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RESEARCH ARTICLE

Association of Hyperuricemia and Urinary Albumin Excretion with Glycosylated Hemoglobin in Patients with Type II Diabetes Mellitus

[1]Bushra Fiza, [2]Jai P Yogi, [3]Jaishree Choudhary, [4]Anita Semar, [5]Maheep Sinha

ABSTRACT

Type II diabetes mellitus (DM) is the most common endocrine disorder and a leading cause of morbidity and mortality across the world. Long-standing diabetes and a poor glycemic control are the major factors which contribute to the development of various microvascular complications of diabetes. Microvascular changes in kidneys lead to microalbuminuria, which may further lead to end-stage renal disease (ESRD) if left untreated. Elevated serum uric acid level has been recognized as a marker of endothelial dysfunction which contributes to the development of microvascular changes in various organs. The main objective of the present study was to assess the association of serum uric acid and urine microalbumin levels with glycosylated hemoglobin (HbA1c) in type II DM patients. One hundred diagnosed cases of type II DM were enrolled for the study. Blood samples were collected and estimated for fasting blood sugar, serum uric acid, and HbA1c. Also, 24-hour urine samples were collected and analyzed for microalbumin. A positive association (r = 0.203) was observed between HbA1c and serum uric acid. The study also suggested a positive association between glycemic control and microalbuminuria (r = 0.237) in diabetic patients. A strong positive association was also observed between uric acid and urine microalbumin levels (r = 0.338). Findings of the study, therefore, recommend that development of microvascular complications in type II DM patients can be averted by adopting dietary control and healthy lifestyle changes. Strict glycemic control and lowering of serum uric acid levels can be helpful in minimizing the risk of developing nephropathy and its progression toward ESRD.

Keywords: Diabetes mellitus, Glycemic control, Glycosylated hemoglobin, Microalbuminuria, Nephropathy, Uric acid.

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[1]Associate Professor, [2]Demonstrator, [3]PhD Student, [4]Senior Technical Assistant, [5]Professor and Head

[1-5]Department of Biochemistry, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

Corresponding Author: Bushra Fiza, Type I/202, Staff Quarters Mahatma Gandhi Medical College & Hospital, Jaipur-302022 Rajasthan, India, Phone: +919828051780, e-mail: bushrafiza786@gmail.com

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INTRODUCTION

Type II diabetes mellitus (DM) is a nonautoimmune, complex, heterogeneous, and polygenic metabolic disease condition in which the body fails to produce enough insulin and hence characterized by abnormal glucose homeostasis.[1] Metabolic derangement syndrome is one of the causes of DM, and it is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, particularly vascular system changes which lead in turn to the development of well-defined clinical entities, which are called the complications of DM that affect the eye, kidney, and the microvascular and nervous systems.

Diabetes mellitus has become a major health problem in India. It has been estimated that by the year 2030, 87 million of the Indian population would be suffering from this disease. Long-standing type II DM has considerable impact on various organs of the body. It increases morbidity and mortality by decreasing the quality of life.[2,3] Currently, India leads the world with the largest number of diabetic subjects and this is expected to further rise in the coming years.[4] Studies on diabetes-related complications are, therefore, vital to assess the burden of diabetes.

Diabetic nephropathy is one of the most common causes for end-stage renal disease (ESRD).[5-7] The early nephropathy stage when urinary albumin excretion is 30 to 300 mg/24 hours or 20 to 200 µg/minute is known as microalbuminuria, and patients with microalbuminuria are referred to as having initial nephropathy.[8] Intervention at this stage can retard or reverse the progression of nephropathy. Diabetic nephropathy in patients with type II diabetes has a growing prevalence of 35 to 40% and is presently the leading cause of ESRD.[9]

Epidemiological statistics exhibit that microalbuminuria amplifies the risk development of cardiovascular and cardiac abnormalities as well as cerebrovascular disease.[10] Recent findings suggest that uric acid is an inflammatory factor and may have a role in endothelial dysfunction and act as a mediator of diabetic nephropathy.[11-13]

Glycosylated hemoglobin (HbA1c) reflects an average blood glucose level over the past 3 months and has been recommended by the American Diabetes Association for evaluating the glycemic control of diabetic patients.[14] Few studies have suggested a positive correlation between microalbuminuria and HbA1c.[15-17] However, this association has not been established yet.

The present study was planned to assess the association of HbA1c (a marker of glycemic control) with serum uric acid and microalbuminuria in type II DM.

MATERIALS AND METHODS

The study was a single-center observational study conducted on type II diabetic patients visiting the Medicine Outpatient Department of Mahatma Gandhi Medical College & Hospital, Jaipur, India. The study was conducted after seeking approval from the Institutional Ethics Committee. One hundred clinically diagnosed type II DM patients were enrolled for the study. The criteria for inclusion were diagnosed cases of type II DM, age between 40 and 60 years. Diabetic subjects with any type of drug or alcohol dependence, on treatment with uric acid lowering drugs or diuretics or any other interfering pathology were excluded from the study. Pregnant and lactating females were also exempted from the study. Patients fulfilling the inclusion criteria and willing to participate were then subjected to thorough physical examination. Fasting blood samples were collected for estimation of blood glucose, uric acid, and HbA1c. For estimation of microalbumin levels, 24 hours urine samples were also collected. The patients were grouped based on the glycemic control. Patients with HbA1c ≤ 8.0% were considered as good control, while those with HbA1c > 8.0% were grouped as poor control.

The data obtained for various parameters in the two groups were presented as mean ± standard deviation and Student's t-test was applied. Pearson's correlation was applied to evaluate the association of HbA1c with serum uric acid and urine microalbumin levels. A p-value ≤ 0.05 was considered as statistically significant.

RESULTS

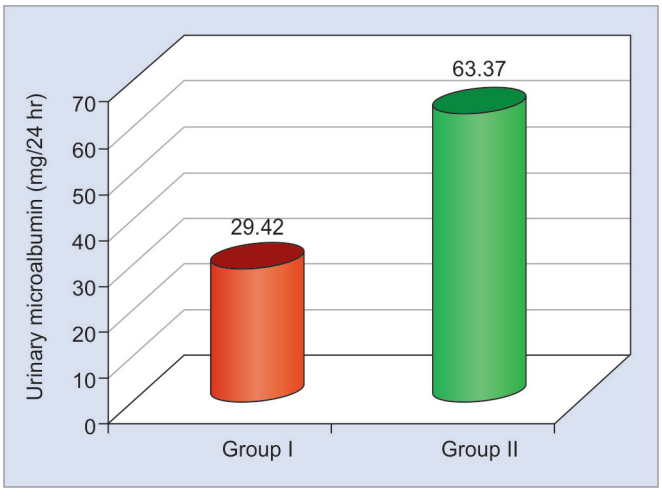
The primary aim of the research was to study the impact of glycemic control on microalbuminuria and serum uric acid levels in patients of type II DM (Graphs 1 and 2). Patients enrolled for the study were grouped based on the HbA1c levels as:

Group I (Good glycemic control) HbA1c ≤ 8.0 n = 48
Group II (Poor glycemic control) HbA1c > 8.0 n = 52

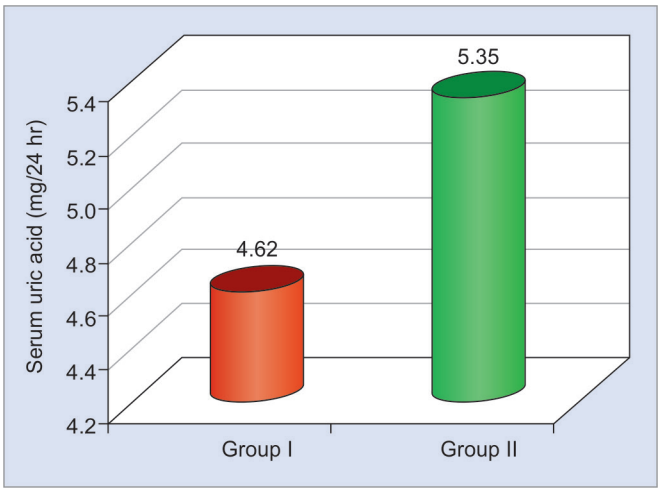
In the above-mentioned groups, mean age of patients was comparable and did not show any correlation with HbA1c or microalbuminuria. The HbA1c levels in the two groups were 6.40 ± 0.86 and 10.59 ± 1.40% respectively (p = 0.000) (Table 1). The mean fasting sugar levels also showed an obvious significant variation as reflected by the HbA1c levels (Table 1 and Graph 3).

In the poor glycemic control group (group II), 24-hour urine microalbumin was noted to be significantly higher (Table 1) and a positive correlation (r = 0.237) was observed between HbA1c and microalbuminuria (Table 2 and Graph 4). Similarly, the study also observed a significant correlation (r = 0.203) between HbA1c and serum uric acid (Table 2 and Graph 5) and, hence, suggested that a poor glycemic status in type II diabetics may lead to hyperuricemia, which in turn may serve as a cardiovascular and renal dysfunction risk factor.

Further, on applying Pearson's correlation, it was observed that microalbuminuria showed a significant correlation with serum uric acid (r = 0.338) (Table 2 and



Graph 1: Level of urinary microalbumin in type II DM patients in the groups based on glycemic control

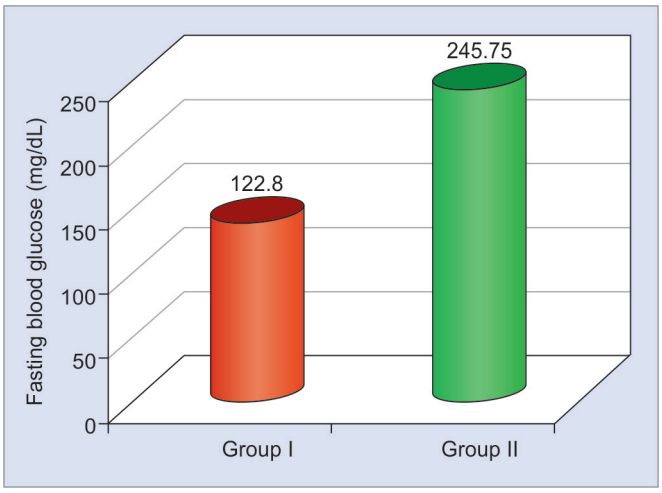


Graph 2: Level of uric acid in type II DM patients in the groups based on glycemic control

Table 1: Distribution of different parameters in the groups based on glycemic control

Parameters	*Group I (HbA1c ≤ 8.0%)*	*Group II (HbA1c > 8.0%)*	*p-value*
No. of cases	40	60	
Age (years)	50.29 ± 9.41	49.17 ± 10.39	NS
Duration of disease (years)	6.79 ± 3.10	9.08 ± 3.00	0.000
Fasting blood sugar (mg/dL)	139.88 ± 36.73	245.75 ± 91.29	0.000
HbA1c (%)	6.40 ± 0.86	10.59 ± 1.40	0.000
Serum uric acid (mg/dL)	4.62 ± 1.21	5.35 ± 1.52	0.010
Uric microalbumin (mg/24 hours)	29.42 ± 26.57	63.37 ± 51.01	0.000

NS: Not significant



Graph 3: Fasting blood sugar levels in type II DM patients in the groups based on glycemic control

Table 2: Correlation coefficients for various factors

Factors	*Correlation coefficient (r)*	*p-value*
HbA1c *vs* uric acid	0.202	0.040
HbA1c *vs* microalbuminuria	0.237	0.017
Microalbuminuria *vs* uric acid	0.338	0.000
Microalbuminuria *vs* duration	0.042	NS

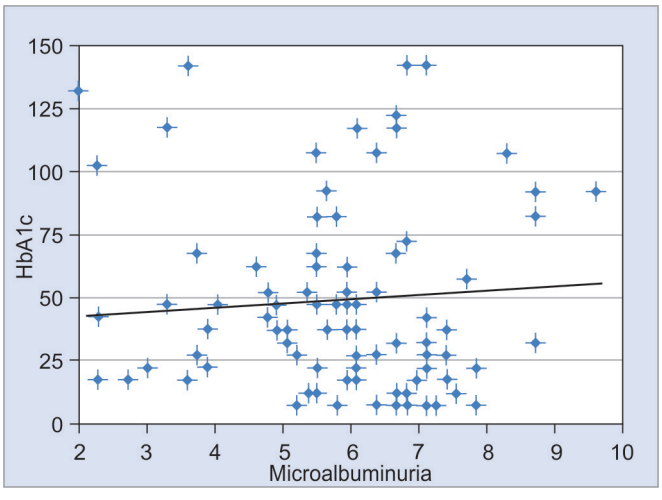
NS: Not significant

Graph 6). The mean duration of disease among the two groups based on glycemic control was significantly higher in the group with poor glycemic control (Table 1 and Graph 7). However, microalbuminuria did not show a significant correlation with the duration of disease (Table 2). This suggests that even in patients with shorter duration of disease, poor glycemic control may be responsible for the development of microalbuminuria and hence nephropathy. Hence, the findings of the study strongly emphasize the fact that complications of type II DM can be averted by proper management of the disease and by maintaining a strict glycemic control.

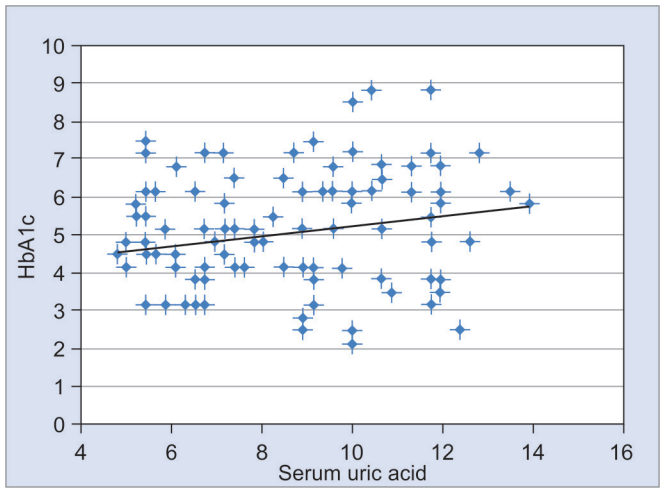
DISCUSSION

Type II diabetes is an independent risk factor for microvascular and macrovascular disease.[18,19] Microalbuminuria represents the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease.[20]

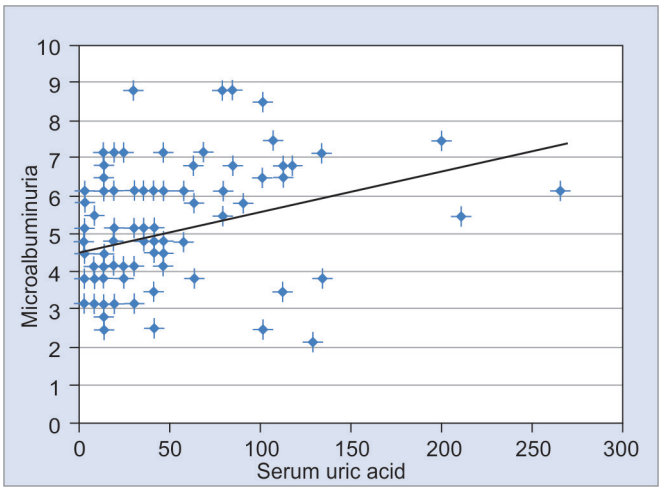
Recent studies suggest that factors causing inflammation and endothelial dysfunction play a major role in development of DN.[11-13] Several studies have observed a strong association between hyperuricemia and progression of chronic renal failure.[21-24] Further elevated/



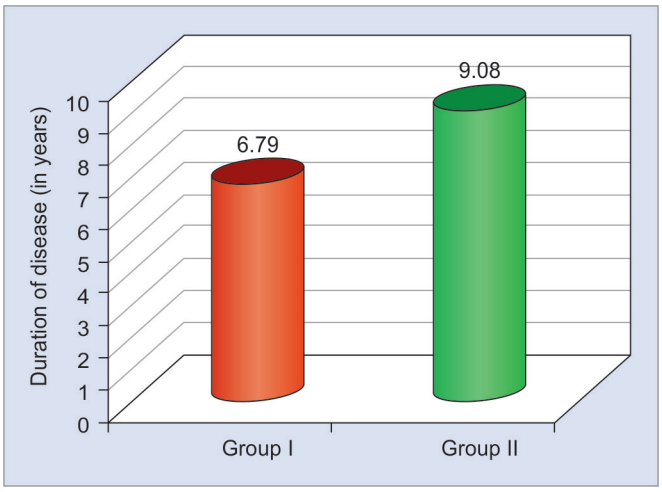
Graph 4: X–Y scatterplot for HbA1c *vs* microalbuminuria (r = 0.237, p = 0.017)



Graph 5: X–Y scatterplot for HbA1c *vs* serum uric acid (r = 0.203, p = 0.040)



Graph 6: X–Y scatterplot for microalbuminuria *vs* serum uric acid (r = 0.338, p = 0.000)



Graph 7: Duration of diabetes in type II DM patients in the groups based on glycemic control

raised serum uric acid in the early course of diabetes is said to be associated with later development of persistent microalbuminuria.[21,22]

In the present study, it was observed that diabetics with poor glycemic control (group II) had high microalbuminuria level compared with those with good glycemic control (group I). The above finding was in accordance with the finding of Kundu et al.[25] In a recent study by Naveen et al,[26] urinary microalbuminuria levels were reported to be 121.0 ± 49.89 mg/24 hours in poor glycemic control group compared with 47.14 ± 39.15 mg/24 hours in the good glycemic control group. The results of the present study were quite close to the above-mentioned findings.

Diabetic nephropathy is said to be a common consequence of long-standing DM. Elevated glucose levels in blood lead to binding of glucose to protein and resulting in excessive protein glycosylation, which in turn leads to elevated glycated end products. Increased deposition of these glycated end products on the glomerulus results in renal and glomerular hypertrophy and thickening of glomerular basement membrane. This results in leakage of low molecular weight protein, especially albumin.[26]

Further, in the present study, a linear correlation was observed between glycemic index (HbA1c levels) and microalbuminuria (r = 0.237). This above finding was similar to the finding of Naveen et al,[26] Kundu et al,[25] and Neupane et al.[27]

On comparing the mean levels of serum uric acid in the groups based on glycemic control, a significant variation was observed. The mean level of serum uric acid in group I was 4.62 ± 1.21 mg/dL compared with 5.35 ± 1.52 mg/dL in group II patients. Safi et al[28] reported serum uric acid levels of 6.2 ± 1.3 mg/dL in diabetic type II patients. Several studies have shown a positive association of serum uric acid with type II DM.[14,29]

The actual mechanism of hyperuricemia in diabetic patients is not clear. Yoo et al[30] studied the relationship between serum uric acid concentrations and insulin resistance in metabolic syndrome. The above association has also been explained based on the genetic predisposition.[31,32]

A significant correlation between microalbuminuria and serum uric acid was also observed. A common underlying pathogenesis of insulin resistance may be responsible for both elevation of serum uric acid and urine albumin excretion. On the contrary, hyperinsulinemia may result in decreased renal output and also increased synthesis of uric acid. The pathophysiological cause of renal dysfunction following hyperuricemia probably includes inhibition of endothelial nitric oxide, activation of renin–angiotensin system, and direct stimulation of endothelial cell and smooth muscle cells.[33] Both microalbuminuria and hyperuricemia have been independently associated with increased risk of progressive kidney diseases, which in turn may be responsible for ESRDs and cardiovascular morbidity and mortality. Similar to the present study, a positive correlation of serum uric acid and microalbuminuria in type II DM was shown in a study conducted by Fukui et al.[34]

From the findings of the present study, we therefore conclude that good glycemic control can be helpful in preventing microalbuminuria and hyperuricemia, hence diabetic nephropathy in chronic diabetes. The study proposes regular screening for microalbuminuria along with HbA1c estimation as important tools for management of DM.

CONCLUSION

The present study reported that a poor glycemic control in type II diabetics may lead to development

of microalbuminuria and hyperuricemia, which in turn may bring about changes resulting in progressive renal disease and other cardiovascular complications. The situation can be averted by maintaining a good glycemic control and adopting a healthy lifestyle. The study suggests a regular screening of HbA1c, microalbuminuria, and serum uric acid in type II diabetic patients for identification and timely management of patients at risk.

The study further proposes assessment of the association of microalbuminuria and hyperuricemia with other cardiovascular risk factors, such as components of lipid profile and blood pressure, etc. Urinary microalbumin levels for the present study were estimated on 24-hour urine samples. A new and more convenient replacement has now been introduced, i.e., albumin creatinine ratio (ACR), which can be estimated with spot urine sample. The study, therefore, suggests further research on correlation of HbA1c and serum uric acid with ACR. The effect of uric acid-lowering drugs and HbA1c variability on risk factors of DM and other cardiovascular complications may also be interesting to explore further.

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