

Prediction of Ischemic Stroke with Serum Uric Acid as Biomarker in Diabetes Mellitus-2

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Abstract:

Background and Objectives:

Patients with DM-2 are at increased risk for stroke. DM-2 patients have either normal or low serum uric acid levels. The significance of hyperuricemia as an independent risk factor for cerebrovascular disease remained uncertain. Therefore the present study is conducted to investigate the association of hyperuricemia with the incidence of stroke in type 2 diabetes mellitus patients free of clinical nephropathy.

Methods:

A total of 100 patients included in study . 50 are simple diabetic and 50 are diabetic with ischemic stroke. Serum uric acid was measured in both of them after other causes of hyperuricemia are excluded.

Results:

Mean age of diabetic patients is 52.9 +/- 10.1 and that of study group is 60.7 +/- 12.2. Male: female ratio in control group is 1.5:1 and that of study group is 1.4:1. Mean serum uric acid level in control group was 3.97 +/- 1.22 and that of study group is 6.8 +/- 1.72. 39 patients (78%) in control group had serum uric acid levels <5 mg/dl and 40 patients (80%) in study group had serum uric acid levels >5 mg/dl

I. Introduction

WHO defines the clinical syndrome of stroke as rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.^[1]

Stroke is the second most common cause of death after heart disease in world (According to WHO 2011). The majority (about 85%) of stroke is ischemic; the remainder result from primary hemorrhage either intracerebral or into the subarachnoid space.^[2,3]

The first edition of diabetes in America documented the strong association of diabetes with risk of stroke, especially strokes due to vascular disease and infarction.^[4]

Diabetes is an important risk factor for stroke when compared with the non diabetic population.^[5] The overall mortality from stroke in diabetic population was 4.4 times higher in male and 5.1 times higher in females. A crude estimate of all strokes ascribed to diabetes mellitus was 18% in men and 22% in women.^[6] Diabetic subjects have a very high risk of death from stroke particularly women and duration of diabetes is an important factor.^[7]

Uric acid is a natural antioxidant that is present in body fluids and tissues throughout the body.^[8] Plasma uric acid levels were elevated in men and women with impaired glucose tolerance and are lowest in diabetic patients especially in diabetic men.^[9]

Serum uric acid concentrations measured in acute ischemic stroke patients at the onset of ischemic symptoms were found to correlate inversely with early neurological impairment and final infarction size on CT or MRI. There is a 12% increase in the odds of good clinical outcome in patients with acute ischemic stroke for each mg/dl increase in serum uric acid.^[10] It has been demonstrated as a neuroprotective agent in acute ischemic stroke by suppressing oxyradical accumulation, stabilization of calcium homeostasis and preservation of mitochondrial function.

Serum uric acid is a significant predictor of acute ischemic stroke in diabetes mellitus type 2 free of nephropathy. Type 2 diabetes patients with stroke have significantly higher mean levels of serum uric acid than simple diabetics.^[11]

The present study was undertaken to compare the levels of serum uric acid in simple diabetic subjects with those of diabetes with acute ischemic stroke.

II. Objectives

Estimation of serum uric acid levels in and its correlation n acute ischemic stroke with type 2 diabetes mellitus.

III. Methodology

The study was done in a cross sectional manner to know the relation of serum uric acid in type 2 diabetes mellitus and also serum uric acid in type 2 diabetes mellitus who presented with acute ischemic stroke.

A total of 100 patients were included in the study conducted on an outpatient as well as inpatient basis in SSIMS &RC, Davangere for a span of 2 years.

50 patients included in the control group have a simple type 2 diabetes mellitus based on FBS > 126 mg % by glucose oxidase method and classifies on the basis of age , body habitus , BMI and a history of ketosis , if any. Out of them 30 were males and 20 were females. Serum uric acid is measured by uricase method in them.

50 patients included in study group are known diabetic patients who presented with acute ischemic stroke. For the purpose of accuracy and consistency, we defined a stroke as a persistent focal neurological deficit lasting more than 24 hours according to WHO. Stroke is defined as ischemic based on CT and MRI brain. Out of them 29 were males and 21 were females. Serum uric acid is measured by uricase method in them.

IV. Results

A total of 50 controls and 50 cases entered the study. They were analysed regarding correlation between serum uric acid in simple diabetic patients and serum uric acid in diabetic patients with acute ischemic stroke.

Table – 1: Age wise distribution

Age group (years)	Controls	Cases (stroke)
31 – 40	6	3
41 – 50	14	7
51 – 60	15	13
61 – 70	14	14
71 – 80	1	13
Total	50	50
Mean age +/-	52.9 +/- 10.1	60.7 +/- 12.2
Range	32 - 74	32 – 82
	T=3.47 , < 0.05, (S)	

The age of patients in control group ranged from 32 – 74 years and mean being 52.9 +/- 10.1. In study group , age ranged between 32 – 82 years and mean being 60.7 +/- 12.2

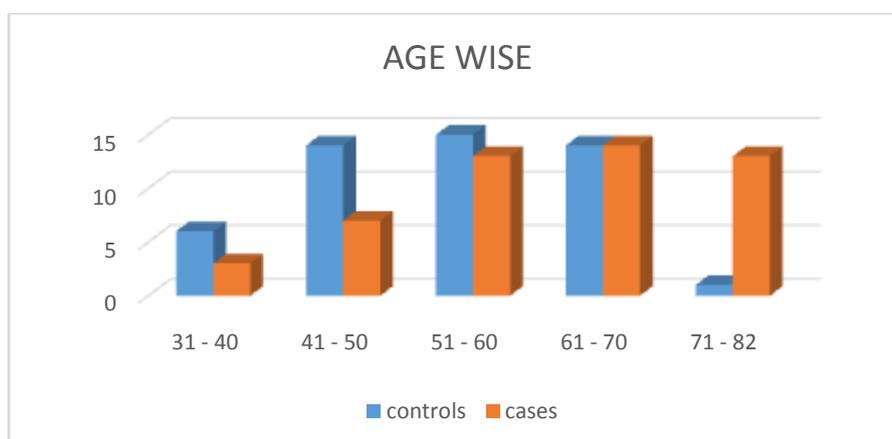


Table 2: SEX WISE

GENDER	CONTROLS	CASES
MALE	30	29
FEMALE	20	21
TOTAL	50	50

In control group there were 30 males (60%) and 20 females (40%). In study group there were 29 males (58%) and 21 females (42%). The BMI in control group ranged from 18.6 – 30 with a mean value of 24.5 +/-3.28 and in study group between 20.4 – 30 with a mean value of 26.12 +/- 2.84



Table 3: FBS and Serum URIC ACID LEVELS IN CONTROLS AND CASES

Groups	N	FBS	SUA (mg/dl)
Controls	50	167 +/- 44.3	3.97 +/- 1.22
Cases	50	178+/-63.2	6.8 +/- 1.72
Cases vs Controls	Mean diff	11	2.82
	T	1.01	9.47
	P	0.32, NS	< .001 HS

FBS in controls ranged from 96 – 310 mg/dl with a mean value of 167.7+/-44.3 and in cases from 85 – 365 mg/dl with a mean value of 178 +/- 63.2. Statistical analysis shows no significant relationship between FBS in control and study group (P=0.32). Serum uric acid in control group ranged from 1.9 – 6.4mg/dl with a mean value of 3.97 +/- 1.22 and in cases ranged from 4.12 – 10.4 mg/dl with a mean value of 6.8 +/- 1.72. Statistical analysis shows a highly significant relationship of serum uric acid with controls and cases (p<0.001)

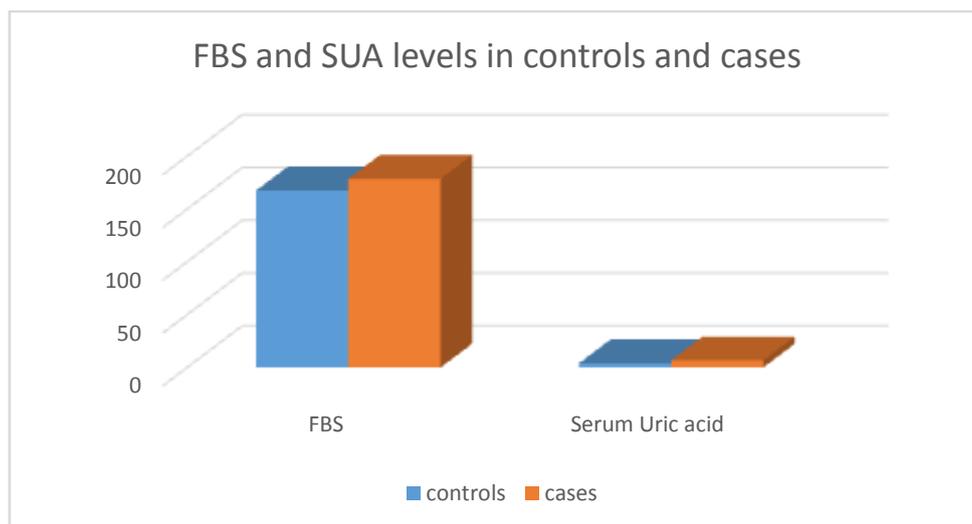


Table 4: Distribution of case and controls with various levels of serum uric acid

Sr. UA	Controls n (%)	Cases (%)
1.6 – 3	14(28)	-
3.1 – 4.5	21(42)	6(12)
4.6-6	13(26)	14(28)
6.1- 7.5	2(4)	12(24)
7.6-10	-	18(36)
Total	50(100)	50(100)

In controls 21 patients (42%) have serum uric acid levels between 3.1 – 4.5 mg% and 14 (28%) have between 1.6 – 3.0 mg/dl. But in cases , 18 patients (36%) between 7.6 – 10 mg/dl and 14 (28%) are between 4.6-6.0 mg/dl.

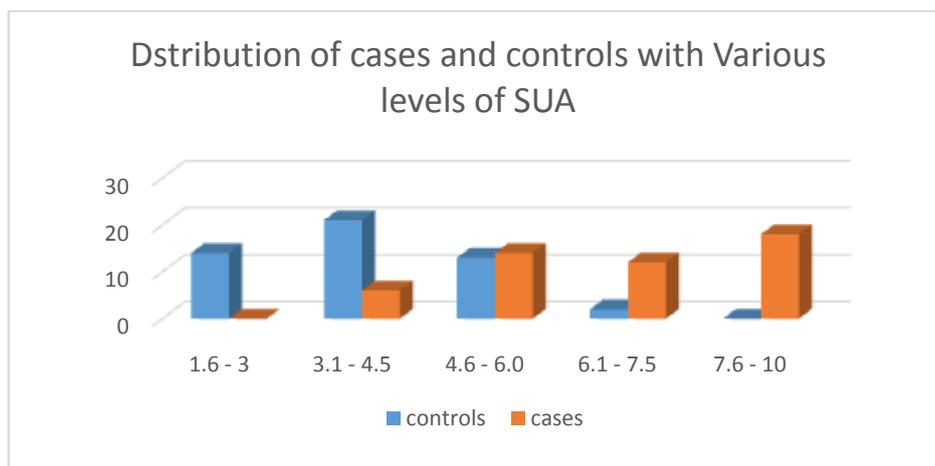


Table 5: Diagnostic value of SUA in prediction of stroke in type 2 diabetes with cut off value Marker = 4.7

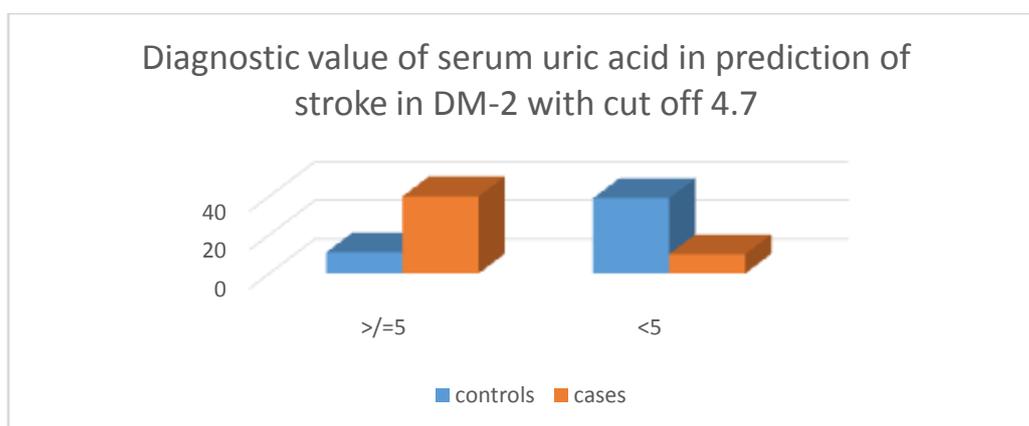
	Cases	Controls	Total
≥5	40	11	51
<5	10	39	49
Total	50	50	100

P<0.001, HS

Among overall 100 patients , 51 patients (40 cases and 11 controls) have serum uric acid levels >5 mg/dl. In remaining 49 patients (39) control and 10 cases have serum uric acid levels < 5mg/dl. Statistical analysis shows a highly significant p value (<.001). sensitivity 80%, specificity 78%, positive predictive value 78% , negative predictive value of 80%.

The cut off value (marker) being 5 mg/dl the overall diagnostic efficiency is 79%.

Our results indicate that serum uric acid levels are significantly low in simple diabetic patients and significantly elevated in diabetic patients with ischemic stroke if cut off value is taken as 5mg.



V. Discussion

Plasma uric acid is the end product of purine metabolism and is relate to the purine bases of thenucleic acids. Its levels are influenced by the various factors including age , sex , obesity alcohol abuse , drugs , climate , season and social status. The normal value of uric acid is highly variable even in a healthy normal individual. It ranged from 2.5 mg% to 5.6% in females and 3.1 – 7 mg% in males.

The finding of a positive relationship between serum uric acid and serum glucose concentration upto about 144 mg/dl glucose and a decrease in serum uric acid thereafter is in keeping with the observations made in a large prospective study.^[12] In this study it was found a negative association at the highest extreme of the glucose distribution and is supported by negative association between serum glucose and uric acid

concentrations seen in simple diabetic group in present study. A negative association of plasma uric acid with overt diabetes was also found in several other studies.^[13-16]

In a population based 7 year follow up study which first demonstrated the independent role of hyperuricemia as a predictor of fatal and nonfatal stroke events in patients with type 2 diabetes mellitus. In univariate analysis the risk of stroke was increased two fold among type 2 diabetes with high uric acid compared with those of low uric acid. Previous studies have indicated that hyperuricemia predicts ischemic heart disease in non diabetic subjects.^[17] and one cross sectional study has suggested that this may apply also to patients with type 2 diabetes.^[18]

In a study, serum uric acid levels were measured in 50 patients with ischemic thrombotic cerebrovascular disease. Hyperuricemia was more frequent in those with abnormal angiograms.^[19] Studies performed with carotid ultrasound^[20] or angiography^[21] have suggested a linear relationship between carotid atherosclerosis and hyperuricemia.

Overwhelming evidence suggests that hyperuricemia is linked to obesity, hypertension, reduced cholesterol, hypertriglyceridemia, hyperinsulemia and reduce insulin sensitivity components of metabolic syndrome. However even after extensive adjustment for cardiovascular risk factors, serum uric acid remained an independent risk factor for stroke.

In a study conducted among patients with acute ischemic stroke there was a statistically significant difference between serum uric acid in diabetic and non diabetic patients^[22]

Hyperuricemia via purine metabolism may also promote thrombus formation.^[23] In another study showed a significant elevation of urate levels in diabetics than non diabetics admitted for TIA and stroke.

In present study 80% of patients with type 2 diabetes mellitus and ischemic stroke had serum uric acid level of >5 mg/dl. So this statistically significant value is taken as cut off value and diabetic subjects with more than this value are at high risk for ischemic stroke. Whether treatment aimed at reducing serum uric acid can be useful to prevent acute cerebrovascular events in those patients remains to be ascertained.

VI. Conclusion

1. Diabetes mellitus patients may either have normal or low uric acid levels but those with stroke have elevated levels of serum uric acid and this association is independent of other risk factors.
2. All patients to be screened for serum uric acid levels and if > 5mg/dl with exclusion of other
3. Causes of hyperuricemia, the patient is at high risk for ischemic stroke.

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