Section: Medicine

Original Research Article

STUDY ON SERUM VITAMIN D LEVEL AND ITS ASSOCIATION WITH SEVERITY AND OUTCOME OF ACUTE ISCHEMIC STROKE

Vinayanand Jha[1], Vikas Kumar[2], Amit Anand[2]

[1]Associate Professor, Department of Medicine, Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga, Bihar, India.
[2] Junior Resident, Department of Medicine, Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga, Bihar, India.

Received : 21/04/2023
Received in revised form : 26/05/2023
Accepted : 10/06/2023

Keywords:
Cerebrovascular accident, vitamin D, calcium, acute ischemic stroke, NIH score and mRS score.

Corresponding Author:
Dr. Vikas Kumar,
Email: drvikaskrpmc@gmail.com

DOI: 10.47009/jamp.2023.5.3.309

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 1536-1547

Abstract

Background: Vitamin D deficiency was discovered to be quite common in cerebrovascular accident (CVA) patients in hospital-based observational investigations involving neuroimaging confirmed CVA patients. So, the current study has been conducted in Darbhanga Medical College and Hospital (DMCH), Bihar, where the role of Vitamin D is established with acute ischemic stroke patients. **Materials and Methods:** The study population was selected as patients with acute ischemic stroke attending MOPD or admitted to DMCH for one year of the study period, and the sample size was 50 or over. The simple design was acute ischemic stroke patients coming in contact with DMCH where written informed consent could be collected will be part of this study. The inclusion criteria of this study were patients with acute ischemic stroke (symptoms of sudden onset Neuro deficit persisting for >24 hours) documented by CT scan of the brain and exclusion criteria of this study were individuals with vasculitis, atrial fibrillation, a hyper-coagulable condition, and valvular heart disease. Also, the result of NIH and mRS scores showed high in patients with low Vitamin D levels (<20 ng/ml). **Results:** As a result, careful consideration must be given to reconsidering the vitamin's role in macro-vascular diseases in order to develop a healthcare strategy to lower the mortality and morbidity resulting from these macro-vascular events. **Conclusion:** We draw the conclusion that vitamin D deficiency is widespread in Bihar's population as a whole.

INTRODUCTION

Stroke, or cerebrovascular accident, is a leading cause of disability and death worldwide. In India, 20% of all hospitalised patients are diagnosed with neurological illness, and stroke accounts for 1% of all hospital-related deaths. A ‘stroke' describes a rapid onset of a focused neurologic condition, most commonly due to cerebrovascular disease.[1]

Any brain abnormality brought on by a pathologic blood vessels process, such as obstruction of the lumen by an embolus/ thrombus, vessel break, permeability change of the vessel wall, or high viscosity or changes in the quality of the blood, is referred to as cerebrovascular disease. Stroke incidence rates have risen dramatically in recent years.[2]

Numerous variables increase a person's likelihood of stroke, including diabetes mellitus (DM), hypertension, an imbalance of lipids, an irregular or often very rapid heart rhythm, and smoking. However, in many situations, the underlying causes remain hidden. As a result, there is a plethora of epidemiological research aimed at identifying and developing unique risk factors, the function of which is still up for question, as is the precise nature of the relationship with stroke.

One such risk factor that has received much attention in recent years is vitamin D deficiency. Vitamin D is a steroid molecule, and it's synthesized in the epidermis from cholesterol and absorbed in the intestines. A growing body of research on its biological roles has garnered attention from the scientific, medical, and nutritional sectors. Recent years have seen increased interest due to its link to a reduced risk of several chronic illnesses.

Vitamin D insufficiency affects people all around the world. Hypovitaminosis D has been linked to many diseases and conditions and, in addition, is known to function as a critical regulator of calcium and bone-related metabolism, systemic-related hypertension, heart-related disease, diabetes mellitus (DM), metabolic syndrome, peripheral artery disease, cancer, and autoimmune diseases has been linked to it.[2]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Very few research studies have linked vitamin D deficiency to an increased risk of stroke and other cerebrovascular accidents (Stroke). It has been hypothesised that a lack of vitamin D might lead to endothelial dysfunction. Because of this, it is crucial to the development of stroke pathology. Several molecular pathways connecting Vitamin D with stroke and associated risk factors have been established, beginning with the finding that the endothelium of blood vessels expresses vitamin D receptors (VDR) and 1 hydroxylase, which is found in both neurons and glial cells. The primary mechanism by which vitamin D protects against cerebrovascular disease and associated risk factors is its upkeep of gene transcription.[2]

While the incidence of stroke among Asians is rising, very little information is known on the possible link between Vitamin D and this condition. Numerous experiments are being conducted to evaluate vitamin D's connection with stroke and determine whether it may be used to prevent stroke. The moment of an acute ischemic stroke would be a good opportunity to assess vitamin D levels. As a result, the goal of this investigation was to look at level of vitamin D among the people who had acute ischemic strokes and find any associations that might be significant.[3]

MATERIALS AND METHODS

Study Area: Darbhanga Medical College and Hospital.

Study population: Patients with acute ischemic stroke attending MOPD or admitted to DMCH.

Study period: One year.

Simple size: 50 or ever.

Simple design: Acute ischemic stroke patients coming in contact with DMCH where written informed consent could be collected will be made part of this study.

Inclusion Criteria

Patients of acute ischemic stroke (symptoms of sudden onset Neurodeficit persisting for >24 hours) documented by brain CT scan.

Exclusion Criteria

Individuals with vasculitis, atrial fibrillation, a hyper-coagulable condition, and valvular heart disease.

Study design: Hospital-based observation study.

Parameters to be used

Clinical parameters: Patients with sudden onset of neuro deficits persisting for >24 hours.

Biochemical parameters

1. Serum Vitamin D level (25 OH Vitamin D)
2. Serum parathormone level (if applicable and feasible)
3. Serum phosphate level (if applicable and feasible)
4. Serum calcium level (if applicable and feasible)
5. Complete hemogram
6. Blood sugar levels in the veins while fasting and after eating, as well as serum levels of urea and creatinine
7. Serum lipid profile
8. Serum sodium and potassium
9. Prothrombine time (if applicable and feasible)
10. Activated partial prothrombine time (if applicable and feasible)
11. Anti-nuclear antibody (ANA) and other markers of vasculitis (if applicable and feasible)
12. Coagulation profile (if applicable and feasible)

Radiological parameters

1. Echocardiographic parameters (if applicable and feasible)
2. CT scan of the brain

Electrocardiography

1. **Ethical Clearance:** The Darbhanga Medical College and Hospital's Ethics Council approved the study protocol for research studies carried out in February 2022.
2. **Informed Consent:** The case and control study groups were made aware of the study's purpose. After obtaining their written informed consent, participants willing to participate in the study were added. The study only included participants who met the inclusion and exclusion requirements.
3. **Data Collection:** A data collecting form was created to record the cases' and controls' names, ages, sexes, smoking, drug use, and any pertinent medical information, as well as their heights and weights. The cases' CT Brain reports were taken notice of.

Laboratory Investigations

- Blood samples were obtained at the time of admission to assess a variety of parameters, including the lipid profile, which comprises HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides (measured using enzymatic methods), and serum levels of 25-hydroxyvitamin D (measured by Chemo-Luminescence Immune Assay Method).
- To ensure that no interpersonal error could be discovered, the same person conducted tests in the same laboratory.

Normal Value of the Parameters

Table 1: The normal value of the parameters assessed is listed below (24, 25, and 26)

Vitamin D levels	Obesity- based on Body Mass Index (for Indian population) BMI = weight (kg)/ Height (m^2)	Lipid Profile - normal values (NCEP guidelines)
Normal 30-100ng/ml	Normal- 18.0-22.9 kg/m^2	Serum triglycerides <150mg/dl
Insufficient 10-30ng/ml	Overweight- 23.0-24.9 kg/m^2	LDL Cholesterol <100mg/dl
Deficient <10ng/ml	Obese >25 kg/m^2	HDL cholesterol

ISSN (O): 2687-5365; ISSN (P): 2753-6556

		>40 mg/dl for men >50 mg/dl for women
		Total cholesterol <200mg/dl

Statistical Tools

A Master Chart was created to store the information gathered for each of the chosen cases. Data analysis was carried out utilising the common SPSS software package (Statistics Products Services Solutions). We computed the range, frequencies, percentages, means, standard deviations, T test, and chi square, and "p" values using this software. The Kruskul-Wallis chi-square test was used to determine the significance of differences between quantitative variables, and the Yate's test was used to determine the significance of differences between qualitative variables. P values below 0.05 indicate significance. Extremely significant with a 'p' value of less than 0.01.

RESULTS

Following the methodology described above 52 CVA patients were included as study population and 52 patients were included as control population.

Table 2: Showing basic demographic parameters of the study and control

	CVA patients	Control
Total number of patients	52	52
Age	61.23 (10.07) years	59.50 (9.70) years
Male	30 (57.69%)	32 (61.54%)
Female	22 (42.31%)	20 (38.46%)
Residence		
Rural	30 (57.69%)	25 (48.08%)
Urban	22 (42.31%)	27 (51.92%)
Type of CVA		Not Applicable
ICH	22 (42.31%)	
Infract	28 (53.85%)	
SAH	2 (3.85%)	
Non HTN, Non DM	11 (21.15%)	24 (46.15%)
Only hypertensive	30 (57.69%)	17 (32.69%)
Only diabetic	24 (46.15%)	21 (40.38%)
Both HTN & DM	13 (25.00%)	10 (19.23%)

Abbreviations: CVA- Cerebrovascular accident, SAH- Sub-arachnoid Hemorrhage, DM- Diabetes Mellitus, ICH-Intracranial Hemorrhage, HTN-Hypertension.

In Table 2, basic demographic characteristics are listed. There were a total of 52 cases, including 30 men and 22 women. The control population consisted of 52 people, including 32 men and 20 women. Age and sex were matched between the study and control populations because there was no significant difference in mean ages, as shown by a p value of 0.37 from an unpaired t test, and there was no significant difference in the proportion of males to females, as shown by a significance value of 0.69 from a Chi square test.

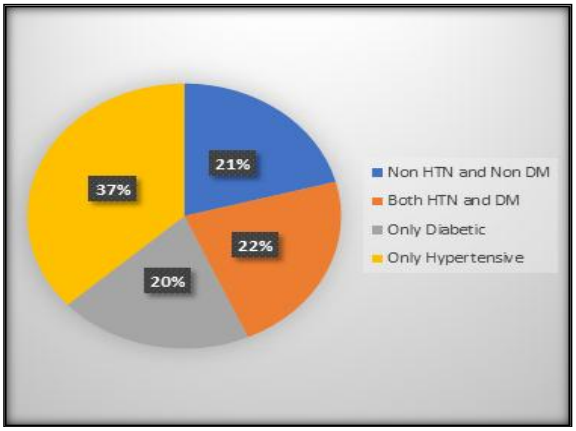

Figure 2: Doughnut diagram showing study population as per BP & DM

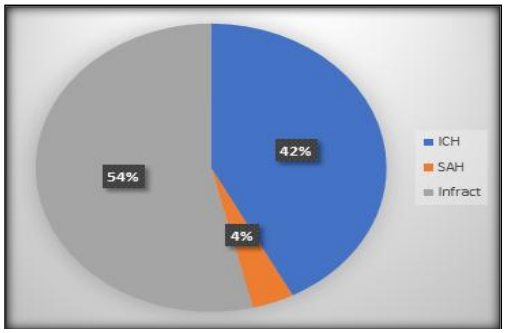

Figure 1: Doughnut diagram showing type of CVA in Study Population

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 3: Showing different study parameters in case & control

		Minimum	Maximum	Mean	Standard deviation	P value
Age (years)	Case	38	85	61.23	10.07	0.37
	Control	40	80	59.50	9.70	
Vitamin D (ng/ml)	Case	5	51	25.37	12.73	0.05
	Control	3.65	61.03	30.49	13.86	
Parathormone (pg/ml)	Case	10.4	100	44.02	26.33	0.48
	Control	11	112	47.52	22.41	
Calcium (mg/dl)	Case	7.4	9.1	8.35	0.44	0.09
	Control	7.6	9.6	8.60	0.49	
Phosphate (mg/dl)	Case	2	4.6	3.25	0.74	0.36
	Control	1.8	4.8	3.83	0.76	

Table 3 lists the mean and standard deviation for age, vitamin D, parathormone, calcium, and phosphate levels in CVA patients and controls. Mean age of the CVA patients was 61.23yrs (±10.07), mean level of vitamin D was 25.37 ng/ml (±12.73), parathormone 44.02pg/ml (±26.33), calcium 8.35mg/dl (±0.44), phosphate 3.25mg/dl (±0.74). For control mean age was 59.50 years (±9.70), mean level of vitamin D 30.49ng/ml (±13.86), parathormone 47.52pg/ml (±22.41), calcium 8.60mg/dl (±0.49), phosphate 3.83mg/dl (±0.76). Serum 25 (OH) D levels were evaluated between the case and control groups, but there was no discernible difference (p=0.05). Comparable comparisons were also made for serum parathormone, calcium, and phosphate, but none of the changes, with the exception of serum calcium, were significant (p=0.09) for parathormone (p= 0.48), for phosphate (p=0.36).

Table 4: Result of routine blood tests in CVA patients

	Mean	Std. Deviation
Hemoglobin (g/dl)	11.95	2.15
Sugar (mg/dl)	152.54	65.00
Urea (mg/dl)	31.52	9.62
Creatinine (mg/dl)	1.21	0.36
Cholesterol (mg/dl)	184.65	45.86
Triglyceride (mg/dl)	127.67	46.24
HDL (mg/dl)	35.83	9.07
SGPT (U/l)	28.85	10.51
ALP (U/l)	191.04	54.47
Albumin (g/dl)	4.09	0.56

Study population was divided into vitamin D sufficient (>30ng/ml), insufficient (20-30 ng/ml), deficient (<20ng/ml) groups and around 72% of the study population were not vitamin D sufficient (38, 39, 76). Only 16 (30.77%) of CVA patients were vitamin D sufficient, 18 (34.62%) were insufficient and rest 18 (34.62%) vitamin D deficient (Figure 3).

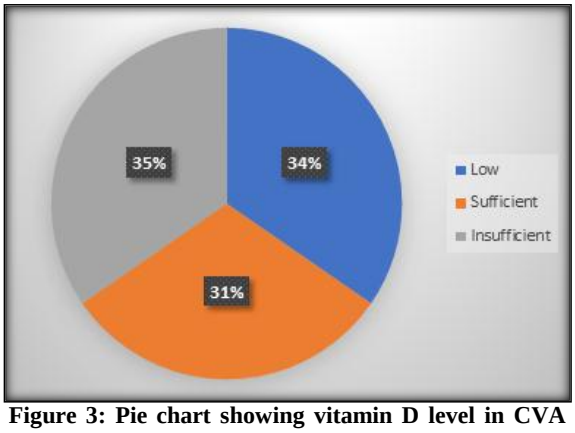

Figure 3: Pie chart showing vitamin D level in CVA patients

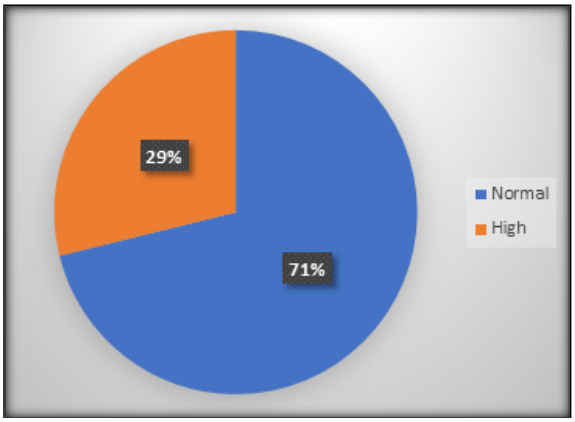

Figure 4: Pie chart showing parathormone level in CVA Patients

Parathormone level was considered normal between 8-51 pg/ml and 28% of CVA patients had high PTH, rest had normal PTH (Figure 4).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

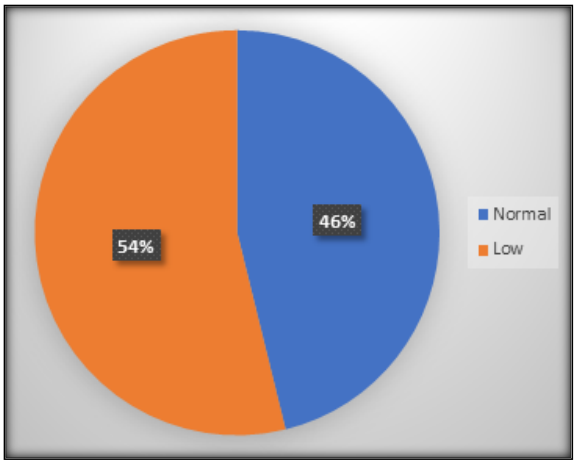

Figure 5: Pie chart showing calcium level in CVA patients

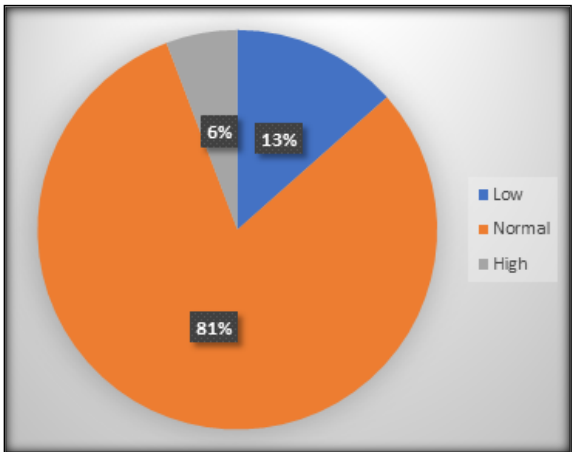

Figure 6: Pie chart showing phosphate level in CVA patients

Normal phosphate and calcium level were considered 2.5-4.5 mg/dl and 8.5-10.5 mg/dl respectively (77-81). Out of 52 CVA patients 24 (46.15%) had normal and 28 (53.85%) had low calcium level (Figure 5) whereas 42 of 52 patients (80.77%) had normal, 3 (5.77%) high and 7 (13.46%) low phosphate levels (Figure 6).

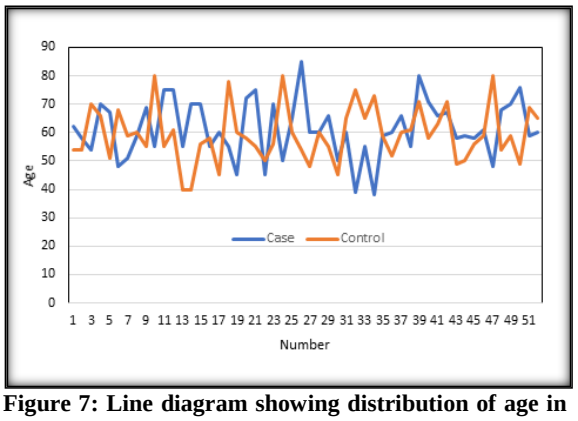

Figure 7: Line diagram showing distribution of age in case & control

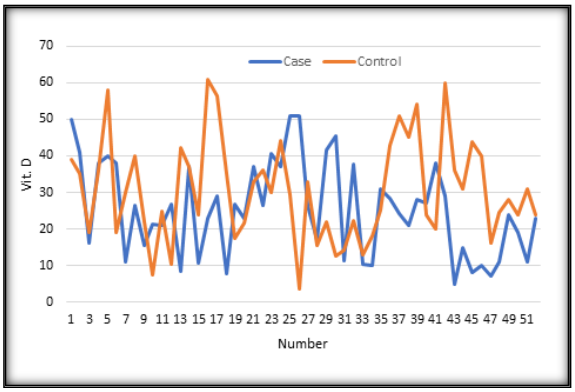

Figure 8: Line diagram showing distribution of vitamin D in case & control

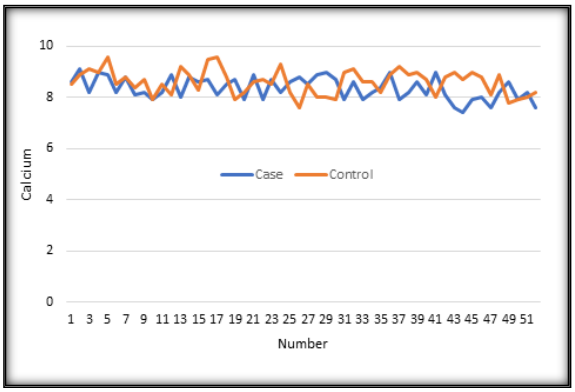

Figure 9: Line diagram showing distribution of calcium in case & control

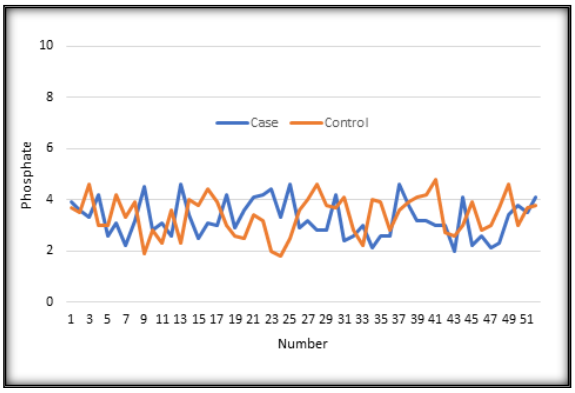

Figure 10: Line diagram showing distribution of phosphate in case & control

Line diagrams (Figure 7-10) given above describe how the distribution of age, vitamin D, calcium and phosphate levels have been overlapping between the cases and controls without significant difference ($p>0.05$) except for calcium ($p=0.09$).

Subgroup Analysis

CVA patients and control were divided into various subgroups according to sex, residence, type of CVA, blood pressure, blood sugar status and analyzed accordingly.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 5: Showing Vitamin D, Calcium level results in CVA patients

	VITAMIN D			CALCIUM		
	Mean	Standard Deviation	P value	Mean	Standard Deviation	P value
Male	30.22	12.73	0.001	8.45	0.44	0.08
Female	18.51	12.49		8.23	0.43	
Rural	31.00	12.73	0.001	8.44	0.44	0.09
Urban	17.45	12.39		8.24	0.43	
Non HTN	23.74	12.86	0.46	8.34	0.43	0.79
HTN	26.39	14.12		8.37	1.15	
Non DM	26.16	12.86	0.84	8.38	0.43	0.93
DM	24.22	12.36		8.33	0.44	
ICH	29.30	12.92	0.18	8.46	0.43	0.16
Infarct	22.00	12.90		8.28	0.43	

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

Vitamin D levels in female CVA patients were considerably lower (in ng/ml), according to a thorough subgroup analysis 18.51 (±12.49) compared to males 30.22 (±12.73) (p=0.001). Also vitamin D was significantly lower in urban 17.45 (±12.39) compared to rural 31.00 (±12.73) population (p=0.001) and infarct 22.00 (±12.90) to ICH 29.30 (±12.92) (p=0.18) as p<0.05. It was also lower in non-hypertensive 23.74 (±12.86) to hypertensive 26.39 (±14.12) (p=0.46), diabetic 24.22 (±12.36) to non-diabetic 26.16 (±12.86) (p= 0.84) patients, however, all data presented above, none of them were significant with P>0.05 (using unpaired Students T-test) (Table 5). Calcium level was significantly lower in females 8.23 (±0.43) compared to males 8.45 (±0.44), (p= 0.08), urban 8.24 (±0.43) compared to rural 8.44 (±0.44) population (p= 0.09). Calcium was also lower in non-hypertensive patients, 8.34 (±0.43) compared to hypertensive patients 8.37 (±1.15), (p= 0.79), diabetic 8.33 (±0.44) to non-diabetic 8.38 (±0.43) (p= 0.93) and ICH 8.46 (±0.43) to infarct 8.28 (±0.43) (p= 0.16) patients, again however all data presented, none of them were significant with P>0.05. Comparable analysis was also conducted on the control group, but no differences were found to be significant (Figure 11-14).

Table 6: Result of epidemiological & biochemical data in CVA patients, Mean (SD)

	Age (years)	Vitamin D (ng/ml)	PTH (pg/ml)	Calcium (mg/dl)	Phosphate (mg/dl)
ICH	61.09 (10.15)	29.30 (12.92)	39.27 (26.87)	8.46 (0.43)	3.44 (0.75)
Infract	62.00 (10.31)	22.00 (12.33)	47.05 (26.57)	8.28 (0.44)	3.10 (0.75)
P Value	0.76	0.04	0.31	0.16	0.11

CVA- Cerebrovascular accident, ICH-Intracranial Haemorrhage

Different parameters for the basic two subtypes of CVA are described above (Table 6). Infarct patients had significantly lower mean vitamin D 22.00 (±12.33) compared to ICH patients 29.30 (±12.92) (p =0.04).

Table 7: Result of epidemiological & biochemical data in case & control, mean (SD)

		Age (years)	Vitamin D (ng/ml)	PTH (pg/ml)	Calcium (mg/dl)	Phosphate (mg/dl)
Population	Case (52)	61.23 (10.07)	25.37 (12.73)	44.02 (26.33)	8.35 (0.44)	3.25 (0.74)
	Control (52)	59.50 (9.70)	30.49 (13.86)	47.52 (22.41)	8.60 (0.49)	3.83 (0.76)
	P Value	0.37	0.05	0.48	0.09	0.36
Male	Case (30)	64.57 (10.07)	30.22 (12.73)	36.76 (26.33)	8.47 (0.44)	3.34 (0.74)
	Control (32)	59.50 (9.70)	30.42 (13.86)	46.99 (24.01)	8.60 (1.20)	3.38 (0.86)
	P Value	0.02	0.24	0.35	0.04	0.54
Female	Case (22)	56.68 (10.27)	18.51 (12.49)	52.91 (26.56)	8.23 (0.43)	3.13 (0.74)
	Control (20)	59.42 (9.92)	30.27 (14.33)	46.26 (23.07)	8.61 (0.50)	3.36 (0.78)
	P Value	0.22	0.07	0.75	0.12	0.04
Rural	Case (30)	63.47 (10.07)	31.00 (12.73)	36.31 (26.33)	8.44 (0.44)	3.33 (0.74)
	Control (25)	59.04 (9.76)	38.08 (14.22)	40.36 (22.86)	8.80 (0.48)	3.42 (0.78)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

	P Value	0.11	0.03	0.47	0.004	0.66
Urban	Case (22)	58.18 (10.36)	17.45 (12.39)	53.52 (26.68)	8.24 (0.43)	3.14 (0.74)
	Control (27)	59.93 (9.84)	23.33 (14.07)	53.12 (22.63)	8.41 (0.50)	3.36 (0.77)
	P Value	0.52	0.06	0.96	0.18	0.35
Non HTN, Non DM	Case (11)	55.64 (10.46)	23.70 (12.31)	43.45 (27.03)	8.42 (0.42)	3.37 (0.76)
	Control (24)	58.50 (9.82)	34.35 (14.12)	44.16 (22.67)	8.64 (0.50)	3.58 (0.76)
	P Value	0.46	0.07	0.93	0.24	0.46
Only HTN	Case (30)	62.90 (10.07)	26.87(12.73)	42.57 (26.33)	8.37 (0.44)	3.13 (0.74)
	Control (17)	61.35 (9.92)	25.00 (14.33)	53.59 (23.07)	8.55 (0.50)	3.12 (0.78)
	P Value	0.61	0.71	0.20	0.19	0.94
Only Diabetic	Case (24)	65.04 (10.17)	24.22 (12.36)	47.83 (26.34)	8.33 (0.44)	3.31 0.74)
	Control (21)	61.52 (9.77)	26.07(13.97)	51.73 (22.60)	8.56 (0.49)	3.21 (0.76)
	P Value	0.22	0.60	0.62	0.13	0.67
Both	Case (13)	67.38 (10.31)	24.60 (12.33)	48.92 (26.57)	8.40 (0.44)	3.19 (0.75)
	Control(10)	64.05 (10.09)	21.51 (14.75)	61.40 (23.61)	8.53 (0.49)	3.03 (0.78)
	P Value	0.51	0.54	0.33	0.55	0.66

Both case and control study population was divided into subgroups according to sex, residence and combined blood pressure and diabetes status (non-hypertensive-non diabetic, only hypertensive, only diabetic, both diabetic and hypertensive). Different parameters of these subgroups like age, vitamin D level, PTH, calcium and phosphate are described in Table 7.

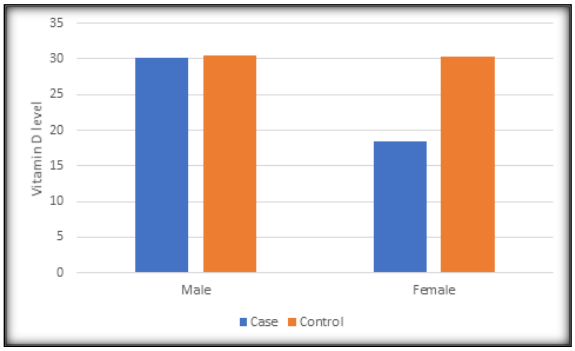

Figure 11. Bar diagram showing Vitamin D level in different sex.

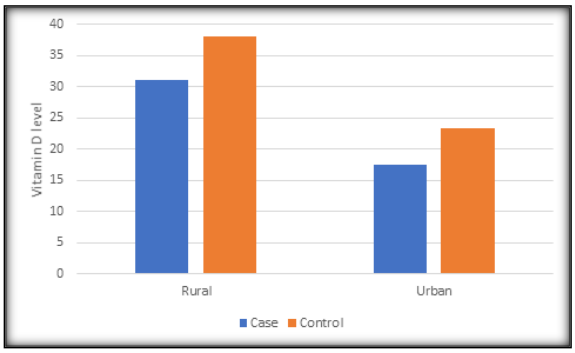

Figure 12. Bar diagram showing Vitamin D level as per residence.

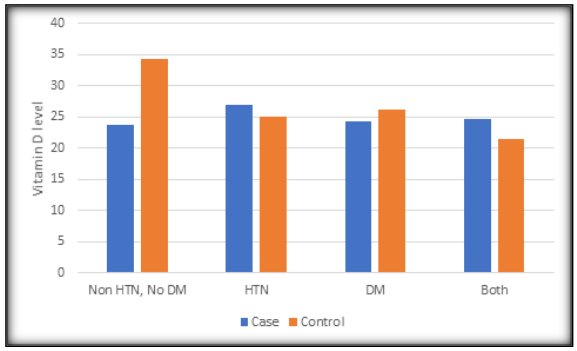

Figure 13. Bar diagram showing Vitamin D level as per HTN and DM.

HTN- Hypertension, DM- Diabetes

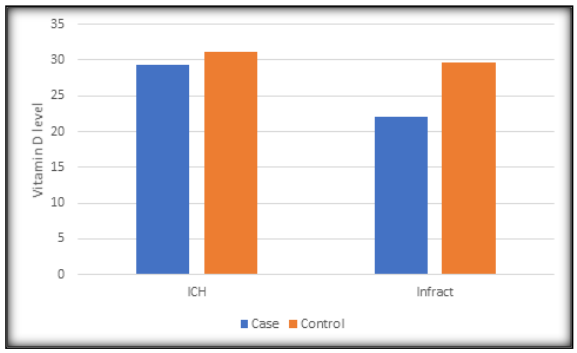

Figure 14. Bar diagram showing Vitamin D level as per the type of CVA

Vitamin D levels were compared between hypertensive and non-hypertensive, intracranial haemorrhage (ICH) patients and diabetic and non-diabetic ICH patients. Similar comparison was done in infarct patients as well as males, females, rural and urban population depending on whether they were hypertensive/ non-hypertensive, diabetic/ non-diabetic.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 8: Vitamin D level difference in various subgroup of CVA patients

	HTN	Non-HTN	P Value	DM	Non- DM	P Value
ICH (22)	n=12	n=10	0.41	n=9	n=13	0.36
	31.41 (12.92)	26.78 (12.69)		26.25 (12.55)	31.42 (13.01)	
Infract (28)	n=16	n=12	0.77	n=15	n=13	0.65
	22.60 (12.33)	21.20 (12.31)		23.00 (12.33)	20.85 (12.35)	
Male (30)	n=20	n=10	0.53	n=11	n=19	0.84
	31.22 (12.73)	28.22 (12.55)		29.62 (12.33)	30.57 (12.82)	
Female (22)	n=10	n=12	0.48	n=13	n=9	0.55
	16.71 (12.40)	20.00 (12.49)		19.66 (12.65)	16.84 (12.39)	
Rural (30)	n=19	n=11	0.96	n=13	n=17	0.34
	30.92 (12.73)	31.13 (12.65)		28.64 (12.36)	32.80 (12.82)	
Urban (22)	n=11	n=11	0.61	n=11	n=11	0.47
	18.55 (12.47)	16.34 (12.31)		19.00 (12.53)	15.89 (12.39)	

ICH- Intracranial Haemorrhage, HTN- Hypertension, DM- Diabetes Mellitus, CVA- Cerebrovascular accident.
Students' unpaired T-test results for the analysis of vitamin D with diabetes and hypertension as independent factors in all the groups were not significant with a p value of 0.05 (Table 8).

Table 9: Showing correlation coefficient between various factors

VARIABLE 1	VARIABLE 2	CORRELATION COEFFICIENT
Age	Vitamin D	0.7145
Vitamin D	Parathormone	0.1668
Vitamin D	Calcium	0.4731
Vitamin D	Phosphate	0.6030
Phosphate	Calcium	0.9472

The level of vitamin D and parathormone had a very weak link, the level of vitamin D and age had a significant correlation, and the level of vitamin D and calcium had a moderately strong correlation. There was strong correlation between calcium and phosphate (Table 9).
The stroke severity was measured among the 52 patients with level of vitamin D as shown in Table 10 below and accordingly the Figure 15 drawn for data comparison of severity of stroke vs. vitamin D level in various patients.

Table 10: NIH stroke scale with the Vitamin D level.

NIH stroke scale range	Stroke severity	Vitamin D level			Total
		Deficient (<20ng/ml)	Sufficient (>30ng/ml)	Insufficient (20-30 ng/ml)	
1-4	Minor	1	8	8	17
5-15	Moderate	5	5	6	16
16-20	Moderate to severe	4	3	3	10
21-42	Severe	8	0	1	9
Total		18	16	18	52

Table 11: mRS scale has been compared between the level of vitamin D and stroke outcome

mRS range	Stroke outcome	Vitamin D level			Total
		Deficient (<20ng/ml)	Sufficient (>30ng/ml)	Insufficient (20-30 ng/ml)	
0	No symptom	1	9	8	18
1	No obvious disability	4	6	7	17
2	Slight disability	5	1	2	8
3	Moderate disability	7	0	1	8
4	Moderately Severe Disability	1	0	0	1
5	Severe disability	0	0	0	0
Total		18	16	18	52

ISSN (O): 2687-5365; ISSN (P): 2753-6556

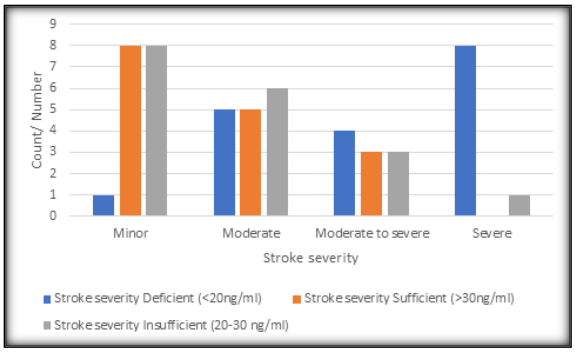

Figure 15: NIH stroke scale with vitamin D level

Similarly, the mRS scale has been compared between the level of vitamin D and stroke outcome as mentioned in Table 11 and accordingly the Figure 16 has been drawn for pictorial representation

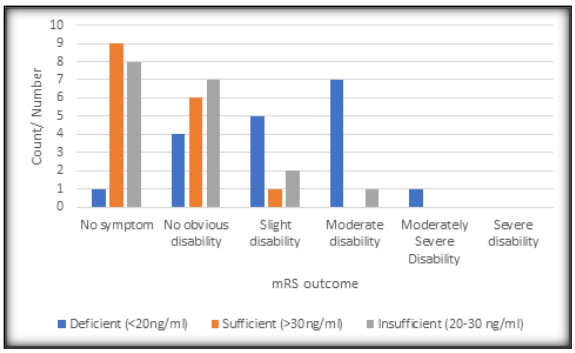

Figure 16: mRS stroke outcome with Vitamin D level

DISCUSSION

Due to evidence demonstrating vitamin D's involvement in numerous critical processes for the body's healthy operation has opened a broad area of research that was previously assumed to be limited to musculoskeletal health and mineral ion balance. As a result of vitamin D functioning through the vitamin D receptor (VDR), calcium and phosphate are absorbed from the intestine, reabsorb from the kidney, and parathyroid hormone secretion is suppressed, maintaining the health of the bone minerals.[2] But during the past 20 years, researchers have found VDR in a number of additional body tissues (82-84). Without the aid of renal 1, hydroxylase, the active form of vitamin D, 1, 25 (OH)2 vitamin D3, can be generated locally.[5-8] Vitamin D has actions that are immunomodulatory, pro-differentiate, and anti-proliferative 8. It affects the processes involved in the aetiology of atherosclerosis, including elastogenesis, immunomodulation, and vascular smooth muscle cell migration, proliferation, and gene expression.[5] It can control renin secretion and thus affect blood pressure.[6] Therefore, it is biologically probable that vitamin D deficiency patients have higher rates of atherosclerosis and hypertension. Vitamin D deficiency has been seen in individuals with cardiovascular disease, peripheral vascular disease, and cerebrovascular accident (CVA) in cross-sectional and prospective studies.[2-8]

1811 non-hypertensive subjects were monitored for 4 years by Forman et al. Comparing those with baseline 25(OH) D levels of 15 ng/mL to those with levels of 30 ng/ml, the relative risk for incident hypertension was 2.67 (95% CI: 1.05 to 6.79).[9] A substantial adverse relationship between vitamin D and hypertension was also discovered by Jorde et al.[10] The effect of vitamin D on decreasing blood pressure has been studied in at least 13 pharmacological trials.[11] In one of the earliest investigations on vitamin D and coronary artery calcification (CAC) mass, Watson et al. found that 173 subjects with a higher chance of developing coronary artery disease (CAD) had a statistically significant negative correlation between their 1, 25 (OH) D concentrations and CAC 4.

A subsample of participants from the population-based Multi-Ethnic Study of atherosclerosis showed a substantial inverse correlation between 25(OH) D and incident CAC.[12] A modest case-control research conducted in New Zealand in 1990 compared the vitamin D levels of patients with acute myocardial infarction (MI) to those in the control group and discovered that patients with ischemic heart disease had considerably lower vitamin D levels.[13] A substantial inverse connection between low serum 25(OH) D and a high prevalence of peripheral artery disease (PAD), as shown by an ankle brachial index of less than 0.9, was found in a nationally representative sample of US individuals participating in the NHANES. The multivariable-adjusted risk for PAD increased by 35% for every 10 ng/mL lower 25(OH)D level (prevalence ratio: 1.35; 95% CI: 1.15-1.59). The risk of PAD in black individuals has repeatedly been observed to be higher than in white adults.[14] In 2005, Kenneth ES Poole (United Kingdom) investigated and compared the serum 1, 25-dihydroxyvitamin D levels in 44 patients admitted to an acute stroke ward who had experienced their first stroke with the findings from 96 elderly ambulant healthy volunteers who had been measured every two months for a year. With 77% of patients falling in the inadequate range, the average Z score for vitamin D in acute stroke patients was 1.4 SD units (95% CI, 1.7-1.1).[8]

In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (South-western Germany), Stefan Pilz examined the baseline levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in 3316 individuals who were referred to coronary angiography between 1997 and 2000. These measurements were made in 3299 and 3315 study participants, respectively. During a median follow-up of 7.75 years, 769 people passed away, including 42 fatal (ischemic and hemorrhagic) strokes.[7] When survivors were compared to them, the odds ratios (with 95% CIs) for fatal stroke were 0.58 (0.43 to 0.78; P-0.001) per z value of 25(OH) D and 0.62 (0.47 to 0.81; P-0.001) per z value of 1, 25(OH) 2D. After controlling for a variety of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

possible variables, these odds ratios were significant for 25(OH) D at 0.67 (0.46 to 0.97; P-0.032) and for 1, 25(OH) 2D at 0.72. (0.52 to 0.99; P-0.047). Lower Z values for 25(OH) D and 1, 25(OH) 2D were observed in the 274 persons who had a history of past cerebrovascular disease occurrences at baseline. In light of his findings, he came to the conclusion that low levels of 25(OH) D and 1, 25(OH) 2D are independently predictive for fatal strokes, indicating that vitamin D supplementation is a promising strategy for stroke prevention. According to a study, vitamin D deficiency is very common in CVA patients, which is consistent with the research of Stefan Pilz and Poole. About 43 (71.67%) of the study population had vitamin D levels that were insufficient. Poole et al. came to the conclusion that rapidly reduced 25(OH)D caused by a reduction in hormone synthesis or existing stockpiles (mainly found in body fat) seemed dubious because there was no link between serum 25(OH)D and the time between a stroke and 25(OH)D sampling. Therefore, it appears likely that this insufficiency predated the stroke.[8] A moderate connection between vitamin D insufficiency and ischemic stroke was discovered in a prospective research conducted by Qi Sin et al and published in 2012 on 464 female patients in the USA. Anu Gupta et al 2014's investigation on 70 patients who had ischemic strokes from the North Indian population found no link between low vitamin D levels and the condition.[19] Another study by Kaushik Chatterjee et al. on 38 West Bengal CVA patients, encompassing both ischemic and haemorrhagic stroke, was unable to detect any statistically significant connection.

So, till now the various researches have given conflicting results. The mean level of vitamin D in our study (25.37 ng/ml) (Table 3) was higher than what Stefan Pilz found. Several explanations seem likely age could be a confounding issue because the mean age of the stroke patients in the LURIC trial was 69.3 years (64-76 years), whereas the mean age of our CVA patients was 61.23 years (38-85 years) (Table 3). Diabetes prevalence in stroke patients from the LURIC trial was 50% compared to 46.15% in our CVA patients (Table 2).

Diabetes patients' decreased mean vitamin D levels could also be a confusing factor. Additionally, Bihar experiences more solar exposure because it is located at a lower latitude than Germany, where the LURIC study was conducted. Apart from the winter months, Bihar's hot weather is another reason why locals like to dress in loose-fitting clothing that exposes more of their bodies to the sun, which raises their vitamin D levels. Even though our CVA patients had higher vitamin D levels, we must remember that Indians are particularly vulnerable to vitamin D deficiency due to dietary inadequacy 10, vegetarianism, genetic factors 6, cultural beliefs, repeated unplanned pregnancies, growing urbanisation, and pollution 7), as is described by Dr. Vikram Londhey.[8]

Similar to earlier research (30 ng/ml in the LURIC trial), the mean parathormone level was normal (44.02pg/ml) in this investigation. The typical inverse association between log 25-(OH) D & log parathormone (PTH) concentration was detected, supporting Poole et al finding's (8) (correlation coefficient - 0.674). However 54% (Figure 5) of our study population had low serum calcium level. Mean calcium of our study is lower (8.35 mg/dl, range 7.4-9.1) (Table 3) than the lowest value found by Stefan Pilz (mean 9.32mg/dl, range 8.96-9.72 mg/dl) 7. According to Bhatia V, the low dietary calcium consumption of Indians may have contributed to the low serum calcium levels found in our study. Further commentary on this discrepancy was not feasible due to the lack of information regarding the normal calcium level in the Indian population.[16] Most of our study population had normal phosphate level (3.28mg/dl, range 2.0-4.6) (Table 3, Figure 6). No suitable data could be found for comparison.

However, vitamin D and phosphate levels in patients and controls with similar ages and sexes did not differ significantly. This runs counter to the findings of the study by Poole et al .[8]

The average age of CVA, according to subgroup analysis, was around 62 years. Conforming to the epidemiology of CVA which is more common in aged population.[3] There was no longer the typical inverse relationship between age and vitamin D level. In actuality, the relationship between age and vitamin D level was only very weakly favourable (Table 9). Table 5 shows that vitamin D levels were significantly lower in CVA females than CVA males (p=0.001), possibly as a result of lower sun exposure due to the fact that most Indian females stay indoors, cultural beliefs regarding the wearing of the pardha and burqa, repeated pregnancies, and inadequate dietary intake.[17] Additionally, it was much lower in urban than in rural areas, most likely as a result of pollution 15 and insufficient sun exposure brought on by a sedentary lifestyle.[18] Patients with diabetes compared to those without diabetes had decreased levels of vitamin D (Table 5), although none of these differences were statistically significant (P>0.05).

But it was significantly lower in the infarct patients than the ICH patients (p=0.04). Similar to how calcium levels were not substantially different between males and females (p=0.08) or between urban and rural populations (p=0.09). Patients with ICH and infarct showed decreased calcium levels when compared to non-infarct, diabetic, and hypertensive patients, although none of these differences were statistically significant (p>0.05) (Table 5). Men with hypertension or without hypertension, men with diabetes or without diabetes, and women with CVA patients all had their vitamin D levels compared. To compare the vitamin levels of urban CVA patients, subgroups of hypertension and non-hypertensive patients as well as diabetic and non-diabetic patients were created. Patients with

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CVA in rural areas underwent comparable analysis as well. Intra-cerebral haemorrhage (ICH) and infarct, the two main forms of CVA patients, were divided into groups based on their blood pressure (hypertensive or non-hypertensive and diabetic or non-diabetic), but none of these comparisons produced statistically significant results. This indicates that they all have low vitamin D levels, regardless of their blood pressure or diabetes condition. Finally, a strong correlation was observed between vitamin D/age, a positive correlation between vitamin D/calcium, and less correlation between vitamin D and parathormone levels (Table 9). The NIH score also indicates that stroke severity was found to be high where the patients with low Vitamin D (<20 ng/ml) compared to patients with sufficient Vitamin D levels. Similarly, mRS score also showed a correlation with the level of Vitamin D as Figure 16 showed that chances of slight to moderate disability were found to be high where the level of Vitamin D was below (<20 ng/ml).

We propose further studies to be done on vitamin D, parathormone, calcium, and phosphate levels in acute stroke patients to make any further comments. As a result, we draw the conclusion that CVA patients, independent of their sex, place of residence, diabetes, or hypertension, have low vitamin D levels. It is nevertheless low in both the age- and sex-matched control populations, and there is no appreciable difference between the CVA group and the non-CVA population. However, because the ischemic stroke patients had significantly low vitamin D levels, we propose a link between ischemic stroke and low vitamin D levels, but it's too early to confirm it given the small population studied and the fact that both the case and control populations' vitamin D levels were inadequate. Therefore, additional prospective studies will be required to prove a correlation.

Limitations/ Future prospective

1. Due to the short study period, we were forced to use a cross-sectional study design; nevertheless, a prospective study would have been perfect for determining the effect of low vitamin D levels on macro-vascular illnesses.
2. Due to financial limitations and compliance concerns, collecting samples for patients and controls on an equal basis throughout the year was impossible to evaluate seasonal fluctuation in vitamin D levels.
3. The only criteria used to choose the control population was history. However, they were not given a thorough examination to look for any subclinical macro-vascular diseases.
4. Severity of CVA was not assessed.
5. Due to a lack of infrastructure, it was not possible to measure the levels of FGF-23, a phosphatonin that is crucial for maintaining vitamin D homeostasis.

CONCLUSION

Vitamin D deficiency was discovered to be quite common in CVA patients in this hospital-based observational investigation involving neuroimaging confirmed CVA patients. Many also suffered from concurrent calcium insufficiency. Phosphorus and parathormone, however, were generally normal. However, there was no significant difference in the levels of vitamin D, parathormone, or phosphate when we compared the results of the research group with appropriate age and sex-matched controls; rather, vitamin D deficiency was just as common in the controls.

However, the calcium level in the case group was much lower. Infarct compared to ICH patients, urban compared to rural population, and female versus male CVA patients all had considerably lower vitamin D levels. The levels of vitamin D were lower in diabetics compared to non-diabetics and hypertensives compared to non-hypertensives, albeit none of the changes were statistically significant. Females had significantly lower mean calcium levels than males, and urban residents had lower mean calcium levels than rural residents. Additionally, it was lower in patients with ICH compared to infarcts, non-hypertension compared to hypertensive, and diabetic compared to non-diabetic, but none of the changes were statistically significant. No of their sex, place of residence, blood pressure, or blood sugar levels, the research group had inadequate vitamin D levels. Also the NIH and mRS scores showed high incase of patients having low Vitamin D levels (<20 ng/ml). Thus, we draw the conclusion that vitamin D deficiency is widespread in Bihar's population as a whole. As a result, careful consideration must be given to reconsidering the vitamin's role in macro-vascular diseases in order to develop a healthcare strategy to lower the mortality and morbidity resulting from these macrovascular events.

Acknowledgment

The authors thank Aziz Writing Solutions (AWS) for assisting in manuscript preparation and publication.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

REFERENCES

1. World Health Organization. World Health Report 2002. Switzerland, Geneva: WHO, 2002
2. Siesjő BK: Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab.1981; 1:115-185
3. Hademenos GJ, Massoud TF. Biophysical mechanisms of stroke. Stroke. 1997;28: 2067 77
4. Schor K, Braun M. Platelets as a source of vasoactive mediators. Stroke. 199; 21:IV32 IV35
5. Norman PE, Powell JT. Vitamin D, Shedding Light on the Development of Disease in Peripheral Arteries.Arterioscler Thromb Vasc Biol 2005, 25:39-46
6. Li YC. Vitamin D regulation of the renin-angiotensin system. J Cell Biochem. 2003;88:327-33

ISSN (O): 2687-5365; ISSN (P): 2753-6556

7. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U. Angiography Low Vitamin D Levels Predict Stroke in Patients Referred to Coronary Angiography.Stroke 2008, 39:2611-2613:
8. Poole KES, Loveridge N, Barker PJ, Halsall DJ, Rose C. Reduced Vitamin D in Acute Stroke. Stroke 2006, 37:243-245:
9. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49:1063–1069.
10. Jorde R, Figenschau Y, Emaus N, Hutchinson M, Grimnes G. Serum 25-hydroxyvitamin D levels are strongly related to systolic blood pressure but do not predict future hypertension. Hypertension. 2010;55:792–798.
11. Vaidya A, Forman JP. Vitamin D and Hypertension : Current Evidence and Future Directions. Hypertension 2010, 56:774-779:
12. De Boer IH, et al. 25- hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. J Am Soc Nephrol 2009, 20:1805-1812
13. Scragg R, et al. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol 1990; 19:559-563
14. Melamed ML, et al. Serum 25- hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arterioscler Thromb Vasc Biol 2008; 28:1179-1185.
15. Babu US, Calvo MS. Modern India and the vitamin D dilemma: evidence for the need of a national food fortification program. Mol Nutr Food Res 2010;54:1134-47.
16. Bhatia V.Dietary calcium intake - a critical reappraisal. Indian J Med Res 127, March 2008, pp 269-273
17. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NONOF) Study. Age Ageing. 2004;33:45-51.
18. Holick MF, Tian XQ, Allan M. Evolutionary importance for the membrane enhancement of the production of vitamin D3 in the skin of poikilothermic animals. Proc Natl Acad Sci USA 1995;92:3124–6.
19. Goswami R1, Gupta N, Goswami D, Marwaha RK, Tandon N;Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi.
20. Portegies ML, Koudstaal PJ, Ikram MA. Cerebrovascular disease. Handbook of clinical neurology. 2016 Jan 1;138:239-61.
21. Thacher TD. Clar e BL. Vitamin D Insufficiency. Foundation for Medical Education and Research. 2011;86(1):50-60.
22. Jamali N, Wang S, Darjatmoko SR, Sorenson CM, Sheibani N. Vitamin D receptor expression is essential during retinal vascular development and attenuation of neovascularization by 1, 25 (OH) 2D3. PLoS One. 2017 Dec 22;12(12):e0190131.
23. Darling AL. Vitamin D deficiency in western dwelling South Asian populations: an unrecognised epidemic. Proceedings of the Nutrition Society. 2020 Aug;79(3):259-71.
24. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Annals of epidemiology. 2009 Feb 1;19(2):73-8.
25. Misra A. Ethnic-specific criteria for classification of body mass index: a perspective for Asian Indians and American Diabetes Association position statement. Diabetes technology & therapeutics. 2015 Sep 1;17(9):667-71.
26. Lee Y, Siddiqui WJ. Cholesterol levels. InStatPearls [Internet] 2021 Jul 26. StatPearls Publishing.

ISSN (O): 2687-5365; ISSN (P): 2753-6556