Study on Association Between Hyperuricemia and Albuminuria in Patients with Type II Diabetes Mellitus

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ABSTRACT

Background: Hyperuricemia and albuminuria is very common among the patients of type II diabetes mellitus. The casual association between hyperuricemia and type II diabetes may be mediated by kidney dysfunction as well as insulin resistance. The objective of the study is to find association between serum uric acid level and albuminuria level in type II diabetic patient. Methods: 60 diabetic patients were taken having both serum uric acid level and albuminuria level increased considerably. Incidence of hyperuricemia and albuminuria were compared taking into association the age, sex, BMI, FBS, HbA1C, serum lipid profile, urinary ACR of the patients. Results: Hyperuricemia was associated with the greater probability of albuminuria in patients with type II diabetes mellitus. Conclusions: Serum uric acid and albuminuria is prevalent among patients of type II Diabetes mellitus, hence strict control of blood glucose level will significantly reduce the level of uric acid and albuminuria preventing further related micro and macrovascular complications of diabetes.

Key words: Diabetes, Hyperuricemia, Albuminuria, Blood glucose

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins resulting from defects in insulin secretion, action or both.[1] Diabetes is the most common endocrine disorder in our country, which is associated with long term complications involving vital organs such as eye, kidneys, nerves and blood vessels.[2] Based on the latest report from the international diabetes federation(IDF)[3] 2015 it is estimated that there are currently 415 million people living with diabetes globally and this number is set to rise to 592 million by the year 2035. As per the IDF estimates Western region (138.2 million people with diabetes) has the most number of people with diabetes and Africa (19.8 million people with diabetes), the least. India, the largest country in the South-east Asian region has 65.1 million people with diabetes as of 2013, this number is expected to increase to 109 million by 2035. Glycosylated haemoglobin is an effective tool to know the glycemic control in type II diabetes mellitus. HbA1C values gives an accurate estimate of the average plasma glucose levels from past 8 to 12 weeks. Now instead of glycemic control, HbA1C is used to detect diabetes and American Diabetes Association (ADA) has set guidelines to diagnose diabetes based on glycosylated hemoglobin values.[4] Hyperuricemia is defined as serum uric acid level ≥ 7 mg/dl (in men) or ≥ 6.0 mg/dl (in women).[5] 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.[6-8] Elevated uric acid levels can result from increased generation or decreased elimination. 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.[11] Diabetic nephropathy is the leading cause of ESRD worldwide and leading cause of DM related morbidity and mortality. Nearly 30% of chronic renal failure in India are due to diabetic nephropathy. In some studies on diabetic patients, it has been reported that hyperuricemia is associated with kidney damage independent of hypertension.[11] On the other hand, higher levels of serum insulin may decrease uric acid clearance by the kidneys.[12] As a rule, hyperinsulinemia is the basis of type 2 DM pathophysiology.[13] Therefore, diabetic patients are more prone to uric acid injury.

The present study is to evaluate serum uric acid level & urinary Albumin Creatinine Ratio (ACR) in patients of T2DM. The study also explores the relationship of normo albuminuria, micro albuminuria & macro albuminuria with serum uric acid levels.

**METHODS**

The present study was carried out in Katihar Medical College and Hospital (KMCH), Katihar. Ethical issue was obtained from the local institutional ethical committee of Katihar Medical College and informed consent was taken by the subject prior to the study. The study was a cross sectional study over a period of one and a half year from December 2015 to June 2017. A cross sectional analytical study was done on 60 patients with type II diabetes mellitus. As per American Diabetes Association Guideline criteria for the diagnosis of diabetes mellitus attending the medicine outpatient/ inpatient department. The sample size of the present study was 60 subjects including both male and female aged between 18 to 70 years and evaluated to calculate a correlation coefficient between albuminuria as measured by urinary ACR and Serum Uric Acid level.

Inclusion criteria:

a) Male and female patients in the age group of 18 to 70 years
b) Clinically proven cases of type II diabetes mellitus attending the medicine outpatient and inpatient department of Katihar Medical College and Hospital fulfilling the A.D.A criteria:-

(American Diabetes Association Guidelines 2011)

- Symptoms of diabetes plus random blood glucose concentration >200mg/dl or 
- Fasting plasma glucose level greater than or equal to 126mg/dl or 
- HBA1C > 6.5% or 
- Two hours of plasma glucose greater than or equal to 200mg/dl during an oral glucose tolerance test.
- Fasting is defined as no calories intake for at least 8 hours.

Confirmatory tests:

- Fasting & post prandial blood sugar (via ‘1’ spot test).
- Urea & creatinine.
- Total cholesterol, triglyceride, HDL, LDL, VLDL.
- Albuminuria/Albumin creatinine ratio (ACR).
- Complete blood count.
- Lipid profile.
- HbA1c.
- Ferritin.
- Scintigraphy of the kidneys.
- 12 lead ECG.
- Other relevant investigations as and when required.

Exclusion criteria:

c) Patient without history of gout and treatment with hypouricemic drug
   - Febuxostat
   - Allopurinol
   - Probenacid
   - Colchicine
d) The patient history, current medication including using of O.H.A drugs and insulin.

Diabetes mellitus was diagnosed as per the American Association Guidelines 2014 on the basis of fasting plasma glucose, two hour plasma glucose and HbA1c.

Exclusion criteria:

a) Other causes of Albuminuria not associated with diabetes.

b) Associated co-morbid conditions like stroke, haemorrhological disorder, malignancy and drug induced in case of hyperuricemia.

c) Pregnancy and gynecological disorder

Subject were enrolled in the study based on the inclusion and exclusion criteria. The selected subjects were briefed about the nature of the study and a written informed consent was obtained before the subject was enrolled in this study. Demographic data like gender, age were collected along with the relevant history and recorded in predesigned proforma. A thorough clinical exam was conducted and findings were also recorded. Anthropometry including height, weight was measured. The patient was then instructed to come the next day in an 8 hours fasting state for the blood investigation. Fasting and post prandial blood sample were collected for analysis in vacuum evacuated tubes.

Investigations were carried out for the following methods:

- Complete blood count by standard method, blood glucose by glucose oxidase/ peroxidase enzymatic method, glycosylated haemoglobin by ion exchange chromatography method, blood urea using Berthlott, urease assay, serum creatinine using Jaffe’s method, serum uric acid using modified phosphotungstate end point assay, urinary albumin measured by immune turbidimeter, total cholesterol was measured by CHOD/ POD method, HDL by phosphotungstate precipitate chylomicrons, triglyceride by calorimetric enzymatic test, VLDL was calculated by the formula triglyceride/5, LDL was calculated by the formula total cholesterol- triglyceride/ 5+ HDL, urine routine by standard microscopy method. USG whole abdomen, 12 lead ECG.

Radiological examination (wherever needed):

- Echocardiography
- Chest X-ray

Other necessary investigations as and when required. GFR was calculated using Cockroft-Gault formula. Types 2 diabetes mellitus diagnosed based on American Diabetes Association Guidelines. Patients enrolled in the study were recommended not to have heavy exercise 24 hours before examination. Urine sample consisted of mid-stream urine spot test. Blood samples were collected after 8 hours of fasting. The data collected were analyzed and expressed as
Mean ± SD. One way Analysis of variance (one way ANOVA), Pearson’s correlation test were used in the present study. Along with logical regression to obtain relative risk and odd’s ratio. Statistical software SPSS 20.0 was used for the analysis of the data and Microsoft Word and Excel to generate graphs and tables. Levels of Significance: P<0.05 was considered as significant while analyzing the data. Regression analysis was performed with Urinary ACR as the dependent variable and Serum Uric acid as the independent variable. ROC Curve was generated for different levels Serum Uric Acid in calculating Sensitivity and Specificity for Albuminuria for all patients as well as separately for Male and Female.

RESULTS
60 diabetic patients were taken having both serum uric acid level and albuminuria level increased considerably. The results were tabulated, graphically represented and analyzed. The present study consisted of 28 male patients and 32 female patients between the age of 18-70 years. Weight, height, BMI, FBG, HbA1C, serum uric acid, lipid profile (TG, HDL, LDL). The mean of above data has been represented in Table1. Hyperuricemia was presented in 34% of total population whereas asymptomatic and symptomatic patients consisted of 12% and 14% respectively. Whereas, albuminuria was divided into two groups of normoalbuminuria and micro + macroalbuminuria which consisted of 49% female, 51% male and 56.9% female and 43.1% male in each group respectively. The p value for each of the above mentioned parameters were calculated to prove their significant relationship. Mean ± standard deviation was calculated for TG, HDL and LDL dividing them into 3 groups of normoalbuminuria, micro albuminuria and macro albuminuria. The values were 119.57±25.33, 121.8±22.45, 47.43±5.88 in normo albuminuria, 127.97±22.37 and 48.22±5.39 in microalbuminuria (p value 0.001) and 154.68±24.69, 151.05±13.58, 45±6.51 (p value =0.160). Hence, albumin correlated positively with increased level of TG & LDL but no such relation seen with HDL.

Distribution of mean triglycerides(TG), LDL & HDL dividing them into two groups of normoalbuminuria, microalbuminuria and macroalbuminuria. The values were 119.84±23.66, 121.8±22.45, 119.84 ±23.66 and 121.8±22.45, 127.62±24.49, 127.97±22.37 and 154.68±24.69, 151.05±13.58, 45±6.51 (p value =0.160). Hence, albumin correlated positively with increased level of TG & LDL but no such relations were seen with HDL.

Finally, it was found that in patients with hyperuricemia 50%(n=13) have microalbuminuria, 36.4% (n=9) have macroalbuminuria & 13.6% (n=4) have normoalbuminuria. In patients with normouricemia 17.9%(n=6) have microalbuminuria, 5.4% (n=2) have macroalbuminuria& 76.8% (n=26) have normoalbuminuria. So, albuminuria is significantly associated with hyperuricemia.

Table 1: Distribution of mean Triglycerides (TG), LDL & HDL in relation to different groups of Albuminuria in study population:

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Normo Albuminuria</th>
<th>Micro Albuminuria</th>
<th>Macro Albuminuria</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Std. Deviation</td>
<td>TG</td>
<td>119.57 ± 25.33</td>
<td>121.8 ± 22.45</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>22.45</td>
<td>22.37</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>47.43 ± 5.88</td>
<td>48.22 ± 5.39</td>
<td>0.160</td>
<td>Not Significant</td>
</tr>
</tbody>
</table>

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

Table 2: Distribution of mean Triglycerides (TG), LDL & HDL in relation to Normouricemia & Hyperuricemia in study population

<table>
<thead>
<tr>
<th>Serum Uric Acid</th>
<th>Normo Uricemia</th>
<th>Hyper Uricemia</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Std. Deviation</td>
<td>TG</td>
<td>119.84 ± 23.66</td>
<td>140.25 ± 29.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>122 ± 21.45</td>
<td>138.86 ± 22.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>47.84 ± 5.91</td>
<td>46.43 ± 5.86</td>
<td>0.238</td>
</tr>
</tbody>
</table>

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

Table 3: Distribution of mean FBG, HbA1C, serum Creatinine, GFR, Urinary ACR & serum Uric Acid among different Albuminuria groups in study population

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Normo Albuminuria</th>
<th>Micro Albuminuria</th>
<th>Macro Albuminuria</th>
<th>P Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± Std. Deviation</td>
<td>FBG</td>
<td>115.43 ± 19.43</td>
<td>104.47 ± 33.56</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>HbA1C</td>
<td>6.03 ± 0.48</td>
<td>7.47 ± 0.72</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>Serum Creatinine</td>
<td>0.79 ± 0.15</td>
<td>0.92 ± 0.23</td>
<td>&lt;0.01</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>GFR</td>
<td>88.2 ± 11.11</td>
<td>75.04 ± 6.86</td>
<td>0.01</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>Urinary ACR</td>
<td>22.28 ± 4.09</td>
<td>134.79 ± 70.65</td>
<td>&lt;0.001</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td>Serum Uric Acid</td>
<td>4.64 ± 1.07</td>
<td>6.38 ± 1.3</td>
<td>0.01</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Table 4: Association of Albuminuria with serum Uric Acid

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Serum uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normo Albuminuria</td>
<td>26(76.8)</td>
</tr>
<tr>
<td>Micro Albuminuria</td>
<td>6(17.9)</td>
</tr>
<tr>
<td>Macro Albuminuria</td>
<td>2(5.4)</td>
</tr>
<tr>
<td>Total</td>
<td>34(100)</td>
</tr>
</tbody>
</table>
DISCUSSION

In the present study there was significantly associated with hyperuricemia with albuminuria in patients with type II diabetes mellitus and there is statistically significant association between hyperuricemia and albuminuria in male as well as female study population. The mean of serum uric acid in patient with type 2 diabetes mellitus in our study population.
population was 6.18±0.89 mg/dl compares well with the study conducted by Sunita Nepane, Raju Kumar Dubey et al (2016) who observed that the mean serum uric acid level in patients with T2DM in study population was 6.75 ± 1.36 mg/dl.

Another study conducted by 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. 1.36 md/dl. In the present study the mean serum Uric Acid levels in the study population in patients with T2DM for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 4.64 ± 1.07 mg/dL, 6.38±1.3 mg/dL, and 7.68 ± 1.0 mg/dL respectively. So the result of this study compares well with the study conducted by Bonakdaran S, Hami M et al (2011) who observed that the mean serum Uric Acid levels in patients with T2DM in study population for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 4.49 ± 1.22 mg/dL, 4.84±1.52 mg/dL, and 6.15 ± 1.68 mg/dL respectively. In the present study the mean urinary ACR levels in patients with T2DM for normouricemic, microalbuminuric, and macroalbuminuric patients were 22.28 ± 4.09 μg/mg, 134.79±70.65 μg/mg, and 469.83 ± 120.14μg/mg respectively. So the result of this study compares well with the study conducted by Bonakdaran S, Hami M et al (2011) who observed that the mean urinary ACR in patients with T2DM in study population was 32.52±54.96μg/mg. There is significant correlation between serum Uric Acid & urinary ACR in our study. Pearson correlation coefficient r =0.675(P value <0.001).Spearman’s coefficient of rank correlation (rho) =0.731(P value <0.001). So the result of this study compares well with the study conducted by Bonakdaran S, Hami M et al (2011) who 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).

**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 & 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 & 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.

**REFERENCES**

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