

# **A CORRELATIVE STUDY OF SERUM PHOSPHORUS, VITAMIN D3 AND URIC ACID LEVELS IN ACUTE ISCHEMIC STROKE**

**Vanama Lakshman sai, Mahesh Mahadevaiah, Ankit Singh, D. Prabhath Suraj,  
Aditi Rao.**

1) Junior Resident, 2) Professor, 3) Junior Resident 4) Senior Resident  
2) 5) Junior Resident.

Department of General Medicine, JSS Medical College and Hospital, Mysuru  
JSS Academy of Higher Education and Research

**Corresponding author and 1st Author:**

**- Dr. Vanama Lakshman sai**

Postgraduate in Department of General Medicine, JSS Medical College and Hospital

## **ABSTRACT**

**AIM:** To correlate and measure Serum Phosphorus, Vitamin D3, Uric acid levels in Patients of Acute Ischemic Stroke in first 24 hours.

**MATERIAL & METHODS:** Analytical Cross Sectional study involving data from 112 patients visiting JSS Hospital, Mysuru over a period of 18 months. 56 patients admitted to JSS Hospital with the diagnosis of acute ischemic stroke were compared with a control group comprising 56 patients. The presence of ischemic stroke was confirmed based on clinical signs, symptoms, brain CT Brain, and MRI stroke protocol. Blood samples were taken from the patients in both the group in the first 24 h of admission to measure serum phosphorus, vitamin D3, calcium, and uric acid levels.

**RESULTS:** Totally 112 patients were registered for the study of which 56 were cases and 56 were controls. Serum phosphorus, vitamin D, serum uric acid levels of both the groups were analyzed and result was suggestive of elevated serum phosphorus and uric acid in stroke cases with significant p value ( $p < 0.0001$ ) whereas serum vitamin D level was low in stroke patients with significant p value ( $p < 0.0001$ ). Correlation of Serum Phosphorus, vitamin D and uric acid were independently associated in acute ischemic stroke.

**CONCLUSION:** The study states that Serum phosphorus, Serum Vitamin D and Serum Uric acid were associated with the development of Ischemic stroke suggesting that inflammation and the dysfunction of the vascular endothelium could lead to stroke. By considering all these parameters in high-risk individuals developing stroke one can predict the early recognition of stroke and take necessary preventive steps and thus decreasing the morbidity and mortality of the disease.

These biochemical blood parameters are easy to estimate and easy to interpret the results and cost effective, this can be used in resource poor setting situations compared to inflammatory markers such as Interleukins and cytokines.

**KEYWORDS:** Cerebral infarction, vitamin D, uric acid, serum phosphorus.

## INTRODUCTION

Stroke causes sudden onset of focal neurological deficit due to vascular cause. Stroke is one among the topmost 3 causes of mortality worldwide (1). Incidence of stroke increases with age and prompt evaluation and early diagnosis is necessary to prevent mortality and morbidity in population. Recently many studies are coming up with serum biomarkers and their correlation with ischemic stroke, though many studies results are conflicting in view of observation with different populations. It is known that main risk factors for CVA are Individuals with a history of heart disease, such as diabetes mellitus, high blood pressure, Atrial fibrillation, are more prone for stroke. (2).

Recent study reported there is association between higher phosphorus levels and vascular diseases (3) in contrast few other studies didn't significantly find any correlation between them. Some prospective studies have shown lower levels of vitamin D are associated with ischemic stroke, whereas in contrast some cross-sectional studies shown no relationship between vitamin D and its correlation to stroke in Indian, south Asian populations. To best of our best knowledge there are very few studies that takes all the parameters of vitamin D, serum phosphorus, uric acid in making a correlation with ischemic stroke. There is currently no reliable study of this type with the link between CVA and various Serum parameters in the Indian subcontinent. This study will help us understand the relationship between these conditions and ischemic stroke. Many of these parameters and its association very studied on coronary heart diseases and very few studies have been published in regard of acute ischemic stroke.

## MATERIAL & METHODOLOGY

An Analytical Cross Sectional study involving data from 112 patients, inpatients of JSS Hospital, Mysuru over a period of 18 months.

Inclusion criteria: All diagnosed Clinically suspected patients presenting with symptoms of CVA are subjected to detailed clinical examination.

1. 56 patients between age 18 to 60 years admitted with Acute Ischemic Stroke in JSS Hospital , Mysuru are taken up for study.
2. 56 Controls with same Age and Gender match will be taken up for study.

Exclusion criteria:

1. Hemorrhagic stroke.
  2. Embolic stroke.
  3. Patients with chronic renal failure.
  4. Patients on thiazide diuretics.
  5. Chronic liver disease.
  6. Chronic kidney disease.
  7. Pregnancy
- Patients with various infections such as urinary infection (UTI), upper or lower respiratory infections, otitis media, any viral infection, chronic liver disease, parasitic infestations, tuberculosis, pyrexia of unknown origin.
  - Patient who does not want to participate for study.

- Haematological disorder, malignancy, poisoning, any steroids (topical or systemic), alcohol, autoimmune disorder.

A structured proforma was used for the evaluation of patients, detailed case history was taken, and the sample collection was done by the primary investigator.

Patient's data was divided into two arms

1. Case group – Admitted with Ischemic stroke
2. Control group – Healthy group.

Details of habits such as smoking, alcoholism, age, drug history, family history, any prior chronic illness, duration of diabetes and hypertension, sex was collected. General physical examination including weight, body mass index, height, heart rate, blood pressure, cyanosis, clubbing, pallor, yellowish discoloration of sclera was done.

Routine Investigations: -

- Complete Hemogram
- Hepatic function tests (LFTs)
- Renal function (RFT)
- ECHO
- CT /MRI Imaging
- B/L Neck vessel doppler.

Specific Investigations: -

- Serum Phosphorus.
- Serum Vitamin D.
- Serum Uric acid.

Patients were followed up to discharge and details about treatment details and whether the patient was discharged or succumbed to the illness were recorded. At the end of the study within a 24-hour period, we measured the levels of vitamin D3, serum phosphorus, and Uric acid in patients with acute ischemic stroke and find associations.

#### **DATA ANALYSIS: -**

The data collected for this study was analyzed using the software known as SPSS 21 after being entered and arranged in MS excel. The student's t test was used to determine the significance of the quantitative data and chi-square tests was used to determine the significance of the qualitative data. p value is considered to be significant if its <0.05.

#### **RESULTS**

In our study 112 patients were included. Among 56 patients were cases and 56 were controls, Cases were confirmed based on Clinical examination with evidence of radiological abnormalities in CT / MRI and controls were selected based on through clinical examination and without history of neurological illness and patients having CKD and gout were excluded from the study and specific investigations such as Serum Vitamin D , Uric acid , Serum phosphorus were sent within 24 hrs of clinical presentation to hospital and results were compared and analysed between cases and healthy control

Age & Sex distribution of the study subjects (TABLE 1& 2)

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Age category	<30	19	33.9%	7	12.5%
	31-40	12	21.4%	7	12.5%
	41-50	11	19.6%	14	25.0%
	>51	14	25.0%	28	50.0%
	Total	56	100.0%	56	100.0%

From the above table it can be observed that this study had distribution across all age groups with maximum representation in the patients aged less than 30 years in case group and aged greater than 51 years in the control group. (P=0.008, chi square test)

		Group			
		Case		Control	
		Count	Column N %	Count	Column N %
Sex	Male	34	60.7%	30	52.7%
	Female	22	39.3%	26	47.3%
	Total	56	100.0%	56	100.0%

This study had males with 60.7 percentage in the cases group indicating the major group of the disease was carried by males. (P=0.4, chi square test).

### DISTRIBUTION OF RISK FACTORS: -TABLE-3

		Group				P
		Case		Control		
		Count	Column N %	Count	Column N %	
Diabetes	Yes	32	57.1%	26	46.4%	0.3
	No	24	42.9%	30	53.6%	
Hypertension	Yes	36	64.3%	17	30.4%	<0.0001
	No	20	35.7%	39	69.6%	
CAD	Yes	4	7.1%	1	1.8%	0.2
	No	52	92.9%	55	98.2%	

<b>Thyroid disorder</b>	Yes	10	17.9%	0	0.0%	0.001
	No	46	82.1%	56	100.0%	
<b>smoking</b>	Yes	14	25.0%	2	3.6%	0.001
	No	42	75.0%	54	96.4%	
<b>Alcohol</b>	Yes	12	21.4%	14	25.0%	0.7
	No	44	78.6%	42	75.0%	

From the above-mentioned table in this study, diabetes, hypertension, thyroid disorder, CAD were the most common comorbidities patients were suffering from. These comorbidities along with smoking were significantly represented in the cases group in comparison to the controls group and smoking and hypertension were significantly associated with case population in developing stroke. (p=0.001).

#### **Study parameters In Stroke vs control subjects: -TABLE -4**

	<b>Group</b>				<b>p</b>
	<b>Case</b>		<b>Control</b>		
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	
<b>Phosphorous (mg/dl)</b>	4.2	.9	3.7	.8	0.004
<b>HDL in mg/dl</b>	42.2	15.1	31.4	10.2	<0.0001
<b>LDL in mg/dl</b>	139.6	32.1	71.6	33.5	<0.0001
<b>TGL in mg/dl</b>	169.4	66.1	134.3	39.8	0.001
<b>Total cholesterol in mg/dl</b>	190.2	50.8	163.7	33.1	0.001
<b>Uric acid mg/dl</b>	9.2	2.4	3.9	1.7	<0.0001
<b>VLDL in mg/dl</b>	25.5	21.7	20.6	14.5	0.2
<b>Vit D ng/ml</b>	10.3	3.0	37.5	38.7	<0.0001
<b>Hb%</b>	13.4	2.2	13.0	2.0	0.2
<b>NIHSS score</b>	14	6	0	0	NA

In this study, HDL, LDL, Triglycerides, total cholesterol, uric acid, phosphorus, vitamin D had a statistically significant correlation with patients suffering from stroke in comparison to the controls. (p <0.0001).

## CORRELATION -CASE GROUP-TABLE-5

Group			Phosphorous (mg/dl)	Uric acid mg/dl	Vit D ng/ml	HDL in mg/dl	LD L in mg/ dl	TGL in mg/dl	Total cholest erol mg/dl	VLDL in mg/dl
Case	Phosphorous (mg/dl)	r	1	.258	-.174	.023	.187	.092	.365**	.263
		p		.054	.200	.867	.168	.498	.006	.050
		N	56	56	56	56	56	56	56	56
	Uric acid mg/dl	r	.258	1	-.127	.024	-.139	.066	.073	.229
		p	.054		.350	.862	.306	.631	.593	.090
		N	56	56	56	56	56	56	56	56
	Vit D ng/ml	r	-.174	-.127	1	.024	-.221	.032	.043	-.179
		p	.200	.350		.859	.101	.814	.755	.188
		N	56	56	56	56	56	56	56	56
	HDL in mg/dl	r	.023	.024	.024	1	-.155	-.088	.339*	.160
		p	.867	.862	.859		.254	.520	.011	.239
		N	56	56	56	56	56	56	56	56
	LDL in mg/dl	r	.187	-.139	-.221	-.155	1	.293*	.167	.062
		p	.168	.306	.101	.254		.028	.218	.650
		N	56	56	56	56	56	56	56	56
	TGL in mg/dl	r	.092	.066	.032	-.088	.293*	1	.214	.621**
		p	.498	.631	.814	.520	.028		.113	.000
		N	56	56	56	56	56	56	56	56
	Total cholesterol in mg/dl	r	.365**	.073	.043	.339*	.167	.214	1	.423**
		p	.006	.593	.755	.011	.218	.113		.001
		N	56	56	56	56	56	56	56	56
	VLDL in mg/dl	r	.263	.229	-.179	.160	.062	.621**	.423**	1
		p	.050	.090	.188	.239	.650	.000	.001	
		N	56	56	56	56	56	56	56	56
**. Correlation is significant at the 0.01 level (2-tailed).										
*. Correlation is significant at the 0.05 level (2-tailed).										

**Correlations in control group -TABLE- 6**

Group			Phosphorous (mg/dl)	Uric acid mg/d l	Vit D ng/m l	HD L in mg/d l	LDL in mg/d l	TGL in mg/d l	Total cholesterol in mg/dl	VLD L in mg/d l	
Control	Phosphorous (mg/dl)	r	1	.091	.204	-.053	.097	.222	.181	.092	
		p		.506	.132	.699	.479	.100	.182	.498	
		N	56	56	56	56	56	56	56	56	56
	Uric acid mg/dl	r	.091	1	.175	.358**	.400**	.014	.131		-.004
		p	.506		.198	.007	.002	.919	.335		.975
		N	56	56	56	56	56	56	56	56	56
	Vit D ng/ml	r	.204	.175	1	-.034	.288*	.128	.116		.124
		p	.132	.198		.805	.031	.349	.395		.363
		N	56	56	56	56	56	56	56	56	56
	HDL in mg/dl	r	-.053	.358**	-.034	1	.229	-.193	-.033		-.119
		p	.699	.007	.805		.090	.155	.809		.382
		N	56	56	56	56	56	56	56	56	56
	LDL in mg/dl	r	.097	.400**	.288*	.229	1	.164	.163		.056
		p	.479	.002	.031	.090		.226	.231		.680
		N	56	56	56	56	56	56	56	56	56
	TGL in mg/dl	r	.222	.014	.128	-.193	.164	1	.330*		.534**
		p	.100	.919	.349	.155	.226		.013		.000
		N	56	56	56	56	56	56	56	56	56
	Total cholesterol in mg/dl	r	.181	.131	.116	-.033	.163	.330*	1		.284*
		p	.182	.335	.395	.809	.231	.013			.034
		N	56	56	56	56	56	56	56	56	56
	VLDL inmg/dl	r	.092	-.004	.124	-.119	.056	.534**	.284*		1
		p	.498	.975	.363	.382	.680	.000	.034		
		N	56	56	56	56	56	56	56	56	56

From the above-mentioned table In this study on correlation of Serum phosphorus and serum vitamin D, uric acid in ischemic stroke showed these are independent factors among them and there is no correlation among these factors in ischemic stroke.

## **DISCUSSION**

The study was conducted among 112 patients among whom 56 were having acute ischemic stroke and 56 were healthy population with no neurological complaints and deficits. Increased Serum phosphorus, Serum Vitamin D, Uric acid levels among ischemic stroke patients.

Multiple studies have been done over the past few decades which shows the role of Serum Vitamin D Serum phosphorus and uric acid levels and correlation with stroke however exact mechanism is still unclear.

The most acknowledged mechanism by recent Studies have shown that a new system controls the production of vitamin D<sub>3</sub>, phosphorus, and calcium by regulating the activity of FGF-23. FGF-23 can be up-regulated in osteocytes when the levels of these nutrients are increased. It also binds to the receptor complex of the FGFR1c and Klotho/FGFR2c in the kidney's tubular epithelial cells (4,5). By activating 24-hydroxylase, it can decrease vitamin D level and the reduction of FGF-23 can also help decrease the levels of various nutrients, such as vitamin D, calcium, and phosphorus (6).

Individuals with diabetes and other risk factors for stroke may have low serum phosphorus levels. This condition can cause tissue insensitivity to insulin and glucose intolerance. Some studies showed hypophosphatemia is associated in development of diabetes mellitus (7).

Over the years several studies have shown that serum phosphorus plays an important role in accelerating the atherosclerosis and cause both cardiovascular and Neurological problems.

However some studies showed no significant association of serum phosphorus and ischemic stroke, study done recently (8), in contrast this study showed increased Serum phosphorus levels showed as an important role in ischemic stroke cases, the possible explanation for this positive correlation is serum phosphorus plays an important role in atherosclerosis mechanism and recently some studies showed similar results with this study however still exact mechanisms were unclear and needs further large group studies but in this study there is no correlation of serum phosphorus with serum vitamin D and uric acid all are independent to each other in developing stroke.

A study conducted on over 3,437 individuals revealed that those who had low phosphorus levels were more prone to experiencing an ischemic stroke. On the flip side, those with high phosphorus levels were more prone to developing hemorrhagic stroke. The study also revealed that a higher level of phosphorus can trigger inflammatory reactions in the body. This mechanism can lead to the development of ruptures in atherosclerotic lesions.

Many studies showed vitamin D association with many neurological and metabolic abnormalities such as diabetes mellitus, hypertension, and several neurodegenerative diseases, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease, are known to be caused by vitamin D deficiency. Other neuropsychiatric disorders such as schizophrenia and autism are also known to be affected by this condition

The study also noted that vitamin D deficiency is a risk factor for ischemic stroke. It further noted that the low levels of vitamin D in the blood could increase the likelihood of suffering from this type of Ischemic stroke.



The study, which was conducted on over 10,000 individuals, revealed that those who were low in vitamin D levels were more prone to develop ischemic type of stroke. (9).

After excluding individuals who had already suffered a stroke, the researchers tracked the data of the remaining participants for about ten years. They found no proof that having low vitamin D levels was associated with an increased risk of stroke. However, they noted that those who suffered a stroke during the follow-up period were more prone to having vitamin D deficiency (10).

The exact mechanism by which low vitamin D levels might increase the risk of stroke is still unclear. However, it's widely believed that the lack of 25-OH-vitD could be linked to various risk factors such as thrombosis and atherosclerosis.

Some studies also suggest that a lower level of 25(OH) D may increase the risk of having uric acid buildup in the blood (5), but in this study there is no correlation of vitamin D with uric acid levels both are independent with respect to stroke.

However recent studies have revealed that the level of SUA in the blood is associated with the incidence of stroke (8,11) it has been known that the presence of UA in the blood is one of the most important antioxidants. It fights against both radical-caused and oxidative damage in humans. Research has also shown that it can protect nerves from damage caused by oxidation.

Various meta-analyses and systematic reviews have been conducted to examine the effects of high SUA on the development of stroke.

A review of 13 prospective studies by Zhong et al. (12) revealed that having a high level of SUA in the blood is associated with an increased risk of stroke. It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome (13,14). On the other hand uric acid has been known to exert neuroprotective effects by acting as a free radical scavenger(14,15).In humans, approximately one half the antioxidant capacity of plasma comes from uric acid (15, 16).

Different studies assessed the uric acid levels exclusively in patients with ischemic stroke where there was significant association between uric acid level and incidence of acute ischemic stroke (17, 18).

Even this study also showed similar findings such as increased levels of uric acid showed positive association with ischemic stroke.

Wannamethee (19) concluded that their study finds a relationship between raised serum phosphorus levels and increased total mortality of stroke cases and Abolfazl Talebi. et al. (8) concluded that there is no association between serum level of phosphate and stroke, this study suggest that serum phosphorus levels are elevated in stroke patients, and we still require large group analysis to find exact association of serum phosphorus and acute ischemic stroke.

Present study also found that in comparison to hypertensives and diabetes among case and control group, hypertensive population showed good association with respect to ischemic stroke with  $p < 0.0001$ , and there is also a positive association of LDL to acute ischemic stroke with  $p < 0.0001$  in this study.

## **CONCLUSION**

This study states that Serum phosphorus, Serum Vitamin D and Serum Uric acid were associated with the development of Ischemic stroke suggesting that inflammation and the

dysfunction of the vascular endothelium could lead to stroke. By considering all these parameters in high-risk individuals developing stroke one can predict the Early recognition of stroke and take necessary preventive steps and thus by decreasing the morbidity and mortality of the disease. These biochemical blood parameters are easy to estimate and easy to interpret the results and is cost effective, this can be used in resource poor setting situations compared to inflammatory markers such as Interleukins and cytokines.

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