

STUDY OF ASSOCIATION OF SERUM URIC ACID WITH ALBUMINURIA IN TYPE II DIABETES MELLITUSPriti Sambhaji Langote¹, Mallanna Shankreppa Mulimani²¹Post Graduate Student, Department of Medicine, Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur.²HOD and Professor, Department of Medicine, Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur.**ABSTRACT****BACKGROUND AND OBJECTIVES**

Diabetic Nephropathy (DN) is the most common cause of chronic kidney disease worldwide.¹⁻² In the wake of the current epidemic of Diabetes Mellitus (DM), the prevalence of DN and End-Stage Renal Disease (ESRD) is projected to rise.³ Different therapeutic strategies targeting DN have been explored such as tight glycemic control,⁴ tight blood pressure control,⁵ and various inhibitors of the Renin Angiotensin Aldosterone System (RAAS).⁶⁻⁸ while these therapies appear to slow the progression of kidney disease due to diabetes, none of them are curative. Thus we require adjunctive therapeutic strategies, especially in patients with complications of treatment or lack of appropriate response.⁹ hence, there is a pressing interest to identify other potentially modifiable factors in the progression of DN. Inflammation and endothelial dysfunction appear to play a central role in the onset and the progression of DN. Recent evidence has emerged in the last decade to suggest uric acid is an inflammatory factor and may play a role in endothelial dysfunction. Studies suggest that treatment of diabetic nephropathy may be benefited by treatment with xanthine oxidase inhibitor.¹⁰ The aim of this study is to find an association between serum uric acid level and albuminuria in Type 2 Diabetes Mellitus (T2DM).

METHODS

This study was carried out in B.L.D.E.U's Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur, Karnataka; during the period from December 2013 to July 2015. A total of 56 patients who were known case of type 2 diabetes mellitus were included in the study. The blood of the selected subjects were analysed for serum uric acid and urine albumin creatinine ratio.

RESULTS

Serum uric acid levels for and

1. Normoalbuminuric patients=4.09±1.36mg/dL.
2. Microalbuminuric patients=5.21±1.60mg/dL.
3. Macroalbuminuric patients=7.38±0.87mg/dL.

Serum uric acid level correlated positively with urinary albumin creatinine ratio ($r = 0.559$, $p = <0.001$).

CONCLUSION

Serum uric acid had a significant positive correlation with albuminuria in type 2 diabetes mellitus.

KEYWORDS

Uric Acid, Albuminuria, Diabetes, Association, Type 2 Diabetes.

HOW TO CITE THIS ARTICLE: Langote PS, Mulimani MS. Study of association of serum uric acid with albuminuria in type II diabetes mellitus. *J. Evolution Med. Dent. Sci.* 2016;5(16):769-773, DOI: 10.14260/jemds/2016/179

INTRODUCTION

Diabetic Nephropathy (DN) is the most common cause of chronic kidney disease worldwide.¹⁻² In the wake of the current epidemic of Diabetes Mellitus (DM), the prevalence of DN and End-Stage Renal Disease (ESRD) is projected to rise.³

Uric acid is a common risk factor for vascular diseases.⁴ hypertension,⁵ type 2 diabetes mellitus and diabetic nephropathy.⁶ Hyperuricemia has an association with type 2 diabetes mellitus and hypertension independently of each other.

Though the cause and effect relationship of hyperuricemia and diabetic nephropathy is debatable; however, some literature mentions the detrimental effects of high uric acid level on the kidney functions.⁷

The main detrimental effect of high uric acid level as a part of the obesity and metabolic syndrome is through its injurious effects on the endothelium and inducing chronic inflammation.⁸

Accumulating data reveal that inflammation, endothelial dysfunction and procoagulant imbalance are associated with nephropathy, retinopathy and cardiovascular disease in Diabetes Mellitus (DM).⁹⁻¹¹ The association of serum UA levels and dyslipidemia with inflammation and endothelial dysfunction are also shown.^{12,13} However, the putative association between serum UA levels and albuminuria is not clear.

Studies suggest that treatment of diabetic nephropathy may be benefited by treatment with xanthine oxidase inhibitor.¹⁴

The aim of this study is to find an association between serum uric acid level and albuminuria in Type 2 Diabetes Mellitus (T2DM).

MATERIALS AND METHODS

A cross-sectional study is conducted on type 2 diabetic patients attending the outpatient department and being admitted to our Hospital from December 2013 to July 2015.

Financial or Other, Competing Interest: None.

Submission 15-01-2016, Peer Review 09-02-2016,

Acceptance 15-02-2016, Published 24-02-2016.

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DOI: 10.14260/jemds/2016/179

With the prevalence rate of overt nephropathy in Diabetes Mellitus 2.2%.¹⁵ at 99% confidence interval and at ±5 margin of error the sample size is 56.

$$N = (2.56)^2 * P * Q / d^2$$

Hence, 56 cases of type 2 diabetes mellitus are included in the study to associate serum uric acid level with albuminuria.

Data is analysed using,

- Diagrammatic presentation.
- Mean±SD.
- Correlation coefficient.
- Linear and multiple regression analysis.

A detailed history, physical examination including blood pressure, BMI, current medications, insulin doses, habits like tobacco and alcohol consumption and family medical history is obtained from all the patients coming to the hospital with type 2 diabetes mellitus.

The biochemical investigations like examination of urine, serum uric acid, serum creatinine, HbA1C is estimated and urine albumin and urine creatinine are measured.

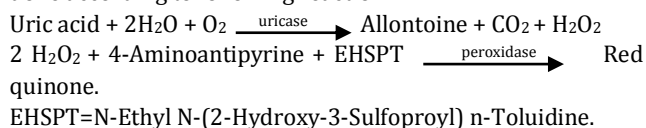
Patients with known case of type 2 diabetes mellitus were included in this study and patients who are on treatment with uric acid lowering agents/diuretics, history of gout/acute febrile illness/UTI/CML/Cancer were excluded from the study.

After obtaining informed and written consent venous blood is collected from each subject and transported to the laboratory. Random spot urine sample is collected at the same time.

Urine Albumin Concentration (UAC) is measured by turbidimetric immunoassay and is expressed as urine albumin creatinine ratio (ACR). Urinary ACR is calculated by dividing UAC in micrograms by urinary creatinine concentration in milligrams.

1. ACR =30.0µg/mg or lower is considered as “normal,”
2. ACR between 30µg/mg and 299µg/mg is considered as “microalbuminuria.”
3. Very high ratio (ACR ≥ 300µg/mg) is defined as “overt albuminuria.”

Serum uric acid level is measured by uricase peroxidase method (Liqui CHEK, AGAPPE). Enzymatic determination is done according to following reaction.



All the subjects are subjected to the following investigations

1. Urine Examination.
2. Serum Creatinine.
3. Serum Uric Acid.
4. HbA1C.
5. Urine Albumin.
6. Urine Creatinine.
7. Random Blood Sugar (RBS) Level.
8. Fasting Blood Sugar (FBS) Level.
9. Post Prandial Blood Sugar (PPBS) Level.
10. HIV Rapid Test.

RESULTS

Clinical characteristics of 56 patients with type2 DM enrolled in this study are shown in Table 1.

Sr. No.	Parameters	Value (Mean±SD)
1	Age(years)	56.61±12.11
2	Gender I. Male II. Female	29 (52%) 27 (48%)
3	BMI(kg/m ²)	23.82±3.43
4	SBP(mmHg)	137.86±14.36
5	DBP(mmHg)	81.39±6.86
6	Duration of duration(years)	6.63±4.03
7	SUA(mg/dL)	5.11±1.70
8	Sr. Creatinine(mg/dL)	1.05±0.40
9	HbA1C(%)	7.30±2.34
10	ACR(µg/mg)	96.05±91.56

Table 1: Characteristics of the study population

Out of 56 patients, males and females were 29(52%) and 27(48%), respectively. The mean age of the patients included in this study was 56.61±12.11 years and mean duration of diabetes of the patients was 6.63±4.03 years. The mean body mass index of study population was 23.82±3.43kg/m², while the mean serum uric acid concentration observed in study population was 5.11±1.70mg/dL.

The mean uric acid concentration was 5.11±1.70mg/dL, which was higher in men than in women (5.12 ± 1.50mg/dL versus 5.09±1.92mg/dL, respectively) But there was no statistically significant difference in serum uric acid concentration between males and females (P=0.939).

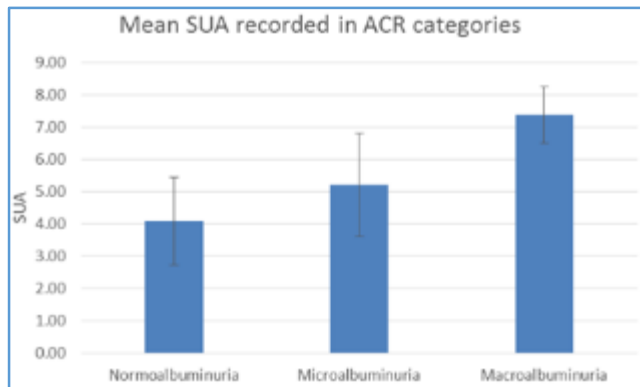
The mean value of Normoalbuminuria, Microalbuminuria and Macroalbuminuria in the enrolled patients was 17.54±5.53, 96.53±52.4 and 327.43±32.6, respectively.

Parameter	Norm albuminuria	Micro albuminuria	Macro albuminuria
Age	54.53±12.96	56.69±12.10	62.20±9.63
Male	10 (67%)	16 (44%)	3 (60%)
Female	5 (33%)	20 (55%)	2 (40%)
BMI	23.41±2.46	24.17±3.84	22.60±2.81
HTN	0 (0%)	9 (25%)	4 (80%)
SBP	133.87±10.89	137.28±13.32	154.00±21.91
DBP	80.27±5.60	80.94±6.82	88.00±8.37
HbA1C	5.81±1.50	7.76±2.37	8.40±2.60
Duration of DM	4.93±2.55	6.44±3.67	13.00±4.70
Serum Creatinine	0.95±0.41	1.06±0.36	1.30±0.58
SUA	4.09±1.36	5.21±1.60	7.38±0.87

Table 2: All parameters compared with ACR classification

In this study it is found that 9 (25%) of microalbuminuric and 4 (80%) of macroalbuminuric patients were having hypertension (Table 2).

The mean HbA1C was more in macroalbuminuric patients (8.40±2.60) than in microalbuminuric patients (7.76±2.37), while in patients with normoalbuminuria, it was found to be 5.81±1.50.



Graph 1: Mean Serum uric acid (mg/dL) in ACR categories

It is found that concentration of serum uric was 4.09 ± 1.36 , 5.21 ± 1.60 and 7.38 ± 0.87 in patients with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively. While considering normoalbuminuria and abnormal albuminuria, serum uric acid concentration was 4.09 ± 1.6 and 5.48 ± 1.68 , respectively.

It was found that there was statistically significant and positive correlation between serum uric acid concentration and albumin creatinine ratio ($r=0.559$, $p<0.001$) in the enrolled type 2 diabetic patients.

Duration of diabetes was also positively correlated with albumin creatinine ratio. It was also statistically significant ($r=0.526$, $P<0.001$).

Also, it was found positive and statistically significant correlation between HbA1C and albumin creatinine ratio ($r=0.429$, $p=0.001$).

The correlation between BMI and ACR was found to be almost nil ($r = -0.001$) and was not statistically significant ($P>0.05$), while SBP showed statistically significant correlation with albumin creatinine ratio ($p = 0.001$)

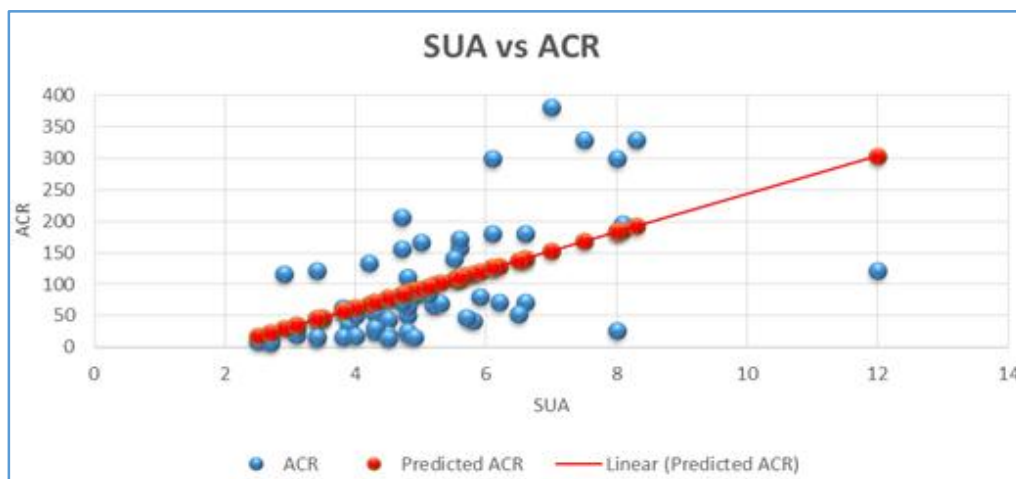
Only those parameters which were found to be significantly correlated with ACR are used in regression. By linear regression, variations in ACR are estimated using different parameters individually.

Considering the R^2 (Coefficient of determination) value, serum uric acid is found to be a significant factor which could predict only 31.2% ($R^2 = 0.312$) variation in albumin creatinine ratio.

Sl. No.	Parameters	Correlation coefficient 'r'	'p' value
1	Age	0.214	0.113
2	BMI	-0.001	0.994
3	SBP	0.431	0.001*
4	DBP	0.254	0.059
5	Duration of Diabetes (years)	0.526	<0.001*
6	Serum Uric Acid	0.559	<0.001*
7	Serum Creatinine	0.310	0.020*
8	HbA1C	0.429	0.001*

Table 3: Correlation between Albuminuria (ACR) and other parameters

* denotes significant correlation



Graph 2: Scattered plot of predicting ACR using SUA

By multiple regression, considering all variables together they predict 47.2% ($R^2 = 0.472$) variation in albumin creatinine ratio.

Thus, it showed that serum uric acid was an independent predictor of albumin creatinine ratio, after using adjusted R^2 value.

DISCUSSION

A cross-sectional study was done in 56 type 2 diabetic patients attending the outpatient department and being admitted to our hospital from December 2013 to July 2015. And the relationship between serum uric acid concentration and degree of urinary albumin excretion in type 2 diabetic patients was evaluated.

In this study, a positive correlation was found between serum uric acid and albumin creatinine ratio. In the study conducted by Fukui, et al. positive correlation of serum uric acid and urinary albumin excretion in 343 men with type 2 diabetes mellitus was shown.⁷ Similarly, Fu et al. in a study on Chinese diabetic patients found that hyperuricemia was significantly associated with abnormal albuminuria in patients without diuretics or use of uricosuric agents or alcohol.¹⁶ Siu and colleagues reported lowering serum uric acid level in patients with hyperuricemia was associated with regression of kidney disease.⁵

In this study, it was found that duration of diabetes and systolic blood pressure was significantly associated with albumin creatinine ratio. Mogensen.¹⁷ had concluded that age, diabetes duration, glycemic control, blood pressure and metabolic syndrome were all associated with albuminuria and decline of GFR.

Studies in rats showed that the renal changes can be prevented by maintaining SUA levels in the normal range by allopurinol.^{18,19} but only partially prevented by the treatment of hypertension with enalapril or losartan.¹⁹⁻²¹ These observations suggested that a pathogenic role of uric acid in the renal abnormalities independent of blood pressure and imply a possible efficacy to lower urinary albumin-to-creatinine ratio in diabetic patients by bringing down the uric acid levels. A recent human study did prove that allopurinol treatment could normalize endothelial dysfunction in type 2 diabetic patients with mild hypertension.²²

This study suggested the importance of uric acid as a predictor of albuminuria in type 2 diabetic patients. The pathogenic role of serum uric acid in renal injury and in increasing urinary albumin excretion rate is worthy of further investigation.

This study had some limitations. The sample size was small. The validity to extrapolate the relationship between uric acid and urinary albumin excretion rate to non-diabetic subjects requires confirmation. As this was a cross-sectional study, further prospective studies should be made to evaluate the relationship between the serum uric acid and albuminuria in type 2 diabetic patients.

CONCLUSION

This study showed that the serum uric acid concentration was significantly and positively associated with albuminuria in patients with type 2 diabetes mellitus. It was hypothesized by this study that serum uric acid may play a pathological role in

the development of albuminuria in type 2 diabetes mellitus. To approve this hypothesis, study of the effect of lowering uric acid with allopurinol on renal function in diabetic nephropathy patients is suggested in future.

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