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THE ROLE OF URIC ACID AND HIGH-SENSITIVITY C-REACTIVE PROTEIN AS RENAL AND CARDIOVASCULAR RISK MARKERS IN TYPE 1 DIABETIC PATIENTS WITH LOW GFR

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ABSTRACT

Background and objective: According to recent research, decreased renal function and cardiovascular disease are significantly linked to elevated serum levels of uric acid and hs-CRP. In order to identify early renal function deterioration before the start of proteinuria and cardiovascular risk in type 1 diabetic patients, this study will examine the roles of uric acid and hs-CRP.

Method: In the cross-sectional study, a total of 140 type 1 diabetic individuals (70 normoalbuminuric and 70 microalbumin uric) were enrolled. Enzymatic colorimetric method and ELISA method were each used to quantify uric acid and hs-CRP, respectively. Blood pressure, body mass index, HbA1c, fasting plasma glucose, plasma lipid profile, serum creatinine, and urine albumin creatinine ratio were also evaluated as metabolic markers. The CKD-EPI equation was used to compute the estimated glomerular filtration rate.

Result: Mean uric acid levels were 3.92+/-1.59 and 4.99+/-2.48mg/dL, respectively, for normoalbuminuria and microalbuminuria (p-0.004). Mean hs-CRP levels were 1.93+/-2.14mg/L in normoalbuminuria and 4.47+/-3.05mg/L in microalbuminuria, respectively (p <0.001). Urinary albumin to creatinine ratios were 15.74+/-8.88 in normoalbuminuria and 129.98+/-85.25 in microalbuminuria (both p<0.001). The mean GFR in individuals with normoalbuminuria was 112.45+/-20.30ml/min, whereas it was 100.25+/-27.12ml/min in individuals with microalbuminuria (p-0.02). A greater than 90 ml/min eGFR was present in 55.6% of normoalbuminurics and 47.5% of microalbuminurics. The eGFR was less than 90 ml/min in 36.8% of normal albuminurics and 67.6% of microalbuminurics. Lower GFR was strongly and independently linked with both elevated blood uric acid and elevated urine albumin creatinine ratio. Uric acid and hs-CRP correlated positively (p-0.04 and p0.001, respectively), whereas uric acid and eGFR correlated negatively.

Conclusion: When blood uric acid levels were in the upper normal range and hs-CRP levels were elevated, renal function was decreased in patients with type 1 diabetes. As a result, in the clinical setting in India, where the detection rate is lower and the repercussions are more frequent, it can be used as markers for identifying cardiovascular risk and early renal function deterioration in patients with type 1 diabetes.

Keywords: hs-CRP, Uric acid, Diabetes type 1, eGFR

INTRODUCTION

A wide range of disorders called diabetes mellitus all have symptoms such as insulin sensitivity and/or hyposecretion. One of the main health concerns of the twenty-first century, diabetes is becoming more common everywhere. Around the world, it was predicted that 366 million people had diabetes in 2013, and that number is expected to rise to 522 million by 2030. almost 62.4 million people in India currently have diabetes, and by 2030, that figure is expected to rise to almost 101.2 million [1,2,3]. The majority of diabetes' burden is carried by its various complications. Diabetic Nephropathy & Coronary Artery Disease are the two microvascular & macrovascular effects of diabetes that are most common. Diabetic nephropathy affects 20–30% of people with Type 1 and Type 2 diabetes. People with Type 1 diabetes have a 50% greater likelihood of acquiring ESRD than those with Type 2 diabetes [4,5].

Indians with diabetes have a 9% to 14% prevalence of coronary artery disease, and that percentage increases as people age and have diabetes for a longer period of time. Microalbuminuria, the earliest clinically noticeable stage of diabetic nephropathy, is regarded to be the stage at which the disease can be delayed or stopped with the use of the appropriate medications. In people with type 1 diabetes, it is also thought to be an indication of cardiovascular mortality & morbidity [6,7]. Uric acid and high-sensitivity CRP are well-known markers for detecting cardiovascular and renal damage sooner, before the onset of microalbuminuria, according to recent studies. Higher blood uric acid concentrations result in the development of microalbuminuria, glomerular hypertrophy, endothelial dysfunction, suppression of nitric oxide synthesis, and thickening of the afferent arteriolar wall. The aim of this study was to assess the effects of uric acid and hs-CRP in type 1 diabetic individuals with poor GFR who were normoalbuminuric and microalbuminuric [8,9].

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MATERIAL AND METHODS

The ethical committee gave its clearance before this cross-sectional case control study could be carried out. The study included a total of 140 Type 1 Diabetes mellitus patients who were visiting the outpatient diabetes clinic at Mallareddy Institute of Medical Sciences, Suraram, Hyderabad, Telangana, India.

INCLUSION CRITERIA:

1. Patients with type 1 diabetes
2. Diabetes duration > 5 years
3. 10 to 40 years old
4. The use of insulin.

EXCLUSION CRITERIA:

1. Patients with macroalbuminuria
2. People with advanced kidney disease
3. Patients who have undergone renal transplants
4. Patients with type 2 diabetes
5. Acutely sick patient with inflammation
6. Patients with heart conditions.

Methodology:

A urine dipstick was used to rule out proteinuria before choosing the patients. Based on the UACR (Urine Albumin Creatinine Ratio), cases were classified into two groups. Group 1 included 70 patients with normoalbuminuria who were type 1 diabetics. (UACR30mg/g of creatinine). 70 patients with Type 1 diabetes and microalbuminuria (UACR 30-300 mg/g creatinine) made up Group 2. Estimates of urine albumin content were made after collecting urine and blood samples. The concentration of creatinine in the urine was also indicated. The following measurements were made: total cholesterol, HDL, triglyceride, plasma glucose, hs-CRP, GRF, serum protein, serum albumin, and serum uric acid levels. When assessing the data using SPSS software version 16.0, p values less than 0.05 were considered statistically significant. The Student t-test was used to compare the study groups' ages, diabetes durations, BMIs, total cholesterols, HbA1cs, uric acid levels, eGFRs, and hs-CRP levels. We determined gender using chi square analysis. The comparison of various factors both within and between two groups was done using a one-way ANOVA. Comparisons between type 1 diabetic patients with normal albuminuria and those who had microalbuminuria were made in terms of eGFR [10,11].

RESULT

Table 1. Contrasting characteristics of type1diabetics with normoalbuminuria and microalbuminuria

	Albuminuria	N	Mean	Std. Deviation	p value
Age	Normal	70	29.15	10.33	0.16-NS
	Micro	70	31.16	9.80	
BMI	Normal	70	21.30	5.55	0.46-NS
	Micro	70	21.80	5.86	
FBS(mg/dL)	Normal	70	150.29	70.51	0.19-NS
	Micro	70	172.89	112.40	
HbA1C(%)	Normal	70	9.40	3.74	0.41-NS
	Micro	70	7.59	3.70	
Total Cholesterol(mg/dL)	Normal	70	149.12	49.35	0.09-NS
	Micro	70	163.45	49.40	
TGL(mg/dL)	Normal	70	98.45	46.29	0.04*
	Micro	70	119.12	63.80	
HDL(mg/dL)	Normal	70	42.54	20.72	0.39-NS
	Micro	70	40.21	14.26	
Creatinine(mg/dL)	Normal	70	1.84	1.26	0.21-NS
	Micro	70	2.31	5.06	
Albumin(g/dL)	Normal	70	5.90	1.58	0.003**
	Micro	70	5.60	1.53	
Total Protein(g/dL)	Normal	70	8.30	1.55	<0.001**
	Micro	70	7.80	1.90	
Urine ACR	Normal	70	15.66	9.66	<0.001**
	Micro	70	125.93	86.26	

Ns-not significant
*-significant.
**- highly significant

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TABLE 2. Normoalbuminuria & microalbuminuria compared with uric acid

	Albuminuria	N	Mean	Std. Deviation	l. ErrorMean
Uric acid	Normal	70	4.95	2.64	0.40
	Micro	70	5.96	3.56	0.84

p = 0.004 (highly significant)

TABLE 3. Normoalbuminuria & microalbuminuria compared for eGFR

	Albuminuria	N	Mean	Std. Deviation	l. ErrorMean
eGFR	normal	70	112.45	25.45	3.66
	micro	70	110.30	28.14	4.46

p= 0.02(Significant)

Table 4. ANOVA test

eGFR				
	N	Mean	Std. Deviation	P value
1	31	116.60	21.04	<0.001
2	31	111.59	18.70	
3	30	109.85	23.73	
4	21	106.15	20.73	
5	25	86.85	33.01	
Total	138	106.10	25.53	

P<0.001(highly significant)

TABLE 5. Study group comparison of uric acid with eGFR

		Uric acid	eGFR
Uric acid	Pearson Correlation	1	-.388**
	Sig. (2-tailed)		.000
	N	140	140
eGFR	Pearson Correlation	-.388**	1
	Sig. (2-tailed)	.000	
	N	140	140
**. Correlation is significant at 0.01 level (2-tailed).			

r = -0.39 p = <0.001

TABLE 6. PARTIAL CORRELATIONS

Control Variables			Uric acid	eGFR
HbA1C	Uric acid	Correlation	1.000	-.262
		Significance (2-tailed)	.	.039
		Df	0	63
	eGFR	Correlation	-.262	1.000
		Significance (2-tailed)	.039	.
		Df	63	0

P<0.05(significant).

TABLE 7. Normoalbuminuric & microalbuminuria compared for hs-CRP

	Albuminuria	N	Mean	Std. Deviation	Std. Error Mean
hsCRP	normal	64	1.9869	2.15451	.28969
	micro	43	4.4885	3.06987	.57742

p< 0.001(highly significant).

Table 8. Correlation of uric acid with hs-CRP in study groups

		Uric acid	hs-CRP
Uric acid	Pearson Correlation	1	.209*
	Sig. (2-tailed)		.045
	N	107	107
hs-CRP	Pearson Correlation	.209*	1
	Sig. (2-tailed)	.044	
	N	107	107
*. Correlation is significant at the 0.05 level (2-tailed).			

r = 0.21 P = 0.04

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Table 9. Multiple regression analysis of eGFR with additional risk factors in patients with type 1 diabetes who are normo- and microalbuminuric.

Model		ıstandardized Coefficients		dardized Coefficients	t	Sig.	ollinearityStatistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	163.06	23.82		9.25	.000		
	Age	-1.01	.45	-.35	-4.25	.002	.55	1.99
	Gender	-5.63	5.98	-.10	-2.20	.235	.90	1.25
	Duration	-.086	.42	-.06	-.23	.885	.58	1.91
	BMI	-.28	.58	-.05	-.55	.625	.96	1.11
	Hypertension	-8.15	6.23	-.15	-2.88	.101	.84	1.23
	Uric acid	-4.46	.89	-.32	-4.80	.000	.83	1.25
	HbA1C	.62	3.19	.06	.55	.715	.81	1.28
	Cholesterol	-.00	.03	-.00	-.09	.951	.95	1.16
a. Dependent Variable: eGFR								

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

DISCUSSION

The most common cause of end-stage renal disease is diabetes. People with Type 1 diabetes are more likely to experience nephropathy (20–30%) and coronary artery disease (7–10%), respectively. The first clinical sign of diabetic nephropathy is often thought to be an increased albumin excretion rate. Recent studies have shown that diabetic nephropathy's primary clinical abnormality, which manifests itself even before the microalbumin uric stage and progresses to overt nephropathy, is a decreased glomerular filtration rate. Hyperglycemia, systemic hypertension, and dyslipidaemia all hasten the development of microalbuminuria [12,13].

Serum uric acid is a key mediator of renal disease. Hyperuricemia causes elevated systemic blood pressure, proteinuria, renal failure, and progressive renal scarring via a pathway reliant on renin-angiotensin and COX-2. It was unaffected by age, gender, or other risk factors, although it is a substantial risk factor for the onset of microalbuminuria. Therefore, identifying those who are more likely to develop microalbuminuria and CKD may be possible with the aid of blood uric acid measurement. In type 1 nonproteinuric diabetes, our study aims to establish the connection between uric acid and glomerular filtration rate. Uric acid frequently causes endothelial dysfunction in patients with both cardiovascular and renal disease by inhibiting the production of nitric oxide. Advanced glycated end products are increased in diabetes, which prompts macrophage activation, increases IL-6 and TNF production, and results in the development of high-sensitivity CRP. Numerous studies have found that Hs-CRP is a marker for future coronary events [14,15].

We therefore looked at uric acid and hs-CRP in our study to predict cardiovascular and renal risk in type 1 diabetes and to be able to treat patients early and arrest the progression of renal and cardiovascular sickness. We split the participants in the current investigation into two groups. Group-I contained 70 patients with type 1 diabetes who were Normoalbuminurics, whereas Group-II contained 70 patients. It was shown that group 1's mean serum uric acid concentration was 3.92+/- 1.59 mg/dL, which is within the normal range. Group II's average blood uric acid levels were found to be 4.99+/-2.48 mg/dL, which is above normal. This result was comparable to that of a Krolewski et al. study, which had shown that most uric acid values were within the normal range. In contrast to normoalbuminurics, it is higher in microalbuminurics. Compared to proteinuria, hyperuricemia has a better predictive ability for the chance of renal failure in Japanese individuals. The same results also hold true for our investigation. An equivalent result was found in experimental studies with rats. The mean GFR ranged from 110.40+/-20.30 ml/min in Normoalbuminuric individuals to 100.25+/-27.12 ml/min in Microalbuminuric individuals [16,17].

The mean GFR in both groups was within the normal range, although hyperfiltration GFR > 130 ml/min was less frequent in diabetics with microalbuminuria than in those with normoalbuminuria. On the other hand, compared to diabetic patients with normoalbuminuria, persons with microalbuminuria had greater rates of moderately impaired renal function (GFR 30-59 ml/min) and slightly impaired renal function (GFR 60-89 ml/min). The independent contributions of factors like Age, Duration, BMI, BP, and HbA1c that were connected to eGFR in Microalbuminuria & normoalbuminuria were evaluated using multiple regression models. HbA1c, BP, and BMI measurements of eGFR did not show distinct effects [18,19].

Significant glomus lesions are associated with long-term diabetes and advancing age, even in the absence of a greater albumin excretion rate. Our investigation discovered a statistically significant difference between age groups with a p value of 0.01, however there was no difference in significance for duration. This could be as a

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result of diabetes developing earlier in life, lasting longer, and only being identified much later. This causes the eGFR to decrease. Human serum CRP concentrations should range from 0.2 to 10 mg/L. The analytical sensitivity of the ELISA test kit is hs-CRP 0.005 g/mL. Hs-CRP levels that were greater than 10 mg/L on two different occasions were ignored since they were more likely the outcome of an illness or an inflammatory condition [19,20].

In our study, Normoalbuminuria had a mean of 1.93+/- 2.14mg/L for hs-CRP in contrast to Microalbuminuria, which had a mean of 4.47+/- 3.05mg/mL. Patients with Microalbuminuric Type 1 Diabetes exhibited hs-CRP levels that were substantially higher than those with Normoalbuminuric Type 1 Diabetes in the Oxford Regional Prospective study.This is consistent with what our investigation revealed. The mean urine albumin to creatinine ratio in Normoalbuminuria was 13.64+/-7.66. It is under the microalbuminuria mean of 127.98+/-81.23. Similar to Microalbuminuria, Normoalbuminuria had a lower mean serum albumin level, 3.90+/-0.56g/dL as opposed to 3.62+/-0.50g/dL [20,21].

Microalbuminuria is related to endothelial dysfunction and subclinical inflammation. It increases the level of hs-CRP, activates macrophages, and controls IL-1, IL-6, and TNF production. It illustrates how microalbuminuria and cardiovascular disease are related. In this study, correlation was employed to evaluate the linear relationships between uric acid and both e GFR and hs-cRP. very negatively A connection was discovered. It demonstrates that as uric acid levels increase, eGFR decreases, suggesting impaired renal function. Urate thickens and hypercellularizes the glomerulus, increases medial thickness and decreases luminal width, and lowers glomerular filtration rate. Urate also starts the epithelial mesenchymal transition of renal tubular cells [21,22].

There was a pronounced and favourable correlation. It demonstrates that an increase in uric acid concentration is accompanied by a rise in hs-CRP. The prooxidant function of uric acid. It stimulates the development of monocyte chemoattractant protein 1, which then increases the production of hs-CRP via the cyclooxygenase-2 & MAP kinase pathway. Hs-CRP is found in lipid-rich plaques and directly binds oxidised LDL. It is a trigger for proinflammatory inflammation that results in macrophage infiltration in atherosclerotic lesions and plaque development. It increases the expression of tissue factor, which can lead to thrombosis, under inflammatory conditions. The mean TGL of normoalbuminuria, 117.13+/-61.79 mg/dL, was lower than the mean TGL of microalbuminuria, which was greater. Our results are in line with the EURODIAB IDDM Complication study, which discovered a connection between microalbuminuria and increased plasma triglyceride levels. Quantitative lipid alterations may occur in Type 1 diabetes and microalbuminuria patients. Hypertriglyceridemia is mostly brought on by decreased lipoprotein lipase activity as a result of inadequate insulin levels[22].

CONCLUSION

The current study was to investigate the correlation between hs-CRP and serum uric acid for predicting cardiovascular risk in Type 1 diabetic patients with normoalbuminuria and microalbuminuria, as well as the correlation between both variables and GFR. Serum uric acid is a solitary predictor of GFR in Type 1 diabetics, we can conclude. Uric acid strongly correlates negatively with GFR in people with type 1 diabetes. Uric acid concentrations and Hs-CRP concentrations are closely related. Serum uric acid and hs-CRP measurements can be used to assess the cardiovascular and renal risk in Type 1 diabetic patients, particularly in those with low GFR. It is also economical to monitor serum uric acid and high-sensitivity CRP in Type 1 Diabetes even in Normoalbuminuria, particularly in Indian clinical settings where the early diagnosis rate of Diabetes was lower and sequelae were more prevalent.

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Conflict of interest:
Nil

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