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Original Research Article

Role of Uric Acid in Detection of Early Renal Function Decline in Type 1 Diabetes

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Abstract: Recent studies have reported that a high serum level of uric acid is strongly associated with impaired renal function and cardio vascular disease. This study aims to find out the role of uric acid in detection of early renal function decline before the onset of microalbuminuria in type 1 Diabetic patient. A total of 130 type 1 Diabetic patients (65 normoalbuminuric & 65microalbuminuric) were recruited in the cross sectional study. Uric acid was measured by enzymatic colorimetric method. Other parameters like blood pressure, body mass index, HbA1c, Fasting Plasma glucose, Plasma lipid profile, serum Creatinine, urine albumin and creatinine ratio were assessed. Estimated Glomerular filtration rate was calculated by CKD-EPI equation. The respective mean uric acid levels in normoalbuminuria & microalbuminuria were 3.92+/-1.59 & 4.99+/-2.48mg/dL(p=0.004). Urinary albumin creatinine ratio in normoalbuminuria was 13.64+/-7.66 and in Microalbuminuria it was 127.98+/-81.23. (p<0.001). In normalbuminuria mean GFR levels were 110.40+/-20.30ml/min and in microalbuminurics it was 100.25+/-27.12ml/min. (p-0.02). eGFR >90ml/min was present in 54.5% of normoalbuminurics & 45.5% of microalbuminurics. eGFR<90ml/min was present in 34.5% of normoalbuminurics and 65.5 % of microalbuminurics. Lower GFR was strongly & independently associated with elevated serum uric acid & increased urinary albumin creatinine ratio. Uric acid was negatively correlated with eGFR (p-<0.001).Serum uric acid in high normal range associated with impaired renal function in patients with type1 diabetes. Therefore it can be used as marker for detecting early renal function decline in patients with type 1 diabetes in Indian clinical setting , where detection rate is lower & complications are higher.
Keywords: Type 1Diabetes, Serum Uric acid, eGFR, Normoalbuminuria, Microalbuminuria

INTRODUCTION

Diabetes Mellitus represents a heterogenous group of disorders, which is characterised by insulin insensitivity and/or hyposecretion. Prevalence of diabetes is increasing globally and it is one of the major health problems of the 21st century. The Estimated number of People with Diabetes Worldwide was 366 Million in 2013 and it is expected to rise around 522 Million by 2030 [1]. About 62.4 Million people currently have Diabetes in India [2] and it is expected to rise to 101.2 Million by 2030 [3]. The burden of Diabetes is due to its many complications. Diabetic Nephropathy is the most common Microvascular complication of Diabetes. Diabetic Nephropathy affects 20-30% of both Type1 and Type 2 Diabetic patients [4]. ESRD develops in 50% of Type1 diabetic individuals compared to 20% in Type 2 diabetic individuals [5]. Microalbuminuria is considered as the earliest clinically detectable stage of Diabetic Nephropathy, at which point appropriate interventions can reverse or retard the progression of Diabetic kidney disease [6]. Recent studies have reported that, Uric acid is a well known marker for detecting renal damage at an earlier stage before the onset of Microalbuminuria.

Increased serum concentrations of Uric acid induce endothelial dysfunction, glomerular hypertrophy, and afferent arteriolar wall thickening, inhibit the production of nitric oxide & promote the development of Microalbuminuria. Thus this study was

conducted with an aim to find the role of uric acid in normoalbuminuric and Microalbuminuric Type 1 Diabetic patients with low GFR.

MATERIALS &METHODS

This is a cross sectional case control study and was conducted after getting Institutional ethical committee approval. The study composed of a total number of 130 subjects of Type1 Diabetes mellitus patients attending Diabetology outpatient department in Rajiv Gandhi General Hospital, Chennai.

Inclusion Criteria were >5 yrs duration of type 1 diabetic patients of age 10-40 yrs on treatment with insulin. Exclusion criteria were Type 2diabetics, Macroalbuminuric patients, renal transplant patients, Patients with acute illness and with cardiac ailments. Patients were selected after doing urine dipstick to rule out proteinuria.

Cases were divided in to two groups based on Urine albumin creatinine ratio. (UACR).Albumin creatinine ratio were obtained by taking 3 consecutive early morning midstream urine samples on three separate visit and average ACR was calculated.

Group1: 65 Type 1 Diabetic patients with normoalbuminuria. (UACR<30mg/g of creatinine)

Group2: 65 Type 1 Diabetic patients with Microalbuminuria. (UACR 30-300mg/g of creatinine)

Blood sample collection

Blood was collected after 8-12 hrs of overnight fasting and the following investigations were performed. Fasting plasma Glucose, HbA1c, plasma lipid (TGL, Total cholesterol, HDL), serum uric acid. The blood samples were analysed within 4 hrs of sample collection and were analysed by the following methodologies. Urine albumin concentration was determined in semiautoanalyser by Latex agglutination method/Immunoturbidimetry. Kit from Bio systems Instruments & Reagents. Creatinine concentration in the urine sample was determined by modified Jaffe's method.

Urine albumin creatinine Ratio was calculated using UACR=

$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine Creatinine (g/dL)}}$$

UACR=mg/g of creatinine.

After classifying the patients based on UACR in to 2 groups, following analytes were estimated. Serum uric acid was measured in a clinical analyser utilising an uricase based commercial kit.

eGFR is calculated using serum creatinine by CKD-EPI formula as follows. eGFR=141*min (Serum Cr/κ, 1) α *Max (Serum Cr/κ, 1)-1.029 *0.993age *(1.018if female)*1.159 if Black. κ = **0.7** (female) or 0.9 (male) ;(b) α = **−0.329** (female and **SC** ≤ 0.7mg/dL), **α=−1.209** (female and SC > 0.7mg/dL) ;(c) α = **−0.411** (male and SC ≤ 0.9mg/dL), **α=−1.209** (male and SC > 0.9mg/dL.

Plasma Glucose was estimated in semiautoanalyser by Glucose oxidase -Peroxidase method (GOD-POD), Urea estimated by UV-SLR, Fixed time Kinetic assay. Estimation of HbA1c :(Bio Rad D-10 Analyser) by Ion exchange high performance liquid chromatography. Total Cholesterol was determined by cholesterol esterase-cholesterol oxidase method. Estimation of Triglycerides by Glycerophosphate oxidase -chlorophenol Amino phenazone (GPO-PAP) method. Estimation of HDL-Cholesterol by Phosphotungstic acid method.

Statistical Analysis

Data was analysed using SPSS software version 16.0 and p value less than 0.05 was considered statistically significant. Age, Duration of Diabetes, BMI, Total cholesterol, HbA1c, Uric acid, eGFR were compared between study groups by Student t-test. Gender was analysed by Chi square test. One way ANOVA was done to compare more than two variables in the same group & between two groups. It was carried out to compare eGFR between Normoalbuminuric & Microalbuminuric type 1 Diabetic patients. Correlation of Parameters namely eGFR, with uric acid were found out by Pearson correlation analysis. To find out the correlation between uric acid &eGFR in the presence of HbA1c, partial correlation was used.

Multiple regression analysis was performed to evaluate the mathematical relationship between eGFR and other variables (Age, duration, Gender, HbA1c, Cholesterol, BMI & Uric acid) in Normoalbuminuric & Microalbuminuric Type 1 Diabetes.

RESULTS

Table-1: Comparison of characteristics of type1 diabetics with norm albuminuria and microalbuminuria

	Albuminuria	N	Mean	Std. Deviation	p value
Age	Normal	65	28.10	8.32	0.16
	Micro	65	30.12	7.78	
BMI	Normal	65	22.26	3.50	0.46
	Micro	65	22.74	3.85	
FBS(mg/dL)	Normal	65	149.28	80.50	0.19
	Micro	65	171.98	111.39	
HbA1C (%)	Normal	65	8.44	1.723	0.41
	Micro	65	8.69	1.69	
Total Cholesterol(mg/dL)	Normal	65	150.06	49.34	0.09
	Micro	65	164.49	47.39	
TGL(mg/dL)	Normal	65	97.49	44.28	0.04
	Micro	65	117.13	61.79	
HDL(mg/dL)	Normal	65	40.52	17.71	0.39
	Micro	65	38.21	12.25	
Creatinine(mg/dL)	Normal	65	.81	.21	0.21
	Micro	65	1.28	3.00	
Albumin(g/dL)	Normal	65	3.90	.56	0.003
	Micro	65	3.62	.50	
Total Protein(g/dL)	Normal	65	6.25	.52	<0.001
	Micro	65	5.81	.79	
UrineACR	Normal	65	13.64	7.66	<0.001
	Micro	65	127.98	81.23	

Table-2: Comparison of uric acid with normoalbuminuria & microalbuminuria

	Albuminuria	N	Mean	Std. Deviation	Std. Error Mean
Uricacid	Normal	65	3.92	1.59	0.20
	Micro	65	4.99	2.48	0.31

p = 0.004

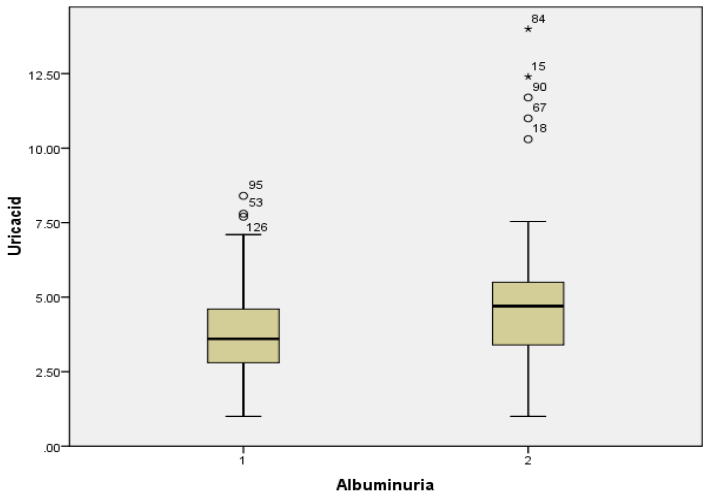

Fig-1: Distribution of uric acid in normalbuminuria &microalbuminuria.

1=Normoalbuminuria, 2=Microalbuminuria, o-Outliers, *-Extreme values.

Table-3: Comparison of egger between normoalbuminuria & microalbuminuria

	Albuminuria	N	Mean	Std. Deviation	Std. Error Mean
eGFR	normal	65	110.40	20.30	2.52
	micro	65	100.25	27.12	3.36

p= 0.02.

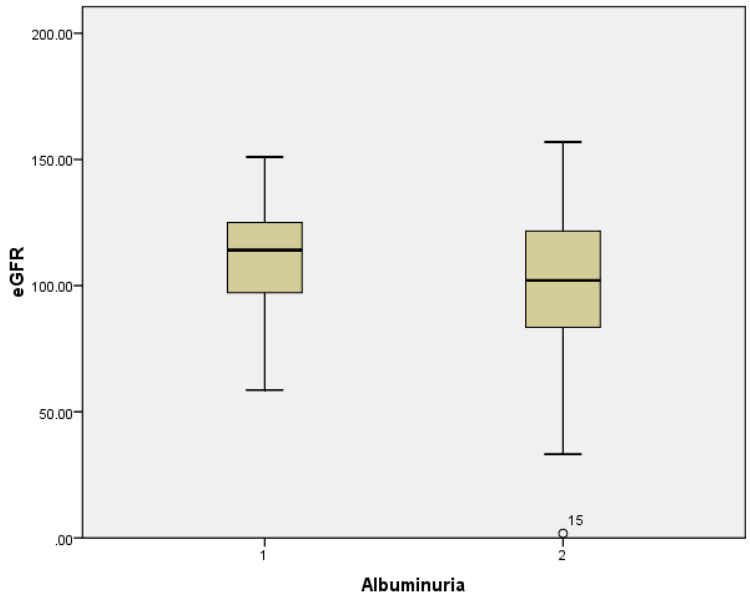

Fig: 2 Distribution of egfr in normoalbuminuria & microalbuminuria

1=Normoalbuminuria, 2=Microalbuminuria, o-Outliers

Table-4: Comparison of mean gfr between two groups.

eGFR				
	N	Mean	Std. Deviation	P value
1	29	114.58	20.03	<0.001
2	29	109.55	17.69	
3	28	107.80	22.72	
4	19	104.12	19.72	
5	23	84.93	32.00	
Total	128	105.07	24.50	

p<0.001.

Uric acid concentrations:

< 3 mg = 1, 3 to 3.9 = 2, 4 to 4.9 = 3, 5 to 5.9 =4,> 6 mg = 5.

Table-5: correlation of uricacid with eGFR in study groups

		Uricacid	eGFR
Uricacid	Pearson Correlation	1	-.389**
	Sig. (2-tailed)		.000
	N	130	130
eGFR	Pearson Correlation	-.389**	1
	Sig. (2-tailed)	.000	
	N	130	130
**. Correlation is significant at 0.01 level (2-tailed).			

r = -0.39 p = <0.001

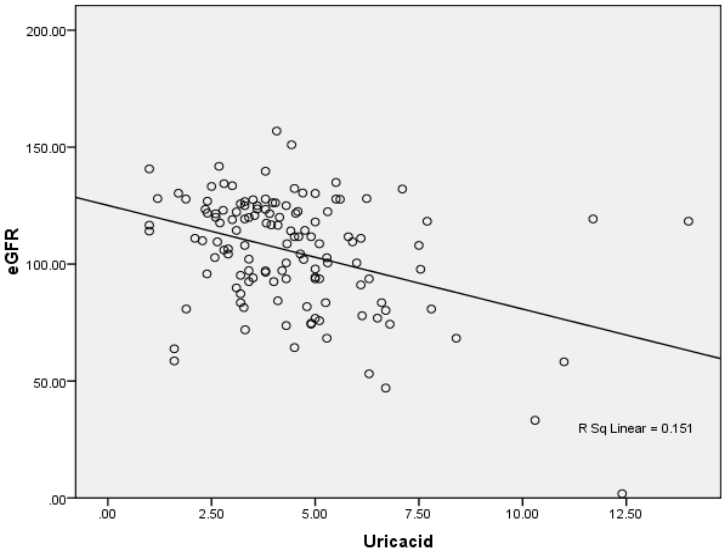

Fig-3: correlation of eGFR with **uric acid**

Table-6: Strength of relationship between uric acid & eGFR after Eliminating HbA1C

Control Variables			**Uric acid**	**eGFR**
HbA1C	**Uric acid**	Correlation	1.000	-.261
		Significance (2-tailed)	.	.038
		Df	0	62
	eGFR	Correlation	-.261	1.000
		Significance (2-tailed)	.038	.
		Df	62	0

p<0.05.

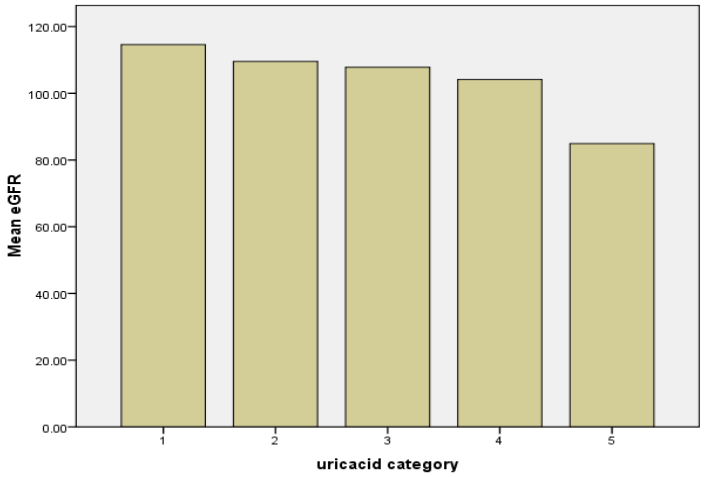

Fig-4: mean eGFR among various uricacid categories

< 3 mg = 1, 3 to 3.9 = 2, 4 to 4.9 = 3, 5 to 5.9 = 4,> 6 mg = 5.

Table-7: multiple regression analysis of eGFR with other risk factors in two groups

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	162.04	19.74		8.20	.000		
	Age	-1.01	.31	-.34	-3.24	.002	.50	1.97
	Gender	-4.61	3.85	-.09	-1.19	.233	.85	1.16
	Duration	-.082	.38	-.02	-.21	.829	.54	1.84
	BMI	-.26	.50	-.04	-.51	.607	.92	1.08
	Hypertension	-7.10	4.22	-.13	-1.68	.095	.82	1.21
	Uric acid	-3.43	.92	-.30	-3.70	.000	.81	1.22
	HbA1C	.58	1.17	.04	.49	.621	.79	1.26
	Cholesterol	-.00	.03	-.00	-.07	.942	.90	1.11
a. Dependent Variable: eGFR								

Age $p < 0.01$, Uric acid $p < 0.001$, Other variables $p > 0.05$

DISCUSSION

Diabetes is the most common disease causing End stage renal disease [7]. About 20-30% of Type1 diabetic patients develop nephropathy and 7-10% develop coronary artery disease. Generally increase in albumin excretion rate is widely accepted as the first clinical sign of Diabetic Nephropathy. Recent studies show that reduced Glomerular filtration rate manifests as the primary clinical abnormality of diabetic nephropathy even before microalbuminuric stage and progresses to overt nephropathy. Dyslipidaemia, hyperglycemia and systemic hypertension have additive effects on the progression of microalbuminuria.

Serum uricacid is a potentially important mediator of renal disease. Hyperuricemia increases systemic bloodpressure, proteinuria, renal dysfunction & progressive renal scarring via renin angiotensin and COX-2 dependent pathway.It is an important risk factor for development of microalbuminuria and this risk was independent of age,gender and other risk factors. Hence estimation of serum uric acid may help to identify individuals with increased risk for developing microalbuminuria & CKD. Our study aims to correlate uricacid with glomerular filtration rate in non proteinuric type 1 Diabetes.

Uricacid also induces endothelial dysfunction by inhibiting nitricoxide production and it is a common finding in patients with both cardiovascular &renal disease. Hence in our study we measured uricacid for predicting renal risk in type1 diabetes,so that we would be able to treat the patients at an earlier stage and slow down the progression of renal disease in type1 diabetes.

In the present study ,we recruited people in to two groups:

Group-I : 65 Normoalbuminurics and Group-II: 65Microalbuminuric type 1 diabetic patients.

In group -1: Mean serum uricacid level was found to be 3.92+/-1.59.mg/dL which is in normal range. In group-II: Mean serum uric acid level was found to be 4.99+/-2.48 mg/dL which is in high normal range. This result was similar to the study by Krolewski *et al* [8], in which they had showed that majority of concentration of uricacid was in the normal range. but it is higher in microalbuminurics than normoalbuminurics. Commmunity based study of Japanese adults [9] showed that hyperuricemia has strong predictive capacity of the risk of renal failure than proteinuria.Our study also reflects the same findings.

Similar result have been found in experimental study in Rats [10]. Mean GFR was higher in Normoalbuminuric individuals and was in the range of 110.40+/-20.30 ml/min and it was lower in Microalbuminuric individuals which is in the range of 100.25+/-27.12ml/min. Although mean GFR in both groups were in the normal range, HyperfiltrationGFR>130ml/min was less frequently seen in Microalbuminurics compared to Normoalbuminuric diabetic patients.

Conversely moderately impaired renal function with GFR 30-59ml/min & mildly impaired renal function with GFR 60-89 ml/min were more in Microalbuminurics than Normoalbuminuric diabetic patients. Variables like Age, duration, BMI, BP, HbA1c that were associated with eGFR in

Microalbuminuria & normoalbuminuria were examined by multiple regression equations to evaluate their independent contributions.HbA1c, BP and BMI measurements did not show independent effects on eGFR.

Increasing age &duration of Diabetes is associated with significant Glomerular lesions even in the absence of elevated albumin excretion rate. In our study,there is a statistically significant difference in age groups with p value of <0.01 was noted ,but the duration was not significant.The possible reason for this,may be that Diabetes had manifested in a much younger age & the duration of Diabetes was longer ,but it was detected later. As a result of this,there is a decrease in eGFR.

Mean of urinary albumin creatinine ratio in Normoalbuminuria was 13.64+/-7.66.It is lower than the mean of Microalbuminuria 127.98+/-81.23. Similarly mean value of serum albumin in Normoalbuminuria, 3.90+/-0.56g/dL was lower compared to Microalbuminuria mean value of 3.62+/-0.50g/dL. In this study, Correlation was done to measure the linear relation ship between eGFR & Uricacid,

Strong negative Correlation was observed . It indicates that when the concentration of Uric acid increases, eGFR decreases which implies impaired renal function. Uric acid causes thickening &hypercellularity of Glomerulus & induces epithelial mesenchymal transition of renal tubular cell resulting in increased medial thickness and decreased luminal diameter & it contributes to the decrease in Glomerular filtration rate[11,12].

Mean TGL of microalbuminuria was 117.13+/-61.79mg/dL which is higher than the mean TGL of Normoalbuminuria 97.49+/-44.28 mg/dL.The results of our study matches EURODIAB IDDM Complication study, where Microalbuminuria was associated with increased plasma triglyceride level[13]. Some Quantitative lipid modifications may occur in Type 1 Diabetic patients with Microalbuminuria. Hypertriglyceridemia occurs mainly due to decreased lipoprotein lipase activity secondary to insulin deficiency.

CONCLUSION

The present study was done with an aim to find out the correlation of serum uricacid with low GFR in normoalbuminuric microalbuminuric Type 1 Diabetic patients.

From this study, we conclude that,

- Serum uric acid is an independent determinant of GFR in Type 1 Diabetic patients.
- There is a significant negative correlation of uric acid with GFR in Type 1 Diabetic patients.
- Even though there is a significant association between elevated uric acid concentration and decline in renal function, follow up studies are essential to evaluate the role of uric acid lowering drugs in the prevention of further impairment of renal function.
- Our study was carried out only in Type 1 Diabetic patients, and the result interpretation in patients with Type 2 Diabetes is uncertain.

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