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HYPERURICEMIA AND ALBUMINURIA IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

Introduction: Hyperuricemia is considered to be an independent risk factor for renal dysfunction in diabetics and albuminuria can be used as a surrogate marker of early diabetic nephropathy. We studied the correlation between hyperuricemia and albuminuria in type 2 diabetes mellitus patients. **Materials and Methods:** In a cross-sectional study of 90 patients (45 men and 45 women) with type 2 diabetes mellitus, serum uric acid, albuminuria and urinary albumin-creatinine ratio were determined. Other parameters namely blood pressure, body mass index, serum cholesterol, serum triglycerides, glomerular filtration rate and fasting blood glucose were also assessed. **Results:** The mean age of the study population was 61.49 ± 11.4 years. Serum uric acid levels for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 5.01 ± 1.46, 6.8 ± 1.16 and 8.58 ± 0.42mg/dL respectively. Serum uric acid level had a significant positive correlation with urinary albumin creatinine ratio even after adjustment for age, sex, body mass index, insulin use, smoking, diabetes duration, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, serum cholesterol, triglycerides, and calculated creatinine clearance. There was also significant association between hyperuricemia and serum triglyceride, fasting blood glucose, cholesterol levels, glomerular filtration rate, serum creatinine levels, age, duration of diabetes mellitus, and body mass index. **Conclusions:** We demonstrated that serum uric acid levels have a significant independent positive correlation with albuminuria.

KEYWORDS: Type 2 diabetes**,** hyperuricemia, diabetic nephropathy, albuminuria.

INTRODUCTION

Hyperuricemia is associated with increased risk of hypertension, cardiovascular events and nephropathy. Studies have shown that high uric acid levels are injurious to the kidneys and are predictive of the progression of renal disease.[1-3] Moreover, mild hyperuricemia can induce glomerular hypertension and renal afferent arteriolar thickening and thus lead to renal disease progression.[4] Hyperuricemia induced glomerular hypertrophy is independent of blood pressure control and moreover, the activation of the renin–angiotensin system may only partly explain the induction of glomerular hypertrophy by uric acid.[4] This study was done to verify the hypothesis that elevated uric acid may be independently associated with the development of increased urinary albumin excretion in diabetic patients.

METHODOLOGY

The objective was to analyse the correlation of serum uric acid and urinary albumin excretion rate in type 2 diabetes mellitus. The study design was cross sectional study of patients at a tertiary care hospital in Southern India between April 2015 and March 2016. The inclusion criteria were type 2 Diabetes Mellitus (according to ADA criteria)[5] and age above 13 years. The exclusion criteria were patients with hypertension, collagen vascular disease, connective tissue disease, current urinary tract infections, sepsis or malignancies, chronic kidney disease or renal calculi, on chemotherapy, thiazides, salicylates, pyrazinamide, nicotinic acids or cyclosporine. A detailed history, physical examination and biochemical test were performed. Early morning first void mid-stream urine sample was collected after overnight fasting for 12 hours, similarly venous sample for serum uric acid, blood glucose, serum cholesterol, triglycerides and serum creatinine was collected after overnight fasting for 12 hours. Creatinine clearance (mL/min) was calculated by the Cockcroft-Gault formula.[6] Urinary albumin - to- creatinine ratio (ACR) was calculated by dividing the urinary albumin concentration in micrograms by the urinary creatinine concentration in milligrams. ACR <30.0 µg /mg was defined as normoalbuminuria, 30.0 to 299.9 µg/mg as microalbuminuria, and ≥300.0 µg /mg as

macroalbuminuria.[7] Abnormal albuminuria was defined as an ACR ≥30.0 µg /mg (i.e., microalbuminuria plus macroalbuminuria). All statistical calculations were performed with the SPSS 17 software. Comparisons between the groups were made with the paired t test where appropriate. The Pearson correlation with two-tailed probability values was used to estimate the strength of association between variables. The level of statistical significance was set at p value of ≤ 0.05. All results were expressed as mean ± SD.

RESULTS

A total of 90 cases of type 2 diabetes mellitus patients were included in the study. The male to female ratio in this study was 1:1 and the age range was 53 -72 years with a mean age of 61.49 ± 11.4 years. 19 (21.1) patients were active smokers. Almost 65% have blood sugar < 140 mg/dl and only 34% have >140 mg/dl fasting blood sugar. Majority of the patients (62%) were on oral hypoglycaemic agents only. 34 (37.8%) and 38 (42.2%) patients had high blood triglyceride levels (>150 mg/ dl) and cholesterol levels (>250 mg/dl) respectively. The uric acid levels in our study population are depicted in the figure -1.

Majority of patients had serum uric levels of 6-7 mg/dl (27.8%), followed by 7-8 mg/dl (21.1%). Table 1 shows the serum creatinine levels and Figure 2 shows the creatinine clearance in the study population. Majority (53.3%) of patients had calculated creatinine clearance of <60mL/min, while 46.7% had creatinine clearance of > 60mL/min. Table 3 shows the baseline characteristics of the study population. There was statistically significant association of increased uric levels with albuminuria (p< 0.001). There was a significant positive correlation between serum uric acid levels and degree of urinary albumin excretion was significant even after adjustment for age, sex, body mass index (BMI), insulin use, smoking, diabetes duration, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose, serum cholesterol, triglycerides, and calculated creatinine clearance. (Table-5). There were significant association between hyperuricemia and serum concentration of triglyceride, serum cholesterol, fasting blood sugar, duration of diabetes, body mass index and hypertension (Table-6).

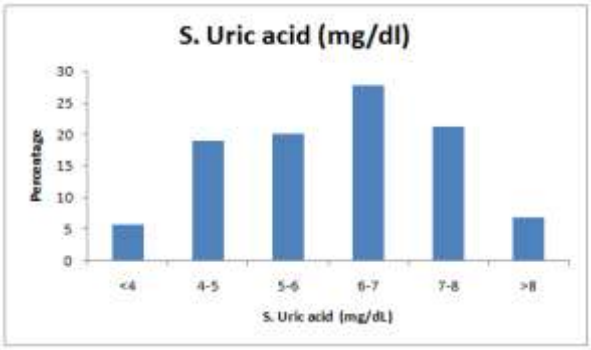

Figure 1: Bar diagram showing serum uric acid levels.

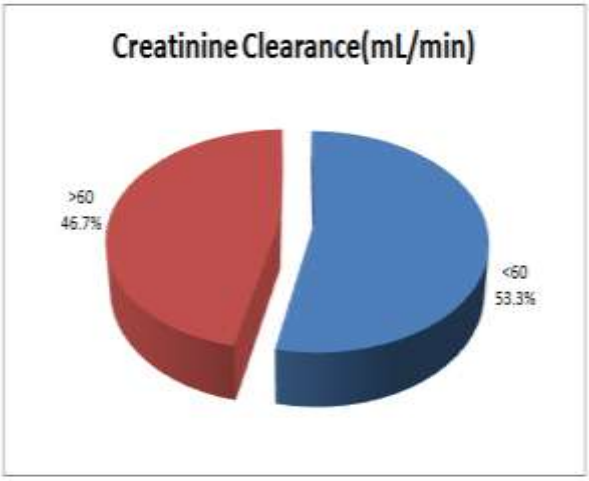

Figure 2: Pie chart showing creatinine clearance.

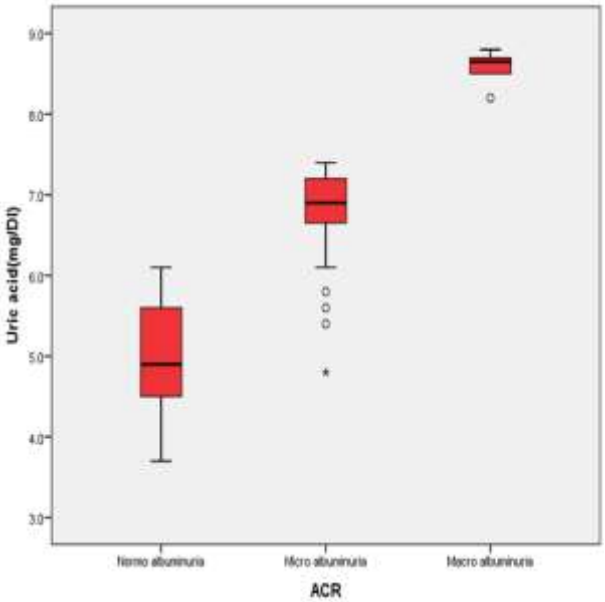

Figure 3: Box plot diagram showing Uric acid levels versus ACR.

Table 1: Serum creatinine levels of the study population.

S. Creatinine (mg/dl)	Frequency	Percent
<1	4	4.4
1-1.5	68	75.6
>1.5	18	20.0
Total	90	100.0

Table 2: Baseline characteristics of the subjects.

Characteristic	Mean	SD	Range
Age (years)	61.49	5.787	53 – 72
BMI kgm2	22.711	1.4858	19 – 26
Diabetic duration (years)	4.96	4.149	1 – 15
SBP (mmHg)	123.62	9.728	100 – 138
DBP (mmHg)	78.02	7.180	68 – 90
Fasten plasma glucose (mg/dl)	128.80	29.000	89 - 227
Serum cholesterol (mg/dl)	228.89	44.645	167 - 318
Triglycerides (mg/dl)	128.66	24.639	94 - 168
Uric acid (mg/dl)	6.101	1.2641	3.7 – 8.8
Creatinine clearance (mL/min)	51.2676	13.03756	27 – 77
Serum creatinine (mg/dl)	1.319	.2723	.7 – 1.9
Serum urea (mg/dl)	39.08	8.042	21 – 57
12 hour urine protein (mg/12hr)	120.911	101.2187	26.5– 315
Urine creatinine (mg/dl)	54.68	20.752	32 – 97
Albumin creatinine ratio (µg/gm)	125.7009	107.40637	26.5 - 317

Table 3: Distribution of serum uric level with respect to levels of albuminuria

Albuminuria	N	Uric acid(mg/dl)	
		Mean	SD
Normalbuminuria	41	5.01	0.73
Micro albuminuria	43	6.80	0.58
Macro albuminuria	6	8.58	0.21
Total	90	6.10	1.26

P value is < 0.001 (ANOVA).

Table 4: Correlation coefficients between uric acid and covariates.

Covariates	Uric acid	
	Pearson Correlation r	p
Age	.849**	<0.001
BMI kgm2	.569**	<0.001
Diabetic duration (years)	.878**	<0.001
SBP(mmHg)	.831**	<0.001
DBP(mmHg)	.843**	<0.001
Fasting plasma glucose(mg/dl)	.877**	<0.001
Serum cholesterol (mg/dl)	.854**	<0.001
Triglycerides (mg/dl)	.841**	<0.001
Calculated creatinine clearance mL/min	-.874**	<0.001
ACR	.856**	<0.001

Table 5: Standardised regression coefficients for ACR and odds ratio for abnormal albuminuria by uric acid treated as a continuous variable.

	Unstandardized Coefficients		Standardised B	p	95% CI for B		OR	95% CI for OR	
	B	Sd			Lower	Upper		Lower	Upper
Step1	1.060	.068	.856	.000	.924	1.195	2.89	2.52	3.3
Step 2	.605	.178	.488	.001	.250	.959	1.83	1.28	2.61
Step 3	.290	.168	.235	.088	-.044	.625	1.34	0.96	1.87
Step 4	.109	.173	.088	.530	-.235	.454	1.12	0.79	1.57

Step 1 - Without adjustment.
Step 2 - Adjusted for age and sex.
Step 3 - Adjusted for age, sex, BMI, triglycerides and calculated creatinine clearance.
Step 4 - Adjusted for age, sex, BMI, insulin use, smoking, diabetes duration, SBP, DBP, fasting plasma glucose, serum cholesterol, triglycerides, and calculated creatinine clearance.

DISSUSSION

We evaluated the relationship between serum uric acid levels and degree of urinary albumin excretion in patients with type 2 diabetes mellitus. The present study shows the prevalence of normoalbuminuria, microalbuminuria and macroalbuminuria as 45.6%,

47.8% and 6.7% respectively. The mean serum uric levels for the respective groups were 5.01, 6.8 and 8.58 mg/dL ($p<0.001$). The higher prevalence of serum uric acid and abnormal albuminuria in our study were probably due to poor diabetic control.[8,9] Since the appearance of albuminuria is an early sign of onset of diabetic nephropathy in patients with diabetes mellitus,[3] the association between ACR and hyperuricemia confirmed the effect of hyperuricemia on diabetic nephropathy. In our study, a significant association was found between these two parameters ($p< 0.001$). Though hyperuricemia can be a consequence of kidney dysfunction,[10] we found that there was a strong positive correlation between serum uric acid concentration and albuminuria even after adjustment for estimated GFR and other factors (age, sex, BMI, insulin use, smoking, diabetes duration, SBP, DBP, fasting plasma glucose, serum cholesterol and triglycerides). A similar significant association between serum uric acid concentration and degree of urinary albumin excretion has also been demonstrated by Shokoofeh Bonakdaran in a large cross-sectional study of 1275 type 2 diabetes mellitus.[11] In our patients, there were significant association between hyperuricemia and serum concentration of triglyceride, serum cholesterol, and fasting blood sugar. We also demonstrated a positive association between hyperuricemia and duration of diabetes, body mass index. Similar relationship between hyperuricemia and serum concentration of triglyceride, serum cholesterol, fasting blood sugar, duration of diabetes, and body mass index has been reported previously.[11,12]

CONCLUSION

1. The level of serum uric acid has significant independent positive correlation with urinary albumin excretion rate.
2. The serum uric acid level has significant association with albumin-creatinine ratio, age, BMI, diabetes duration, smoking, fasting plasma glucose, serum triglycerides, serum cholesterol and calculated creatinine clearance.
3. As hyperuricemia is a common finding in diabetes mellitus patients, and its treatment is easy and available, early diagnosis and treatment may prevent or decrease the onset of overt kidney disease in this population.

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