) compared to males 21.85 (6.65) (p=0.01). Even though vitamin D was lower in urban 19.87 (7.56) compared to rural 20.24 (6.60) population (p=0.88), non-hypertensive 19.62 (8.08) to hypertensive 20.32 (6.46) (p= 0.76), diabetic 18.12 (6.09) to non-diabetic 20.68 (7.46) (p= 0.33) and infarct 18.31 (6.09) to ICH 21.69 (7.68) (p= 0.16) patients; how-

ever, none of them were significant with P>0.05. Similarly calcium level (in mg/dl) was lower in females 8.5 (0.58)compared to males 8.71 (0.64) (p= 0.35), urban 8.63 (0.59) compared to rural 8.70 (0.69) population (p= 0.75), hypertensive 8.62 (0.74) to non-hypertensive 8.70 (0.46) (p= 0.71), non-diabetic 8.59 (0.65) to diabetic 8.83 (0.52) (p= 0.31) and infarct 8.5 (0.55) to ICH 8.86 (0.62) (p= 0.08) patients, again however, none of them were significant. Vitamin D level was lowest in the diabetic. Similar analysis was done for control group as well; however none of the differences were significant. Infarct patients had lower mean vitamin D 18.31 (6.09) to 21.69 (7.68), lower PTH 40.32 (23.30) to 45.23 (31.21), lower calcium 8.50 (0.55) to 8.86 (0.62), and lower phosphate 3.41 (0.85) to 3.51 (0.98) when compared to ICH.

Vitamin D level was found to be significantly lower in male diabetic compared to male non-diabetic patients (p=0.03). Such analysis for vitamin D using Students unpaired t-test with hypertension, diabetes as independent factors in all the other subgroups were not significant with p>0.05.

There was no correlation between the level of vit D and parathormone, vitamin D and calcium, calcium and phosphate, or age and vitamin D.

DISCUSSION

Vitamin D acting through vitamin D receptor (VDR) leads to calcium and phosphate absorption from intestine, reabsorption of the same from kidney, suppression of parathyroid hormone secretion thus maintaining bone-mineral health.[6] However in the last two decades after the discovery of VDR in various other body tissues burst of research activities tried to elucidate extraskeletal effects of vitamin D[17,1]. It was found that the active form of vitamin D i.e. 1,25 $(OH)_2$ vitamin D_3 can be produced locally without the help of renal 1, α hydroxylase[25,2]. At the cellular level presumably through VDR, vitamin D promotes cell differentiation and inhibits cell proliferation[26]. Similarly it influences proliferation of vascular smooth muscles along-with their migration and gene expression. It also influences elastogenesis and immunomodulation. All these are processes involved in the pathogenesis of atherosclerosis.[27] In addition vitamin D can modulate renin secretion thus influence blood pressure as well.[28]Thus it seems that increased incidence of atherosclerosis in vitamin D deficient patients are biologically plausible and through this vitamin D may influence various macrovascular disease processes. In support various cross-sectional & prospective studies have demonstrated vitamin D deficiency in cardiovascular disease, peripheral vascular disease, and cerebro vascular accident (CVA) patients.[29,27,30] Forman et al[16] followed 1811 non-hypertensive participants for 4 years. Those with baseline 25(OH) D levels 15 ng/mL had a relative risk for incident hypertension of 2.67 (95% CI: 1.05 to 6.79) compared with those whose levels were 30 ng/ml. Jorde et al[31] found a significant inverse association between vitamin D and hypertension too. There are at least 13 drug trials on blood pressure lowering effect of vitamin D.[32] In one of the first reported studies of vitamin D and coronary artery calcification(CAC) mass, Watson KE et al [11]observed a statistically significant inverse association between 1,25(OH) D concentrations and CAC among 173 participants at increased risk for CAD. As early as 1990 , a small New Zealand case-control study evaluated vitamin D levels in patients with acute myocardial infarction (MI) compared with a control group and found significantly lower vitamin D levels in those with ischemic heart disease.[33] Kenneth ES Poole[30] in 2005 compared the serum 25-dihydroxyvitamin D levels of 44 patients admitted to an acute stroke unit with first-ever stroke with results obtained by measuring 96 healthy ambulant elderly subjects every 2 months for 1 year. The mean *Z* score of vitamin D in acute stroke was 1.4 SD units (95% CI 1.7-1.1), with 77% of patients falling in the insufficient range. Stefan Pilz, in his study[34], concluded that low levels of 25(OH)D and $1,25(OH)_2D$ are independently predictive for fatal strokes, suggesting that vitamin D supplementation is a promising approach in the prevention of strokes. In line with the foundation works by Stefan Pilz and Kenneth E.S. Poole, our study has also found vitamin D deficiency to be highly prevalent in CVA patients. About 95% (36 of 38) of our study population was below sufficiency level for vitamin D. Poole et al[30] mentions that the half-life of 25(OH)vitamin D_3 is approximately 3wks. Acutely reduced 25OHD attributable to a decline in hormone synthesis or existing stores (largely found in body fat) seems unlikely because there was no relationship between serum 25(OH)D and time between stroke and 25(OH)D sampling. So it seems likely that this deficiency has been present from before the stroke. The mean level of vitamin D in our study (20.01 ng/ml) was higher than what Stefan Pilz found (27.5 nmol/L or 11.01 ng/ml) despite higher percentage of females (38.1% to 28.94%) in his study. Several explanations seem likely. Mean age of LURIC study stroke patients was 69.3yrs (64-76yrs) whereas our CVA patients had a mean age 60.55yrs (35-85yrs) .Thus age

could be a confounding factor. Percentage of diabetics in LURIC study stroke patients was 50% compared to 26.3% in our CVA patients. As diabetics have a lower mean vitamin D level this may have confounding effect as well. Adding to these is the higher sun exposure in West Bengal as it is at lower latitude than Germany where LURIC study was performed. Also because of hot and humid weather people of West Bengal prefer wearing loose fitting clothes with higher percentage of exposed body part which further increase the sun exposure and hence the subsequent vitamin D level. Despite finding higher vitamin D level in our CVA patients we must also keep in mind Indian people are especially prone to develop vitamin D deficiency because of dietary inadequacy (Khadilkar AV[35]) , vegetarian diet, genetic factors (Awumey et.al[36]), cultural beliefs, repeated unplanned pregnancies, growing urbanization, pollution (Babu et.al[37]) as is described by DrVikram Londhey[38] in his article 'Vitamin D deficiency , Indian scenario'. The mean parathormone level was normal (45.02pg/ml) like previous studies (30 ng/ml in LURIC study). In agreement with Poole et al's finding[30] usual inverse relationship between log 25-OH & log parathormone(PTH) concentration was not observed (correlation coefficient 0.20) as bone resorption following CVA tries to maintain normal serum calcium level suppressing PTH secretion.[30,34] However 50% of our study population had low serum calcium level. Mean calcium of our study is lower (8.65 mg/dl, range 7.3-9.9) than the lowest value found by Stefan Pilz (mean 2.33 mmol/L, i.e. 9.32mg/dl, range 2.24-2.43 mmol/L, i.e. 8.96-9.72 mg/dl). Bhatia V[39] writes dietary calcium intake in Indians is low which may have been reflected in our study as low serum calcium.

However when cases were compared with age and sex matched control population vitamin D, calcium, phosphate were not significantly different. This is in contrast to Poole et al' study[30] result. The low vitamin D level in our control population could be due to sampling error as most of our controls were urban living (urbanization decrease vitamin D level, as Dr Londhey mentioned[38] many were diseased (26% of control population were diabetic who had lower vit D levels 18.73ng/ml), and instead of collecting vit D samples throughout the year most were taken during rainy season. In rainy season cloudy sky may prevent adequate sun-exposure lowering the serum vitamin D level.

Subgroup analysis revealed mean age of CVA was around 60yrs. However mean Vitamin D level of those aged over 60yrs was 20.48 ng/ml. Thus the normal inverse relation between age and vitamin D level was absent. In fact there was no correlation between age and vitamin D level . Vitamin D level was significantly less in CVA females compared to CVA males (p=0.01) ; possibly because of lower sun-exposure as most Indian females stay inside the house, cultural beliefs regarding use of 'purdha' and 'burqa', repeated pregnancies & dietary inadequacy[38]. It was lower in urban compared to rural population likely because of pollution[37] and inadequate sun exposure due to sedentary lifestyle[38]. Vitamin D was lower in non-hypertensive to hypertensive, diabetic to non-diabetic and infarct to intracranial hemorrhage(ICH) patients, however, none of them were significant with P>0.05. Diabetics however had the lowest serum vitamin D in both the study and control group. Similarly calcium level was lower in females compared to males, urban compared to rural population, hypertensive to non-hypertensive, non-diabetic to diabetic and infarct to ICH patients, again however, none of them were significant with P>0.05. Vitamin D level was also compared between male hypertensive or non-hypertensive and male diabetic or non-diabetic CVA patients, similar comparison was done for female CVA patients as well. Urban CVA patients was divided into hypertensive or non-hypertensive subgroups and diabetic or non-diabetic subgroups for comparison of their vitamin levels. Similar analysis was done for rural CVA patients as well. Two major types of CVA patients, intra-cerebral hemorrhage (ICH) and infarct were divided into hypertensive or non-hypertensive and diabetic or non-diabetic group. Except between male diabetic or non-diabetic subgroup none of these comparisons yielded significant result. This means vitamin D level is low irrespective of the blood pressure or diabetes status. We propose further studies to be done on vitamin D, parathormone, calcium and phosphate levels in acute stroke patients to make any further comments.

CONCLUSION

Vitamin D level is low in CVA patients irrespective of their sex, residence, diabetes and hypertension. However it is equally low in age, sex matched control population as well with no significant difference between CVA patients or non-CVA population. So the role of vitamin D deficiency in the causation of CVA needs reevaluation, especially in Indian patients.

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