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Study on the association between Hyperuricemia and Albuminuria in patients of type 2 Diabetes Mellitus

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Abstract

Introduction: Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy. Type 2diabetes patients with increased urinary albumin excretion suffer increased morbidity and mortality as compared to normoalbumiuric patients. In clinical studies, serum uric acid concentration has been found to be associated with diabetic nephropathy. On the other hand, we also know that albuminuria is the main marker of diabetic nephropathy independent of hypertension.

Aim: This hospital-based observational (cross-sectional) study aimed to evaluate the relationship of serum uric acid level & urinary albumin creatinine Ratio (ACR) in patients of T2DM.

Material and methods: The study group comprised of 100 patients of type 2 diabetes mellitus of age between 40 to 80 years. Age, body weight, height, body mass index (BMI),serum uric acid, urinary albumin to creatinine ratio (ACR), fasting blood glucose (FBG), glycated haemoglobin (HbA1c), lipid profile, serum creatinine were recorded for each patient. Patients were diagnosed to have diabetes mellitus on the basis of American Diabetes Association (ADA) criteria.

Results: Albuminuria was found to be significantly associated with hyperuricemia. Serum uric acid as found to be a significant factor which could predict only 40.2% (R^2 = 0.4028) variation in albumin creatinine ratio.

Conclusion: This study showed that the serum uric acid concentration was significantly and with greater probability associated with albuminuria in patients with type 2 diabetes mellitus.

Keywords: hyperuricemia, Albuminuria, Type 2 diabetes mellitus, creatinine ratio.

Introduction

India leads the world with largest number of diabetic subjects, and has been termed as the "diabetes capitalol the world". According to the Diabetes Atlas 2006 published by the IDF, the number of people with diabetes in India currently around40.9 million is expected to rise to 69.9 million by 2025and to 109 million by 2035.[1]

Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy. In United States, diabetes mellitus is the leading cause of end stage renal disease (ESRD).[2]

The cumulative incidence of proteinuria in type 2 diabetic patients is more variable, ranging from 5 to 20%.[3-5] Between 20-40% of patients with type 2 diabetes will develop kidney disease.[6] This will manifest as either microalbuminuria, albuminuria or reduced glomerular filtration rate. Type 2diabetes patients with increased urinary albumin excretion suffer increased morbidity and mortality as compared to normoalbumiuric patients. It has been demonstrated that increased urinary albumin excretion, endothelial dysfunction and chronic inflammation are interrelated processes that develop in parallel, progress over time and are strongly and independently associated with increased risk of death in type 2 diabetes patients.[7] Once microalbuminuria is present, it progresses over 5-10 years to proteinuria in 20-50% subjects.[8]

Its been suggested that uric acid may contribute to the development of hypertension, metabolic syndrome & kidney diseases. Elevated uric acid levels can result from increased generation or decreased elimination. Increased generation, in turn, can be caused by ingesting a purine-rich diet or alcohol, by certain genetic disorders (such as the Lesch-Nyhan syndrome), and by increased turnover of cells (such as in myeloproliferative diseases or tumor lysis syndrome). On the other hand, decreased renal excretion can be a consequence of decreased glomerular filtration rate (GFR), increased tubular reabsorption induced by volume depletion when using diuretics, or inhibition of renal tubular secretion induced by inhibition of the anion-exchange transport system by lactate or keto acids.[9,10]

There is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage.[11] Also higher levels of serum insulin may decrease uric acid clearance by the kidneys. As a rule, hyperinsulinemia is the basis of type 2 DM pathophysiology. Therefore, diabetic patients are more prone to uric acid injury.[12]

Though in clinical studies, serum uric acid concentration has been found to be associated with diabetic nephropathy.[12,13] On the other hand, we also know that albuminuria is the main marker of diabetic nephropathy independent of hypertension.

Therefore, this study was undertaken which is a hospital-based, observational (cross-sectional) study to evaluate serum uric acid level & urinary albumin creatinine Ratio (ACR) in patients of T2DM. The study also evaluates relation between normo albuminuria (ACR <30 ug/ mg), micro albuminuria (ACR between 30 ug/mg & 299 ug/mg) & macro albuminuria (ACR ≥ 300ug/mg) with serum uric acid levels.

Materials and Methods

The study group comprised of 100 patients of type 2 diabetes mellitus of age between 40 to 80 years. Written informed consent was taken from enrolled patients and conducted after seeking permission from Institutional Ethics Committee.

Study variable: Age, body weight, height, body mass index (BMI),serum uric acid, urinary albumin to creatinine ratio (ACR), fasting blood glucose (FBG), glycated haemoglobin (HbA1c), lipid profile, serum creatinine.

Inclusion criteria: Type 2 diabetes mellitus (T2DM) patients of age between 40 to 80 years.

Exclusion criteria: Patients using diuretics, Patients on angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), Patients of alcohol abuse, Urinary tract infection, Patients with malignancy.

Patient were diagnosed to have diabetes mellitus on the basis of American Diabetes Association (ADA) criteria. A fasting plasma glucose (FPG >126 mg/dL, a two hours plasma glucose >200 mg/dl or HbA1c >6.5% warrants diagnosis of diabetes mellitus. A random plasma glucose concentration >200 mg/dL accompanied by classical symptoms of diabetes mellitus (polyuria, polydipsia and weight loss) is sufficient for diagnosis of diabetes mellitus. Hemolysed samples were excluded.

Statistical analysis: Statistical software SPSS 20.0 was used for the analysis of the data and Microsoft Word and Excel to generate graphs and tables. The data collected were analyzed and expressed as Mean ± SD. The correlation between serum uric acid concentrations and age, sex, duration of DM, BMI, GFR, creatinine, FBG, hemoglobin A1c (Hb A1c), cholesterol, triglyceride, and urinary ACR were examined by the Pearson correlation analysis andLogistic regression was used to obtain relative risk and odd's ratio. The Chi-square test was used to evaluate differences in distribution of covariates such as albuminuria, GFR, metabolic syndrome, hypertension, gender, FBG, and Hb A1c with each quartiles of uric acid level. The Kruskal Wallis test was used to evaluate relations between normoalbuminuria, microalbuminuria, and macroalbuminuria with uric acid levels, as the data had a skewed distribution. Regression analysis was performed with Urinary ACR as the dependent variable and Serum Uric acid as the independent variable. *p* values less than .05 were considered significant.

Results

Out of total 100 patients of type 2 DM, the age range of the sample was 40-80 years with the mean age of 57.64± 10.07 years and male: female ratio of 1.08:1. The mean body mass index of study population was 25.20±2.17 kg/m2, mean systolic blood and mean diastolic blood pressure was 128.96±14.62 mmHg and 77.1±7.53 mmHg respectively. Mean fasting blood sugar levels for the study population was 157.38±53.22 mg/dl and mean HbA1c levels were 6.99±1.21 %. Mean value of lipid profiles of the study population including triglycerides, LDL and HDL came to be 127.7±27.92 mg/dl, 126.47±23.47 mg/dl, 37.38±4.07 mg/dl respectively. Mean serum creatinine levels in the study population and mean GFR of the same were recorded as 0.890±0.19 mg/dl (max: 1.5 & min: 0.58) and 77.66±14.95 ml/min/1.73 m^2 respectively.

Table 1: Descriptive variables of study population with type 2 DM enrolled in the study:

Parameters	n	Maen values (Mean±SD)	Max	Min
Age (years)	100	57.64± 10.07	80	40
Gender (%age) Male Female	100	 52% 48%	-	-
BMI (kg/m^2)	100	25.20±2.17	31.25	21.10
SBP (mmHg)	100	128.96±14.62	160	110
DBP (mmHg)	100	77.1±7.53	90	60
HTN (%age)	100	49%	-	-
Fasting blood sugar (mg/dl)	100	157.38±53.22	330	87
HbA1C (%)	100	6.99±1.21	10.6	5.2
Triglycerides (mg/dl)	100	127.7±27.92	200	84
LDL (mg/dl)	100	126.47±23.47	174	58
HDL (mg/dl)	100	37.38±4.07	48	30
Serum creatinine (mg/dl)	100	0.890±0.19	1.5	0.58
GFR (ml/min/1.73 m^2)	100	77.66±14.95	112.90	44.91
Urinary ACR (µg/mg)	100	146.4±171.46	750	14.1
Serum uric acid (mg/dl)	100	6.03±1.75	8.9	3.2

The mean urinary ACR observed in study population of our study came to be 146.4±171.46(µg/mg).In the present study on basis of urinary ACR, albuminuria was divided into 3 groups of normoalbuminuria (ACR <30 ug/mg), microalbuminuria (ACR between 30 ug/mg & 299 ug/mg) & macroalbuminuria (ACR ≥ 300ug/mg). The mean urinary ACR values in these three study groups came to be 22.3±4.53, 144.6±71.11 and 421.3±150.33 respectively.

Table 2: Comparison of mean urinary ACR among three groups based on urinary ACR in study population:

Groups	No. of patients (n)	Mean urinary ACR (µg/mg)	Max	Min	
Normo albuminuria (Group 1)	46	22.3±4.53	30	14	
Micro Albuminuria (Group 2)	33	144.6±71.11	380	56.2	
Macro Albuminuria (Group 3)	21	421.3±150.33	750	51.8	

The normoalbuminuria population showed values of TG, LDL and HDL was 118.30±24.77 mg/dl, 120.06±22.54 mg/dl, 37.63±4.02 mg/dl respectively, while microalbuminuria group showed 146±29.38 mg/dl, 141.47±17.69 mg/dl and 37.71±3.5 mg/dl respectively and lastly macroalbuminuria group showed 129.15±25.69 mg/dl, 125.84±24.23 mg/dl and 36.81±4.48 mg/dl respectively. The results from our study showed that albumin levels showed a statistically significant positive correlation with both triglycerides levels ($r=0.373$, $p<0.0001$) and LDL levels ($r=0.326$, $p<0.0002$) in diabetic patients, whereas no such correlation was observed with HDL levels in the same population ($p=0.265$).

Table 3 : Distribution of mean values of TG, LDL& HDL in relation to different groups of albuminuriain study population:

Variable	Normo albuminuria (Group 1)	Micro albuminuria (Group 2)	Macro albuminuria (Group 3)	Correlation coefficient (R value)	Significance (p value)
TG (mg/dl)	118.30±24.77	146±29.38	129.15±25.69	0.373	0.0001*
LDL(mg/dl)	120.06±22.54	141.47±17.69	125.84±24.23	0.3263	0.0002*
HDL(mg/dl)	37.63±4.02	37.71±3.5	36.81±4.48	0.1125	0.2651

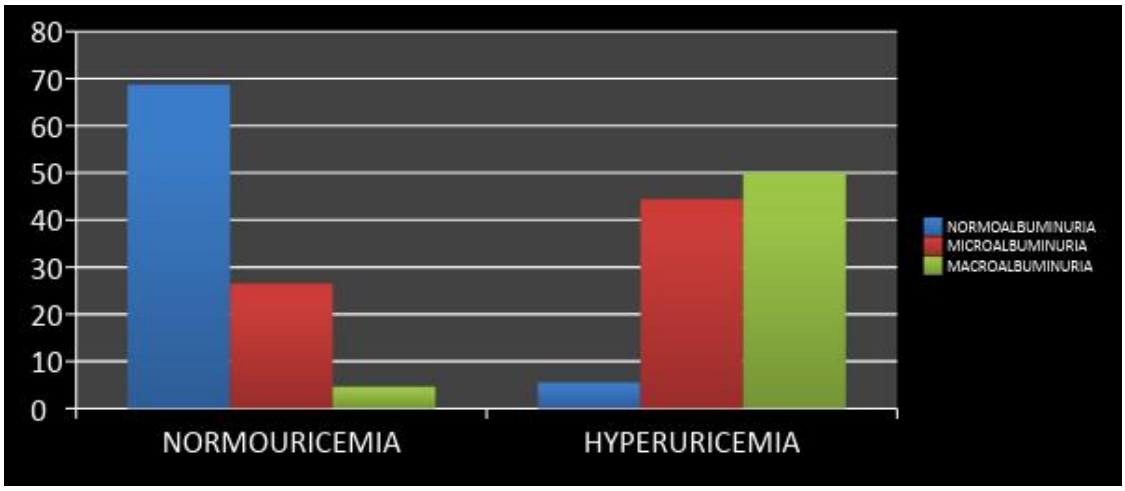
*P<0.05 was taken as significant

In patients with normouricemia 68.7% (n=44) had normoalbuminuria, 26.5% (n=17) had microalbuminuria; and 4.6% (n=3) had macroalbuminuria. In patients with hyperuricemia 44.4% (n=16) had microalbuminuria ; 50 % (n=18) hadmacroalbuminuria& 5.5% (n=2) had normoalbuminuria. Thus albuminuria was significantly associated with hyperuricemia.

Table 4: Association of albuminuria with serum uric acid:

	Serum uric acid				
Albuminuria	Normouricemia	Hyperuricemia	Total	p Value	Significance
Normalbuminuria	44(68.7)	2(5.5)	46(46)	<0.001	Significant
Microalbuminuria	17(26.5)	16(44.4)	33(33)		
Macroalbuminuria	3(4.6)	18(50)	21(21)		
Total	64(100)	36(100)	100(100)		

Graph 1:Association of albuminuria with serum uric acid:



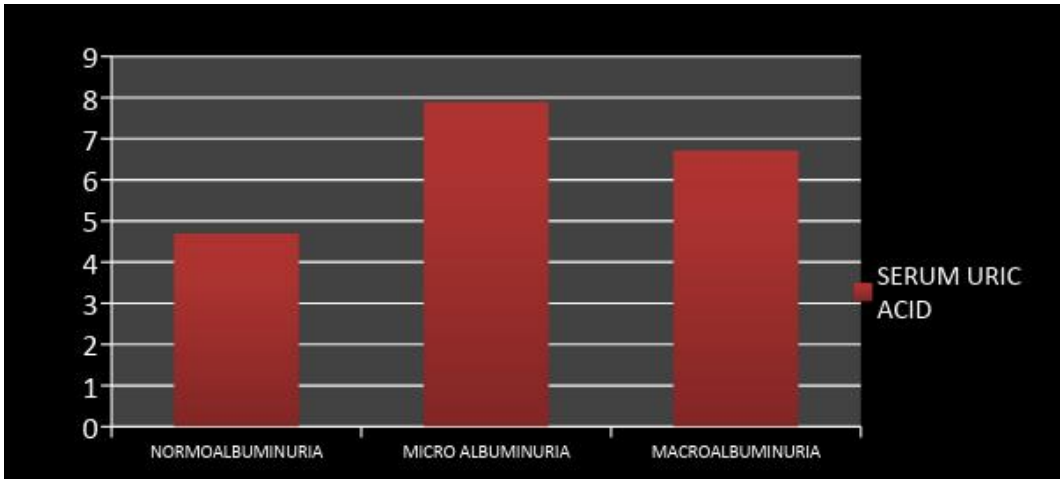
The concentration of serum uric was 4.69±1.13 mg/dl, 7.89±0.87 mg/dland 6.71±1.38 mg/dl in patients with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively. On comparison, the results were found to be statisticallty significant. On univariate analysis the value of R was 0.6347 and it shows a moderate positive correlation. R^2, the coefficient of determination, was 0.4028. Considering the R^2 (Coefficient of determination) value, serum uric acid was found to be a significant factor which could predict only 40.2% (R2 = 0.4028) 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.

Table 5: Evaluation of relationship of mean value of serum uric acid in relation to different groups of albuminuriain study population:

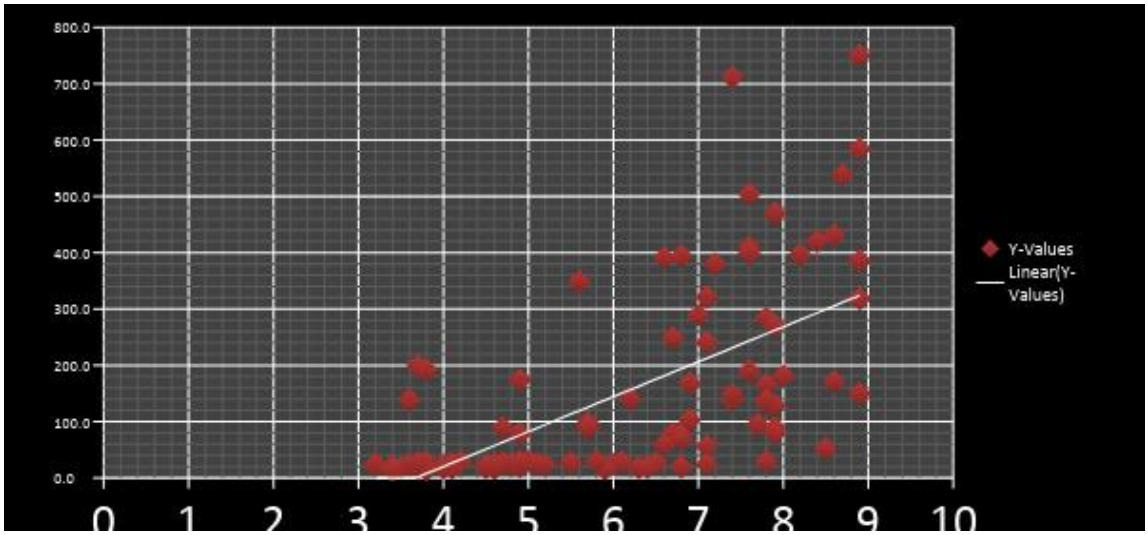
Variable	Normo albuminuria (Group 1)	Micro albuminuria (group 2)	Macro albuminuria (Group 3)	Correlation coefficient (R value)	coefficient of determination (R^2)
Uric acid	4.69±1.13	7.89±0.87	6.71±1.38	0.6347.	0.4028

P<0.05 was taken as significant.

Graph 2:Evaluation of relationship of mean value of serum uric acid in relation to different groups of albuminuriain study population:



Graph 3: Scattered plot diagram to show relationship between urinary ACR and serum uric acid:



Discussion

In clinical studies, serum uric acid concentration has been found to be associated with diabetic nephropathy. On the other hand, we also know that albuminuria is the main marker of diabetic nephropathy independent of hypertension. Therefore, this study was undertaken which is a hospital-based, observational, cross-sectional study to evaluate serum uric acid level & urinary albumin creatinine Ratio (ACR) in patients of T2DM. The study also evaluate relation between normoalbuminuria, microalbuminuria & macroalbuminuria with serum uric acid levels.

The results of our study showed that albuminuria is significantly associated with hyperuricemia. Serum uric acid was found to be a significant factor which could predict only 40.2% (R^2 = 0.4028) variation in albumin creatinine ratio. Thus, it showed that serum uric acid was an independent predictor of albumin creatinine ratio.

The mean urinary ACR values in these three study groups came to be 22.3±4.53µg/mg, 144.6±71.11µg/mg and 421.3±150.33µg/mg respectively. Kaifee M, et al [14] also grouped their study subjects according to mean urinary ACR levels in patients with T2DM as normoalbuminuric, microalbuminuric, and macroalbuminuric patients and recorded the mean values as 22.28 ± 4.09 µg/mg, 134.79±70.65 µg/mg, and 469.83 ± 120.14µg/mg respectively.

Out of total 100 patients of type 2 DM, mean age of the study population was 57.64± 10.07 years. This age represents the peak age of social and economic responsibility and also a risk factor for increased renal dysfunction. Similar to our study Chin-Hsiao Tseng et al reported that mean age in study population was 62.8±10.8 years.[15] While Bonakdaran S et al showed mean age in the study population was 52.45±10.11 years.[16]

Regarding gender distribution it was observed that over all male: female ratio in the present study was 1.08:1 thus showing male predominance. In accordance to our study, Prabhuswamy K M also reported male predominance in their study.[17] But few studies are reported to have female predominance as well. This can be justified saying that Diversities in biology, culture, lifestyle, environment, and socioeconomic status have an impact on differences between males and females in predisposition in these studies. Also this disparity in the present study may represent the health-seeking behavior of the patients attending the hospital, as this study is a hospital based study and not a population based one.

Further, it was observed that females predominated in just macroalbuminuria group (60.6 %), while in rest two groups males predominated. No significant correlation was found with gender distribution and Urinary ACR values in the present study.

In similarity to ours Kaifee M, et al [14] reported that normoalbuminuria and micro+ macroalbuminuria groups consisted of 49% female, 51% male and 56.9% female and 43.1% male in each group respectively. Where as in contrary, Yakoob Ahmedani et al reported that microalbuminuria was more frequent in males (37.1% vs. 29.9%) as compared to females.[18]

The mean fasting blood sugar levels for the study population was 157.38±53.22 and mean HbA1c levels were 6.99±1.21 mg/dl (max.: 10.6 mg/dl& min: 5.2 mg/dl). Chin-Hsiao Tseng et al[15] reported similar results in their study while on contrary Bonakdaran S, Hami M et al [16] observed that the mean of the FBS in patients with T2DM in study higher as compared to ours. The high mean HbA1C may due the poor glycemic control in patients included in their study.

Also Mean value of lipid profiles of the study population including triglycerides, LDL and HDL came to be 127.7±27.92 mg/dl, 126.47±23.47 mg/dl, 37.38±4.07 mg/dl respectively. Mean serum creatinine levels in the study population and mean GFR of the same were recorded as 0.890±0.19 mg/dl and 77.66±14.95 ml/min/1.73m^2 respectively.

The results from our study showed that albumin levels showed a statistically significant positive correlation with both triglycerides levels (r=0.373, p<0.0001) and LDL levels (r=0.326, p<0.0002) in diabetic patients, whereas no such correlation was observed with HDL levels in the same population (p=0.265). Yakoob Ahmedani et al[18] reported that the microalbuminuria positive group had a more deranged lipid profile with higher serum total cholesterol, triglycerides, LDL cholesterol and lower HDL levels compared to the microalbuminuria negative group.

It was revealed that FBS, HbA1c and serum creatinine presented a significant and positively correlation with albumin levels in the study population. Whereas, GFR presented a significant but a weak negative correlation with albumin levels in the study population.

The mean serum uric acid concentration was 6.03±1.75 mg/dL, which compares well with the study conducted by Kaifee M, et al.(2017)[14] observed that the mean of the serum Uric Acid in patients with T2DM in study population as 6.18 ± 0.89mg/dl. Bonakdaran S et al (2011)[16] also observed that the mean of the serum uric acid in patients with T2DM in study population was 5.55 ± 1.47 mg/dl. Chin-Hsiao Tseng et al (2005)[15] reported that the mean of the uric acid in patients with T2DM in study population was 5.6 ± 1.9 mg/dl.

Mean serum uric acid was 4.09±1.36mg/dl, 7.89±0.87mg/dl and 6.71±1.38mg/dl in patients with normoalbuminuria, microalbuminuria and macroalbuminuria respectively. Similarly, Chin-Hsiao Tseng et al (2005)[13] reported that the mean serum uric acid levels in patients with T2DM in study population for normoalbuminuric, microalbuminuric and macroalbuminuric patients were 5.2 ± 1.6 mg/dL, 5.6± 1.9 mg/dL, and 6.7 ± 2.1 mg/dL respectively. Various authors like Kopaei MR et al[19], Razi F et al[20]and Kuwabara M et al[21] reported Serum uric acid is associated with decreased GFR as well as albuminuria and can be used as an indicator of Diabetic nephropathy.

In the present study there were positive significant correlations between serum uric acid concentration and SBP, DBP, FBG, HbA1c, triglycerides, LDL, serum creatinine and urinary ACR (P < .001). Whereas presence of a negative correlation of serum uric acid was seen in parameters like age, BMI, HDL and this relationship was statistically non significant.

Kaifee M et al.(2017)[14] also reported that hyperuricemia correlated positively with FBG, HbA1C, serum creatinine, LDL & triglycerides in patients with T2DM. No significant correlation found between hyperuricemia and age, sex, weight, height, BMI & HDL.

Thus overall it is seen from the results of our study that albuminuria is significantly associated with hyperuricemia. In accordance to our study Bonakdaran S et al[16] also observed that there is significant correlation between serum uric Acid & urinary ACR. Pearson correlation coefficient r between serum uric acid & urinary ACR =0.097(P value <0.05).

Neki NS et al[22] also revealed that levels of serum uric acid have linear positive corelation with the amount of proteinurea, Diabetic nephropathy can be suspected by increasing serum uric acid levels and it is seen that serum uric acid level correlates well with proteinuria, blood urea and serum creatinine level.

In yet another study by on Taiwanese patients with type 2 DM, Liang CC et al[23] reported that an increased serum uric acid level was significantly correlated with the severity of albuminuria. Also in another study by De Cosmo S et al [24], Serum uric acid was found to be significantly associated with albuminuria and thus they reported that mild hyperuricemia is strongly associated with the risk of CKD in patients with type 2 diabetes. Lastly, Behradmanesh S et al[25] also demonstrated that after adjustment for weight, a significant positive association of serum uric acid with level of proteinuria was seen.

Conclusion

This study showed that the serum uric acid concentration was significantly and with greater probability associated with albuminuria in patients with type 2 diabetes mellitus. As hyperuricemia is a common finding in this group of patients, and its treatment is easy and available, early diagnosis and treatment may be helpful to prevent or decrease the rate of development of overt kidney disease in this population of patients.

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