Original Research Article

Association of hyperuricemia and renal involvement in type 2 diabetes mellitus

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Received: 28 July 2018
Accepted: 16 August 2018

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ABSTRACT

Background: Hyperuricemia maybe an independent risk factor for renal dysfunction in diabetic patients. On the other hand, albuminuria is considered as an indicator for early stages of diabetic nephropathy. The aim of our study was to find out any association between hyperuricemia and simple renal function tests to detect early renal involvement in type 2 diabetes mellitus for its early treatment and prevention for diabetic nephropathy.

Methods: This hospital based cross-sectional study was conducted in 265 patients coming to medicine OPD and IPD in a tertiary care hospital in Assam, India. The subjects included were patients complaining of signs and symptoms of gout with or without Type 2 diabetes mellitus. The subjects were divided into two groups A and B, with and without type 2 diabetes respectively. They were selected randomly under the age group of 20 - 70 years old of both genders. Tests performed were serum uric acid, serum creatinine, blood urea, microalbuminuria, FBS and HbA1c estimated by standard methods.

Results: In both diabetic and non-diabetic group, serum uric acid correlated positively and significantly with serum creatinine (>1.3mg/dl), blood urea (>40mg/dl) and microalbuminuria (p<0.05). Though serum uric acid did not correlate with HbA1c and FBS (p>0.05) in both the group. In non-diabetics, males were 6.95 times likely to have hyperuricemia than females.

Conclusions: Hyperuricemia may be associated with early onset or incipient nephropathy in both diabetes and non-diabetic patient.

Keywords: Hyperuricemia, Microalbuminuria, Nephropathy, Type 2 diabetes mellitus

INTRODUCTION

The tide of type 2 diabetes is rising all over the world, thereby becoming an increasingly powerful threat to global health.1 It has also become the leading cause of end-stage renal disease in the world, and the number of patients diagnosed each year with end-stage renal disease attributed to type 2 diabetes is rising.2 The pathophysiology of diabetic nephropathy is complex and still not fully elucidated. Several prospective studies have suggested that hyperuricemia is associated with an increased risk of incident cardiovascular events and death in both non-diabetic and type 2 diabetic individuals.3,4

Although hyperuricemia can be associated with decreased renal function, based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus.5,6 Hyperuricemia, a highly prevalent condition in the adult population, is associated with obesity and insulin resistance. Metabolic syndrome and insulin resistance are well-established key risk factors for diabetes, but the role
of uric acid as risk factor in diabetes remains controversial.\textsuperscript{12} Recent evidence has suggested that uric acid plays a role in immune activation and cytokine secretion.\textsuperscript{13,14} Moreover, uric acid has been identified as a mediator of endothelial dysfunction and systemic inflammation.\textsuperscript{15}

Increasing evidence suggests that hyperuricemia is an independent risk factor for impaired fasting glucose (IFG) and type 2 diabetes. Patients with hyperuricemia are at a significantly higher risk of progressing to Type 2 diabetes.\textsuperscript{16,17} A large number of researchers have begun to consider uric acid as a serum indicator of glycometabolic disorders, because of a correlation between uric acid and glucose metabolism.\textsuperscript{18,19}

Though the cause and effect relationship of hyperuricemia and diabetic nephropathy is debatable, however some literature mentions the detrimental effects of high uric acid level on the kidney functions.\textsuperscript{11} The main detrimental effect of hyperuricemia as a part of obesity and metabolic syndrome, is through its injurious effects on the endothelium and inducing chronic inflammation.\textsuperscript{20}

This study was designed to see any association between serum uric acid and overt diabetic nephropathy in type 2 diabetes mellitus.

**METHODS**

This cross-sectional study was conducted in 265 subjects within a period of one and half years in Assam Medical College and Hospital, Assam, India.

Only diagnosed patients with type 2 diabetes not on medication were selected and patients suffering from type 1 diabetes were excluded. The subjects were first divided into two groups according to the presence or absence of type 2 Diabetes; those with diabetes were named group A and the non-diabetics as group B. They were again sub grouped as hyperuricemic and normouricemic in each group A and B. Hyperuricemic subjects were diagnosed as gout based on the guidelines by American College of Rheumatology preliminary criteria for the clinical diagnosis of gout without joint aspiration and also included those who were on allopurinol drug.\textsuperscript{21} The rest which did not fulfil the above criteria and whose serum uric acid value was within normal reference range were grouped as normouricemic group.

Around 20 subjects were excluded from the study which did not fall in any of the above groups (like suffering from rheumatoid arthritis, and type 1 diabetes).

**Inclusion criteria**

- The study subjects were patients presenting with signs and symptoms of Gout with or without Type 2 diabetes mellitus attending the OPD and IPD of Medicine department.
- The subjects were randomly selected of both genders, between the age group of 20 to 70 years old.

**Exclusion criteria**

- Pregnant women
- Patients with cardio vascular disease, SLE, malignancies, rheumatoid arthritis, Chronic kidney disease
- Type 1 diabetes were excluded from the study
- Those patients who were having proteinuria due to causes other than diabetes mellitus, like urinary tract infection and glomerulonephritis as evidenced by the urine examination or past record.

A questionnaire was prepared and prior information to the subjects and their written consent were taken. Fasting blood samples (10-12 hours overnight fasting) and early morning midflow urine samples were collected and analysed for Fasting plasma glucose, HbA1c, serum uric acid, serum creatinine, blood urea and urine sample for microalbuminuria. All tests were performed on the same day within two hours of collection in the instrument MERCK Microlab 300 semi autoanalyzer at Advanced Clinical Biochemistry Laboratory (ACBL), Assam Medical College and Hospital. The estimation of plasma glucose was done by glucose oxidase-peroxidase (GOD-POD) method, HbA1c by Ion exchange resin method, serum uric acid by uricase method, serum creatinine by Modified Jaffe’s reaction, blood urea by GLDH-urease method and microalbuminuria by turbidimetric immunoassay method. Subjects were considered to have hyperuricemia if their serum uric acid level was \( \geq 416\mu\text{mol/L} \) (\( \geq 7.0\text{mg/dl} \)) in men and \( \geq 386\mu\text{mol/L} \) (\( \geq 6.5\text{mg/dl} \)) in women or if they were on allopurinol therapy. Microalbuminuria was defined as urinary albumin >20mg/L.

**Statistical analysis**

Pearson’s chi-square test is used to see if there is any association between categorical variables. We used Pearson correlation coefficient to assess the correlation between variables. Logistic regression analysis was used to estimate the odds ratio (OR) and their 95% confidence limits (CL). Statistical analysis was performed with IBM SPSS Statistics version 21 Software. A p-value of less than or equal to 0.05 was established as statistical significance.

**RESULTS**

The 265 subjects included in the study, were grouped as group A with type 2 diabetes mellitus and non-diabetics patients were named group B. They were again sub grouped into hyperuricemic and normouricemic in each group.
Group A had 58 subjects and group B had 207 subjects. In group A, 20 subjects were hyperuricemic and 38 normouricemic. In group B, 62 were hyperuricemic and 145 were normouricemic.

Table 1: Age and gender wise distribution in Group A (Diabetic) and group B (Non-Diabetic).

| Variables       | Diabetic (group A) (n=58) | Non-diabetic (group B) (n=207) | p value |
|-----------------|---------------------------|---------------------------------|---------|
|                 | Hyper uricemic (n=20)     | Normo uricemic (n=38)           |         |
|                 |                           | Hyper uricemic (n=62)           | 0.004*  |
|                 |                           | Normo uricemic (n=145)          |         |
| Sex             | Male                      | 12 (60.0%)                      | 51 (82.3%) | 0.814 |
|                 | Female                    | 8 (40.0%)                       | 11 (17.7%) |         |
| Age -group      | ≤40 years                 | 12 (60.0%)                      | 51 (82.3%) | 0.019* |
|                 | > 40 years                | 29 (76.3%)                      | 36 (58.1%) |         |

*Expressed in number (n) and percentage (%)

Table 2: Biochemical variables of the study subjects.

| Clinical tests | Diabetic (A) | Non-diabetic (B) | p value |
|----------------|--------------|------------------|---------|
|                 | Hyper uricemic (n=20) | Normo uricemic (n=38) |         |
|                 | Hyper uricemic (n=62) | Normo uricemic (n=145) |         |
| Blood urea      | ≤40mg/dl      | 13 (65.0%)       | 51 (82.3%) | 0.051* |
|                 | >40mg/dl      | 7 (35.0%)        | 11 (17.7%) |         |
| Serum creatinine| ≥1.3mg/dl    | 12 (60.0%)       | 46 (74.2%) | 0.020* |
|                 | >1.3mg/dl     | 8 (40.0%)        | 16 (25.8%) |         |
| Microalbuminuria| Normoalbuminuria | 12 (60.0%)       | 53 (85.5%) | 0.041* |
|                 | Microalbuminuria | 8 (40.0%)        | 9 (14.5%)  |         |

*Microalbuminuria is urinary albumin >20mg/L and normoalbuminuria is ≤20mg/L.

From Table 1, authors observed that in the non-diabetic group (B), hyperuricemia was found significantly more in males (82.3%) as compared to female (17.7%). As for the age, >40 years were hyperuricemic (58.1%) than in the age group ≤40 years (41.9%).

There was a significant association between hyperuricemic and normouricemic in both diabetic (A) and non-diabetic (B) groups. Blood urea >40mg/dl, serum creatinine >1.3mg/dl, which are above the normal reference range are more in hyperuricemic group than in the normouricemic group and microalbuminuria is higher in hyperuricemic than in the normouricemic in both A and B groups (Table 2).

This shows that hyperuricemic patients have significant association for renal involvement more than in the normouricemic subjects in both diabetics and non-diabetics.

The study showed that in diabetic group, blood urea (>40mg/dl), serum creatinine (>1.3mg/dl) and microalbuminuria were associated with a statistically significant increased risk for gout (hyperuricemia). (Table 3) For blood urea (Odds ratio [OR] 3.55, [95% CI 0.954-13.236], p=0.059), serum creatinine (OR 4.40 [95% CI 1.201-16.114], p=0.025) and for microalbuminuria (OR 3.55, [95% CI 1.019-12.401], p=0.047).

In non-diabetic group, males are 6.95 times likely to have hyperuricemia than females. For age group, >40 years were 1.85 times more likely to have hyperuricemia than the age group ≤40 years. Blood urea (>40mg/dl), serum creatinine (>1.3mg/dl) and microalbuminuria were associated with a statistically significant increased risk of hyperuricemia. For blood urea (>40mg/dl) (OR 4.25 [95% CI 1.56-11.56], p=0.005), for serum creatinine (>1.3mg/dl) (OR 6.85, [95% CI 2.655-17.709], p= 0.005) and for microalbuminuria (OR 5.98, [95% CI 1.768-20.263], p=0.004) (Table 3).

It was observed that both in diabetic group and non-diabetic group, serum uric acid was positively correlated with serum creatinine (>1.3mg/dl); (p<0.05) and r=0.62, r= 0.28 respectively for group A and group B. In both the groups A and B, serum uric acid was positively correlated with microalbuminuria (p<0.05) and r=0.48, r=0.27 respectively for diabetic and non-diabetic.

Similarly, serum uric acid was positively correlated with blood urea (>40mg/dl) (p<0.05) for both the group A and B and r=0.68, r= 0.30 for diabetic and non-diabetic group respectively.
On the other hand, in diabetic and non-diabetic groups, serum uric acid was not well correlated with HbA1c and FBS since for both p>0.05 (Data not shown).

**Table 3: Association of demographic data and biochemical variables in Diabetic and Non-diabetic groups**

| Variables      | Diabetic (A) | Non-diabetic (B) |
|----------------|--------------|------------------|
|                | Hyperuricemic (n=20) | Non-hyperuricemic (n=38) | OR (95% CI) | p value | Hyperuricemic (n=62) | Non-hyperuricemic (n=145) | OR (95% CI) | p value |
| Sex            |              |                  |              |          |              |                  |              |        |
| Male           | 12 (60.0%)   | 24 (63.2%)       | 0.875 (0.288-2.658) | 0.814    | 51 (82.3%)   | 58 (40.0%)       | 6.95 (3.347-14.451) | 0.000* |
| Female         | 8 (40.0%)    | 14 (36.8%)       | 1             |           | 11 (17.7%)   | 87 (60.0%)       | 1             |        |
| Age -group     |              |                  |              |          |              |                  |              |        |
| ≤ 40 years     | 8 (40.0%)    | 9 (23.7%)        | 1             |           | 26 (41.9%)   | 83 (57.2%)       | 1             |        |
| > 40 years     | 12 (60.0%)   | 29 (76.3%)       | 0.46 (0.145-1.494) | 0.199    | 36 (58.1%)   | 62 (42.8%)       | 1.85 (1.01-3.38) | 0.045* |
| Blood urea     |              |                  |              |          |              |                  |              |        |
| ≤ 40mg/dl      | 13 (65.0%)   | 33 (86.8%)       | 1             |           | 51 (82.3%)   | 138 (95.2%)      | 1             |        |
| > 40mg/dl      | 7 (35.0%)    | 5 (13.2%)        | 3.55 (0.954-13.236) | 0.059*   | 11 (17.7%)   | 7 (4.8%)         | 4.25 (1.56-11.56) | 0.005* |
| Serum creatinine |             |                  |              |          |              |                  |              |        |
| ≤1.3 mg/dl     | 12 (60.0%)   | 33 (86.8%)       | 1             |           | 46 (74.2%)   | 138 (95.2%)      | 1             |        |
| >1.3 mg/dl     | 8 (40.0%)    | 5 (13.2%)        | 4.40 (1.201-16.114) | 0.025*   | 16 (25.8%)   | 7 (4.8%)         | 6.85 (2.655-17.709) | 0.000* |
| Micro albuminuria |          |                  |              |          |              |                  |              |        |
| Normo albuminuria | 12 (60.0%)  | 32 (84.2%)       | 1             |           | 53 (85.5%)   | 141 (97.2%)      | 1             |        |
| Micro albuminuria | 8 (40.0%)  | 6 (15.8%)        | 3.55 (1.019-12.401) | 0.047*   | 9 (14.5%)    | 4 (2.8%)         | 5.98 (1.768-20.263) | 0.004* |

*Significant (p<0.05)

**DISCUSSION**

Diabetes mellitus is a metabolic disorder characterized by variable degrees of insulin resistance and impaired insulin secretion. Insulin is a hormone that regulates the body’s use of glucose. Diabetes is characterized by hyperglycaemia and insufficiency of the secretion or the action of endogenous insulin.

Although the aetiology of the disease has not been well defined, viral infections, autoimmune diseases, and environmental factors have been implicated. The prevalence of diabetes has been growing rapidly from 135 million in 1995 to an estimated 380 million in 2025.

Although decreased kidney function can be associated by hyperuricemia, based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus (DM). Hyperuricemia may be a marker of or by itself be responsible for microvascular disease through stimulation of the rennin-angiotensin system and inhibition of endothelial nitric oxide. Hyperuricemia has been associated with hypertension and recently with initiation and progression of non-diabetic renal disease.

Some studies have suggested that uric acid could be related to the development of diabetes. Serum uric acid has shown to be associated with oxidative stress and production of tumor necrosis factor-α, which are both related to the development of diabetes. In addition, a study in rats showed that fructose-induced hyperuricemia plays a pathogenic role in the metabolic syndrome. These findings support high serum uric acid as a precursor of type 2 diabetes.

In type 2 diabetes, hyperuricemia seems to be associated with insulin-resistance syndrome and with early onset or increased progression to overt nephropathy.
Shokoofeh et al, found a significant relationship between hyperuricemia and FBS, serum creatinine levels (p<0.001). In their study serum uric acid level correlated positively with urinary albumin-creatinine ratio.31

A few previous cross-sectional studies have suggested a positive association between uric acid and diabetes in several populations, including Italian adults, Asian, and inhabitants of Seychelles.33,37 Another cross-sectional study of 1877 Turkish men and women showed that those in the highest uric acid tertile had an odds ratio of 1.89 (95% CI, 1.45-2.46) for a diagnosis of diabetes, compared with the lowest tertile.38

In this study, it was observed that both in diabetic and non-diabetic group, the serum uric acid was positively and significantly correlated with microalbuminuria, blood urea and serum creatinine. But, serum uric acid was not well correlated with HbA1c and FBS in diabetic and non-diabetic group. In non-diabetic group, males were 6.95 times likely to have hyperuricemia than females. More than 40 years old were 1.85 times more likely to have hyperuricemia than the age group ≥40 years. Blood urea (>40mg/dl), serum creatinine (>1.3mg/dl) and microalbuminuria were associated with a statistically significant increased risk of hyperuricemia.

There are limitations inherent in this study. First, our study was cross-sectional and therefore does not elucidate the causal relationships between serum uric acid and the degree of microalbuminuria or albuminuria in patients with type 2 diabetes mellitus. Second, ACR (albumin creatinine ratio) could not be analysed and for microalbuminuria test, 3 days sample of urine or 24 hours of urine could not be collected as some patients were outpatient coming from faraway place. Finally, the relatively small sample size limits the generalizability of present study conclusions.

CONCLUSION

In this study, it was found that hyperuricemia was associated with microalbuminuria and simple renal function tests like blood urea and serum creatinine in both type 2 diabetes patients and also in non-diabetes. As treatment of hyperuricemia is easy and available, early diagnosis and treatment may be helpful to prevent or decrease the rate of development of overt kidney disease in these patients.

ACKNOWLEDGEMENTS

Authors would like to thank Mr. Santosh Das, Laboratory Technician, AMCH, Assam, India.

Funding: Indian Council of Medical Research, India
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Deori R, Kotokey RK, Bhuyan B, Baruah SD. Association of hyperuricemia and renal involvement in type 2 diabetes mellitus. Int J Res Med Sci. 2018;6:2958-63.