Study of Association between Hyperuricemia and Albuminuria in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Hyperuricemia is defined as serum uric acid level ≥ 7 mg/dl (in men) or ≥ 6.0 mg/dl (in women). Uric acid is an end product of purine metabolism and approximately, one-third of it is degraded in the gut, and two-thirds is excreted by the kidneys. 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). **Method:** This is a Hospital Based, cross-sectional study conducted in the Department of General Medicine. Age, Body weight, Height, BMI, serum uric acid, urinary albumin to creatine ratio (ACR), Fasting Blood Glucose (FBG), HbA1C, lipid profile, serum creatinine. Total number of cases were 100 (hundred) including both male and female and evaluated to calculate a correlation coefficient between albuminuria as measured by urinary ACR & serum uric acid level. Complete blood count, Serum uric acid, Urine RE/ ME & C/S, Urinary Albumin to Creatinine Ratio (ACR), Fasting Blood Glucose (FBG), HbA1C, Lipid profile, Serum Urea & Creatinine, USG whole abdomen, ECG in all leads. **Results:** In people with Hyperuricemia 50%(n=22) have microalbuminuria ; 36.4%(n=16) have macroalbuminuria & 13.6%(n=6) have normoalbuminuria. In people with Normouricemia, 17.9% (n=10) have microalbuminuria; 5.4%(n=3) have macroalbuminuria & 76.8%(n=43) have normoalbuminuria. So Albuminuria is significantly associated with Hyperuricemia. In people with Normoalbuminuria 87.8%(n=43) have Normouricemia and 12.2%(n=6) have Hyperuricemia. In people with Microalbuminuria 31.2%(n=10) have Normouricemia and 68.8%(n=22) have Hyperuricemia. In people with Macroalbuminuria 15.8%(n=3) have Normouricemia and 84.2%(n=16) have Hyperuricemia. In female population with Normoalbuminuria 79.2% (n=19) have Normouricemia & 20.8% (n=5) have Hyperuricemia. In female population with Microalbuminuria 40%(n=8) have Normouricemia &

60%(n=12) have Hyperuricemia. **Conclusion:** 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, Hypertension & HDL. Urinary ACR correlated positively with FBG, HbA1C, serum creatinine, LDL & Triglycerides in patients with T2DM. patients with T2DM serum Uric Acid level correlated negatively with GFR. In patients with T2DM serum uric acid level correlated positively with urinary albumin creatinine ratio. This study showed that Hyperuricemia was associated with a greater probability of Albuminuria in patients with type 2 diabetes mellitus. Serum uric acid is an independent correlate of urinary ACR in patients with type 2 diabetes mellitus.

Keywords: Hyperuricemia, Albuminuria, Type 2 Diabetes Mellitus.
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Introduction

Type 2 Diabetes Mellitus (T2DM) is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.[1] Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM1 . In Asia, the prevalence of diabetes is increasing rapidly and the diabetes phenotype appears to be different from that in the United States and Europe—onset at a lower BMI and younger age, greater visceral adiposity, and reduced insulin secretory capacity.[2]

In United State, Diabetes Mellitus is the leading cause of End Stage Renal Disease (ESRD).[1] The number of patients diagnosed each year with ESRD due to Type 2 diabetes mellitus is rising. The complex pathogenesis for the development of diabetic nephropathy is not fully understood. One factor that has been associated with cardio vascular & renal disease is serum uric acid. Recently experimental and clinical studies have suggested that uric acid may contribute to the development of hyper tension, metabolic syndrome & kidney diseases. There is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage.[3]

Hyperuricemia is defined as serum uric acid level ≥ 7 mg/dl (in men) or ≥ 6.0 mg/dl (in women)4.Uric acid is an end product of purine metabolism and approximately, one-third of it is degraded in the gut, and two-thirds is excreted by the kidneys.[5-7] 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).[7,8] 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.[7,8]

Although decreased kidney function can be associated by hyperuricemia.[9,10] based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus (DM).[10] It is suggested that increased serum level of uric acid is an injurious factor for kidneys.[6] as it is shown that hyperuricemia-induced endothelial dysfunction, glomerular hypertension, and renal hypertrophy decrease renal perfusion via stimulation of the afferent arteriolar vascular smooth muscle cell proliferation.[11-15] In some studies on diabetic patients, it has been reported that hyperuricemia is associated with kidney damage independent of hypertension.[6] On the other hand, higher levels of serum insulin may

decrease uric acid clearance by the kidneys.[16] As a rule, hyperinsulinemia is the basis of type 2 DM pathophysiology.[16] Therefore, diabetic patients are more prone to uric acid injury.

We know albumiuria is the main marker of diabetic nephropathy in this group of patients, independent of hypertension.[6] We studied the relationship between hyperuricemia and albuminuria in our diabetic patients.

Materials and Methods

This is a Hospital Based, cross-sectional study conducted in the Department of General Medicine SCB Medical College, Cuttack

Age, Body weight, Height, BMI, serum uric acid, urinary albumin to creatine ratio (ACR), Fasting Blood Glucose (FBG), HbA1C, lipid profile, serum creatinine.

Inclusion Criteria

a. Patient who provided the consent
b. Type 2 Diabetics Mellitus (T2DM) patients,
c. Age: between 40 to 80 years.

Exclusion Criteria

a. Patients on uric acid lowering agents.
b. Patients using diuretics or any other medication that influnces serum uric acid level.
c. Patients on angiotensin converting enzyme (ACE) inhibitor or Angiotensin Receptor Blocker (ARB)
d. Alcoholic
e. Acute illness
f. UTI
g. Patients with malignancy
h. Glomerular Filtration Rate (GFR) < 60 ml / min

Sample Size

Total number of cases were 100 (hundred) including both male and female and evaluated to calculate a correlation coefficient between albuminuria as measured by urinary ACR & serum uric acid level.

Method of Data Collection

Interview / history taking Physical examination, Laboratory examination, Record analysis.

Laboratory Investigations

Complete blood count, Serum uric acid, Urine RE/ ME & C/S,

Urinary Albumin to Creatinine Ratio (ACR), Fasting Blood Glucose (FBG),

HbA1C, Lipid profile, Serum Urea & Creatinine, USG whole abdomen, ECG in all leads

Statistical Analysis

Categorical variables were expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes. Continuous variables were expressed as Mean ± Standard Deviation and compared across the groups using one Way ANOVA test. Correlation coefficient has been calculated to understand the degree of linear dependency among the continuous variables and test for significance have been performed. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

Results

Table 1: Sex distribution of study population in normouricemia & hyperuricemia group

	Serum uric acid				
Sex	**Normo Uricemia**	**Hyper Uricemia**	**Total**	**P Value**	**Significance**
FEMALE	29(51.8)	24(54.5)	53(53)	0.784	Not Significant
MALE	27(48.2)	20(45.5)	47(47)		
Total	56(100)	44(100)	100(100)		

Table 2: Relation of Hypertension with Hyperuricemia & Normouricemia groups in study population: Not significant

	Serum uric acid				
	Normo Uricemia	Hyper Uricemia	Total	P Value	Significance

Hypertensive	22(39.3)	24(54.5)	46(46)	0.129	Not Significant
Normotensive	34(60.7)	20(45.5)	54(54)		
Total	56(100)	44(100)	100(100)		

Table 3: Relation of HbA1C with Albuminuria in study population

	Albuminuria				
HbA1C	Normo Albuminuria	Micro + Macro Albuminuria	Total	P Value	Significance
<7%	48(98)	10(19.6)	58(58)	<0.001	Significant
>7%	1(2)	41(80.4)	42(42)		
Total	49(100)	51(100)	100(100)		

People with Normo albuminuria have higher proportion of patients with HbA1C < 7%. People with Albuminuria (Micro+Macro) have higher proportion of patients with HbA1C>=7%.

Table 4: Distribution of mean Triglycerides (TG), LDL & HDL in relation to different groups of Albuminuria in study population

	Albuminuria				
	Normo Albuminuria	Micro Albuminuria	Macro Albuminuria		
	Mean ± Std. Deviation	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
TG	119.57 ± 25.33	127.62 ± 24.49	154.68 ± 24.69	<0.001	Significant
LDL	121.8 ± 22.45	127.97 ± 22.37	151.05 ± 13.58	<0.001	Significant
HDL	47.43 ± 5.88	48.22 ± 5.39	45 ± 6.51	0.160	Not Significant

Table 5: Distribution of mean Triglycerides (TG), LDL & HDL in relation to Normouricemia & Hyperuricemia in study population

	Serum Uric Acid			
	Normo Uricemia	Hyper Uricemia		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
TG	119.84 ± 23.66	140.25 ± 29.03	<0.001	Significant
LDL	122 ± 21.45	138.66 ± 22.97	<0.001	Significant
HDL	47.84 ± 5.91	46.43 ± 5.86	0.238	Not Significant

Serum Uric Acid correlated positively with increased level of TG & LDL but no such relation seen with HDL.

Table 6: Distribution of mean FBG, HbA1C, serum Creatinine, GFR, Urinary ACR & serum Uric Acid among different Albuminuria groups in study population

	Albuminuria				
	Normo Albuminuria	Micro Albuminuri a	Macro Albuminuria		
	Mean ± Std. Deviation	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
FBG	115.43 ±	184.47 ±	233.11 ± 53.95	<0.001	Significant

	19.43	33.56			
HbA1C	6.03 ± 0.48	7.47 ± 0.72	8.53 ± 1.3	<0.001	Significant
Serum Creatinine	0.79 ± 0.15	0.92 ± 0.23	1.04 ± 0.2	<0.001	Significant
GFR	86.2 ± 11.11	75.04 ± 8.85	64.91 ± 5.43	<0.001	Significant
Urinary ACR	22.28 ± 4.09	134.79 ± 70.65	469.83 ± 120.14	<0.001	Significant
Serum Uric Acid	4.64 ± 1.07	6.38 ± 1.3	7.68 ± 1	<0.001	Significant

There is statistically significant relation between mean of FBG, HbA1C, serum Creatinine, GFR & serum Uric Acid with different Albuminuria groups in study population. Microalbuminuria & Macroalbuminuria related positively with mean of FBG, HbA1C, serum Creatinine & serum Uric Acid and related negatively with mean eGFR. Mean urinary ACR in Normoalbuminuria, Microalbuminuria & Macroalbuminuria are 22.28±4.09, 134.79±70.65 and 469.83±120.14 respectively.

Table 7: Distribution of mean FBG, HbA1C, serum Creatinine, GFR, Urinary ACR & serum Uric Acid among Normouricemia & Hyperuricemia groups in study population

	Serum uric acid			
	Normo Uricemia	Hyper Uricemia		
	Mean ± Std. Deviation	Mean ± Std. Deviation	P Value	Significance
FBG	130.84 ± 42.56	196.84 ± 52.06	<0.001	Significant
HbA1C	6.31 ± 0.86	7.81 ± 1.17	<0.001	Significant
Serum Creatinine	0.82 ± 0.18	0.96 ± 0.21	<0.001	Significant
GFR	83.74 ± 11.99	72.02 ± 10.11	<0.001	Significant
Urinary ACR	59.99 ± 101.05	249.38 ± 199.75	<0.001	Significant
Serum Uric Acid	4.54 ± 0.93	7.35 ± 0.76	<0.001	Significant

Table 8: Correlation of Urinary ACR with serum Uric Acid, FBG, HbA1C, serum Creatinine, GFR

Correlations		
		Urinary ACR
Sr.Uric Acid	Pearson Correlation	0.675
	p Value	<0.001
FBG	Pearson Correlation	0.794
	p Value	<0.001
HbA1C	Pearson Correlation	0.771
	p Value	<0.001
Serum Creatinine	Pearson Correlation	0.489
	p Value	<0.001
GFR	Pearson Correlation	-0.627
	p Value	<0.001

There is strong positive correlation of serum Uric Acid, FBG, HbA1C, serum creatinine with urinary ACR. But there is strong negative correlation between GFR & urinary ACR.

Table 9: Correlation of Serum Uric Acid with Urinary ACR, FBG, HbA1C, serum Creatinine, GFR

Correlations		
		Sr.Uric Acid
Urinary ACR	Pearson Correlation	0.675
	p Value	<0.001
FBG	Pearson Correlation	0.666
	p Value	<0.001
HbA1C	Pearson Correlation	0.668
	p Value	<0.001
Serum Creatinine	Pearson Correlation	0.449
	p Value	<0.001
GFR	Pearson Correlation	-0.553
	p Value	<0.001

There is strong positive correlation of Urinary ACR, FBG, HbA1C, serum creatinine with serum Uric Acid. But there is strong negative correlation between GFR & serum Uric Acid.

Table 10: Association of Albuminuria with serum Uric Acid

	Serum uric acid				
Albuminuria	Normo Uricemia	Hyper Uricemia	Total	P Value	Significance
Normo Albuminuria	43(76.8)	6(13.6)	49(49)	<0.001	Significant
Micro Albuminuria	10(17.9)	22(50)	32(32)		
Macro Albuminuria	3(5.4)	16(36.4)	19(19)		
Total	56(100)	44(100)	100(100)		

In people with Hyperuricemia 50%(n=22) have microalbuminuria ; 36.4%(n=16) have macroalbuminuria & 13.6%(n=6) have normoalbuminuria. In people with Normouricemia, 17.9% (n=10) have microalbuminuria; 5.4%(n=3) have macroalbuminuria & 76.8%(n=43) have normoalbuminuria. So Albuminuria is significantly associated with Hyperuricemia.

Table 11: Association of Hyperuricemia with Albuminuria

	Albuminuria					
Hyper Uricemia	Normo Albuminuria	Micro Albuminuria	Macro Albuminuria	Total	P Value	Significance
Normo Uricemia	43(87.8)	10(31.2)	3(15.8)	56(56)	<0.001	Significant
Hyper Uricemia	6(12.2)	22(68.8)	16(84.2)	44(44)		
Total	49(100)	32(100)	19(100)	100(100)		

In people with Normoalbuminuria 87.8%(n=43) have Normouricemia and 12.2%(n=6) have Hyperuricemia. In people with Microalbuminuria 31.2%(n=10) have Normouricemia and 68.8%(n=22) have Hyperuricemia. In people with Macroalbuminuria 15.8%(n=3) have Normouricemia and 84.2%(n=16) have Hyperuricemia.

Table 12: Association of Hyperuricemia with Albuminuria in respect to sex (FEMALE & MALE) of the study population

		Albuminuria					
Female	Serum uric acid	Normo Albuminuria	Micro Albuminuria	Macro Albuminuria	Total	P Value	Significance
	Normo Uricemia	19(79.2)	8(40)	2(22.2)	29(54.7)	0.003	Significant
	Hyper Uricemia	5(20.8)	12(60)	7(77.8)	24(45.3)		
	Total	24(100)	20(100)	9(100)	53(100)		
		Albuminuria					
Male	Serum uric acid	Normo Albuminuria	Micro Albuminuria	Macro Albuminuria	Total	P Value	Significance
	Normo Uricemia	24(96)	2(16.7)	1(10)	27(57.4)	<0.001	Significant
	Hyper Uricemia	1(4)	10(83.3)	9(90)	20(42.6)		
	Total	25(100)	12(100)	10(100)	47(100)		

In female population with Normoalbuminuria 79.2% (n=19) have Normouricemia & 20.8% (n=5) have Hyperuricemia. In female population with Microalbuminuria 40%(n=8) have Normouricemia & 60%(n=12) have Hyperuricemia. In female population with Macroalbuminuria 22.2%(n=2) have Normouricemia & 77.8%(n=7) have Hyperuricemia.

Discussion

In our study Mean age in the study population was 56.6 ±9.84 years (Maximum- 80 years, Minimum-40). Chin-Hsiao Tseng et al (2005) reported that mean age in study population was 62.8±10.8 years.[17] Bonakdaran S, Hami M et al (2011) showed mean age in the study population was 52.45 ±10.11 years.[18]

In study population 47% (n=47) were Male & 53% (n=53) were Female. The slightly increased number of females could be explained by the fact that women come more to the health care set up. Another cause may be that our study was hospital based not population based and the disorder (T2DM) is more common in women.[19]

The mean of the HbA1C in patients with T2DM in study population was 7.0 ± 1.25% (maximum=11.4%, minimum= 5.4%). Bonakdaran S,Hami M et al (2011) observed that the mean of the HbA1C in patients with T2DM in study population was 8.68 ± 1.96%.[18] The high mean HbA1C may be due the poor glycemic control in patients included in this study.

The mean of the serum Creatinine in patients with T2DM in our study population was 0.90 ± 0.21 mg/dl (maximum=1.6 mg/dl, minimum= 0.5 mg/dl). Bonakdaran S,Hami M et al (2011) observed that the mean of the serum Creatinine in patients with T2DM in study population was 0.95 ± 0.32mg/dl.[18]

The mean of the GFR in patients with T2DM in study population was 78.6 ± 12.59 ml/min (maximum=121.4ml/min, minimum= 60.5ml/min). Chin-Hsiao Tseng et al (2005) reported that the mean of the GFR in patients with T2DM in study population was 63.4 ± 27.9 ml/min.[17] Bonakdaran S,Hami M et al (2011) observed that the mean of the GFR in patients with T2DM in study population was 102.68 ± 35.52 ml/min.[18]

The mean of the (Triglycerides) TG in patients with T2DM in our study population was 128.8 ± 27.94 mg/dl (maximum=199 mg/dl, minimum= 84 mg/dl). Chin-Hsiao Tseng et al (2005) reported that the mean of the TG in patients with T2DM in study population was 173.9 ± 117.3 mg/dl.[17] Bonakdaran S, Hami M et al (2011) observed that the mean of the TG in patients with T2DM in study population was 202.02 ± 130.10 mg/dl.[18]

The mean of the LDL in patients with T2DM in our study population was 129.3 ± 23.54 mg/dl (maximum=186 mg/dl, minimum= 84 mg/dl). Bonakdaran S,Hami M et al (2011) observed that the mean of the TG in patients with T2DM in study population was 127.50 ± 33.07 mg/dl. The mean of the HDL in patients with T2DM in our study population was 47.2 ± 5.90 mg/dl (maximum=57 mg/dl, minimum= 36 mg/dl). Bonakdaran S, Hami M et al (2011) observed that the mean of the HDL in patients with T2DM in study population was 43.05 ± 9.82 mg/dl.[18]

The mean of the serum Uric Acid in patients with T2DM in our study population was 5.8 ± 1.65 mg/dl (maximum=8.8 mg/dl, minimum= 3.2mg/dl). Chin-Hsiao Tseng et al (2005) reported that the mean of the Uric Acid in patients with T2DM in study population was 5.6 ± 1.9 mg/dl.[17] Bonakdaran S, Hami M et al (2011) observed that the mean of the serum Uric Acid in patients with T2DM in study population was 5.55 ±1.47 mg/dl.[18]

Mean urinary ACR levels in patients with T2DM in our study population for normouricemic & hyperurecimic patients were 59.99±101.05 µg/mg, and 249.38±199.75 µg/mg, Mean urinary ACR levels in patients with T2DM in our study population for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 22.28 ± 4.09 µg/mg, 134.79±70.65 µg/mg, and 469.83 ± 120.14µg/mg respectively. Bonakdaran S,Hami M et al (2011) observed that the mean urinary ACR in patients with T2DM in study population was 32.52±54.96µg/mg.[18]

Conclusions

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, Hypertension & HDL. Urinary ACR correlated positively with FBG, HbA1C, serum creatinine, LDL & Triglycerides in patients with T2DM. No significant correlation found between urinary ACR and Age, Sex, Weight, Height, BMI, Hypertension & HDL. In patients with T2DM serum Uric Acid level correlated negatively with GFR. In patients with T2DM serum uric acid level correlated positively with urinary albumin creatinine ratio. This study showed that Hyperuricemia was associated with a greater probability of Albuminuria in patients with type 2 diabetes mellitus. Serum uric acid is an independent correlate of urinary ACR in patients with type 2 diabetes mellitus.

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