Correlation of hyperuricemia with microalbuminuria in patients with type 2 diabetes mellitus in relation to glycemic control.

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Abstract:
Background: *Type 2 diabetes mellitus is a disorder characterized by elevated blood glucose level. Prolonged duration of the disease may lead various complications including cardiovascular diseases and diabetic nephropathy. Poor glycemic control causes microalbuminuria which in is a risk factor for end stage renal disease. On the other hand, elevated uric acid is identified as an independent cardiovascular risk factor.*
Aim: *The present study was planned to assess the correlation of hyperuricemia with microalbuminuria in relation to glycemic control in type 2 diabetes mellitus.*
Methodology: *100 patients diagnosed for type 2 DM, age 40-60 years with no evidence of any other pathology involving proteinuria were selected and HbA1C, 24 hr urine microalbumin and serum uric acid were estimated in the above patients. The patients were grouped as good glycemic control (HbA1C < 8.0%) n= 40 and poor glycemic control (HbA1C > 8.0%) n= 60.*
Results: *S uric acid was significantly higher in the poor glycemic control group and a positive correlation was observed between Uric acid and HbA1C (r = 0.211). A strong positive correlation (r = 0.340) was also observed between uric acid and microalbumin levels.*
Conclusion: *Poor glycemic control in type 2 DM may lead to development of microalbuminuria and hyperuricemia which in turn may lead to development of both progressive renal disease and cardiovascular complications. The situation can be avoided by maintenance of good glycemic control, regular screening and adopting a healthy lifestyle.*
Keywords
Microalbuminuria, glycemic control, Diabetes Mellitus, microvascular, macrovascular, Glycated hemoglobin, serum urea

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I. Introduction

Type 2 Diabetes Mellitus [Type 2DM] is a non-autoimmune, complex, heterogeneous and polygenic metabolic disease condition in which the body fails to produce enough insulin and hence characterized by abnormal glucose homeostasis [Diabetes Care, 2003][1] . Patients with Type 2DM often have a long asymptomatic period of hyperglycaemia and many have complications at the time of diagnosis [Satchell S et al., 2008][2].

Type 2 Diabetes is primarily characterized by elevated blood glucose levels and by microvascular and macrovascular complications that substantially increase the morbidity and mortality associated with the disease and reduce the quality of life [Fauci et.al. 2008][3]. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor blood flow in the limbs leading to amputations.

A major association between microalbuminuria and duration of diabetes had also been shown by other studies [Young BA et al.2005[4]; Sheikh SA et al. 2009[13]]. Early detection of diabetic nephropathy is important so that strategies could be made to prevent progression to ESRD.

Glycosylated hemoglobin is a blood glucose control marker in diabetic patients. HbA1c results from post-translation changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. Glycosylation of hemoglobin takes place under physiological condition by a reaction between glucose and N-terminal valine of beta chain of molecules [Kareem I et.al.2004][5].

Currently, India leads the world with the largest number of diabetic subjects and this is expected to further rise in the coming years [Ramachandran A et al. 1997[6]; King H et al. 1998][7]. Therefore, studies on diabetes related complications are vital to assess the burden of diabetes.

OBJECTIVES
* To determine association of other factors such as serum urea levels, serum creatinine levels and duration of diabetes with glcosylated hemoglobin in type 2 diabetics

II. Material & Method
The study was conducted in the Out-Patient Department of Tertiary care Hospital, Jaipur, Rajasthan. Approval from the Institutional Ethics Committee was obtained to conduct the study. It was a single center observational study. A total of 100 patients, fulfilling inclusion and exclusion criteria as listed below were enrolled in the study after obtaining informed consent in writing.

Inclusion Criteria
i. Diagnosed cases of type 2 diabetes mellitus.
ii. Age 40 to 60 years, either gender.
iii. Patients who are willing to participate and sign consent document.

Exclusion Criteria
i. Pregnant or lactating women.
ii. Patients with alcohol or drug dependence.
iii. Patients who had any major surgery within 4 weeks of screening.
iv. Patients with acute illness, fever and urinary tract infection.

Study Design and Methodology:-
It was a single center observational study. The study was conducted in Department of Biochemistry in association with other Clinical Departments of Tertiary care Hospital, Jaipur Rajasthan, Jaipur. Total 100 subjects with type 2 DM were enrolled. Patients enrolled in the study were recommended not to have heavy exercise at least 24 hours before examination. This study was one shot visit; no follow ups had been done.

Each enrolled patient was subjected to the detailed medical history, general physical examination and biometrics. Fasting blood samples were collected by venipuncture for biochemical analysis and 24 hours urine samples were also collected for estimation of microalbuminuria. In view of measuring urinary albumin concentration correctly, patients were given necessary instructions regarding the collection of urine samples. When no evidence of infection and/or haematuria was found in the urinalysis, urine samples were examined for microalbuminuria.

Biochemical Investigations:
All tests were performed in Randox Daytona auto analyzer. All parameters were calibrated by use of saline and Randox calibration serum level 3 (Cal 3). Quality control was performed by using Randox assayed multisera, level 2 and level 3.
The major investigations were included:-
* Blood Glucose (Fasting)
* Blood Urea
* Serum Creatinine
* HbA1c
* Urinary Microalbuminuria

Diagnostic Criteria:-
· **Blood glucose**
Fasting blood glucose was estimated by Glucose Oxidase method.
Sample Type: Venous blood was taken in fluoride vial for plasma seperation.

Normal Value (Fasting Plasma Glucose)	75-115 mg /dl

- **HbA1c**

Glycated hemoglobin [HbA1c] is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. Measurement of HbA1c is used to determine average glycemic control over an 8-12 week period, and HbA1c level has been linked to development of microvascular complications [Jesudason DR et al.2003][8].

- **Serum Creatinine**

Serum creatinine was estimated by Jaff's method by colorimetrically.
Sample Type: Venous blood was taken in plain vial for serum seperation.

	Normal values
Male	0.6 – 1.1 mg/dl
Female	0.5 – 0.9 mg/dl

Microalbumin in urine
Immunoturbidimetric assay for urinary albumin liquid stable

	Albumin level (mg/day)
Normal	2-20
Microalbuminuria	20-300
Macroalbuminuria	>300

The results obtained were presented as Mean + SD and subjected to statistical analysis. The values of different parameters in the two groups were compared by applying **z-test**.
Further, to assess the correlation of HbA1c and microalbuminuria with serum urea, creatinine and also with the age and duration of diabetes,

Pearson's correlation was applied. XY scatter plots were plotted for all the correlations.
A p-value of < 0.05 was considered to be statistically significant.

Observations
Tablle 1: Level of Uric acid in T2D patients in the groups based on Glycemic control

Group	No. of cases (n)	S. Uric acid (mg/dl)	P-value
I	40	4.39 ± 0.99	0.000
II	60	5.44 ± 1.57	

- Values presented as Mean + SD
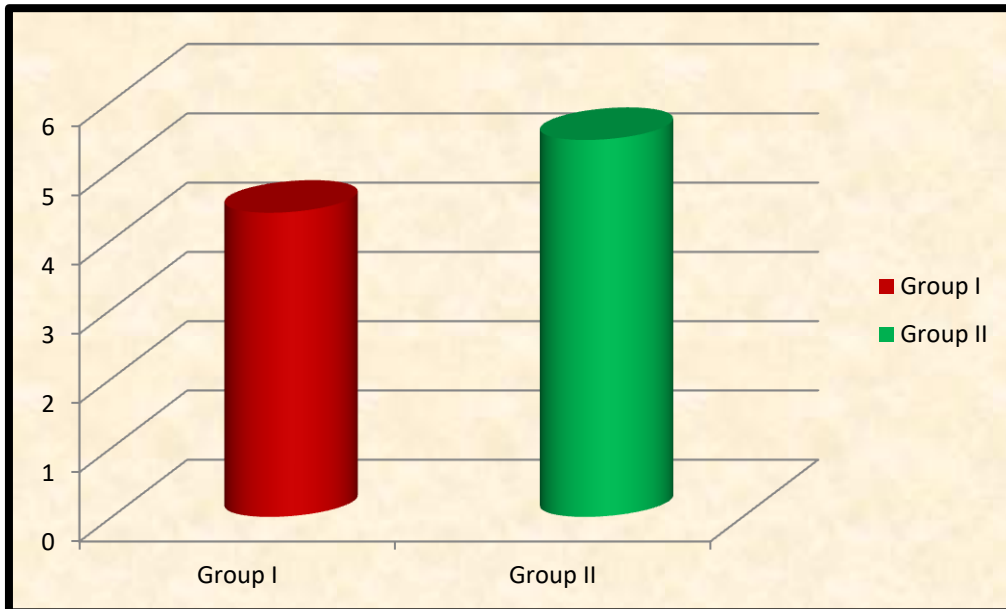- P-value as obtained on applying **z-test**

Figure 1: Level of Uric acid in T2D patients in the groups based on Glycemic control

Table 2: Level of urinary microalbumin in T2D patients in the groups based on Glycemic control

Group	No. of cases (n)	U. Microalbumin (mg/24 hr)	P-value
I	40	40.92 ± 24.03	0.000
II	60	120.9 ± 88.26	

- Values presented as Mean + SD
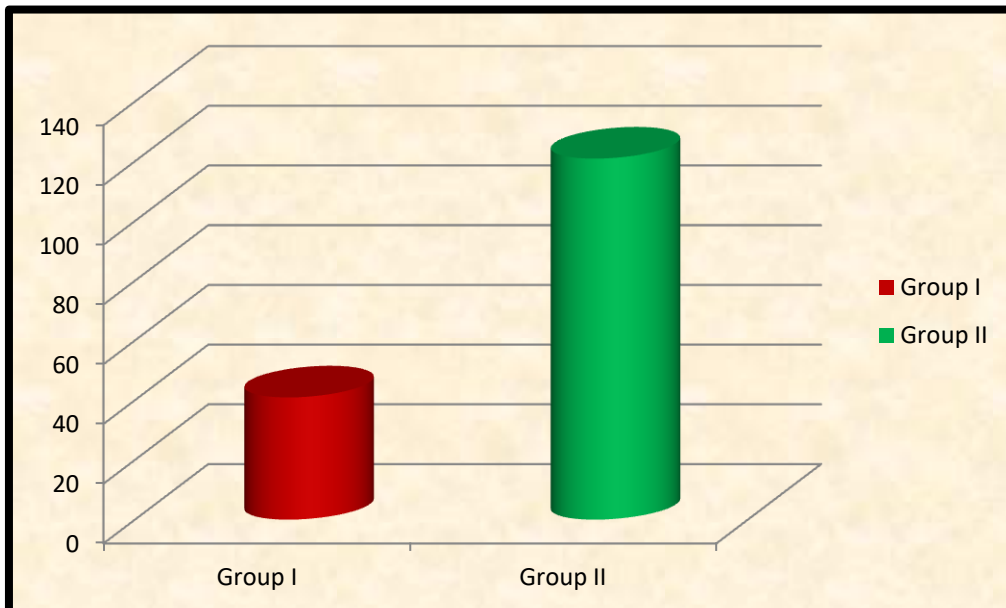- P-value as obtained on applying **z-test**

Figure 2: Level of urinary microalbumin in T2D patients in the groups based on Glycemic control

Table 3: Level of S. Creatinine in T2D patients in the groups based on Glycemic control

Group	No. of cases (n)	S. Creatinine (mg/dl)	P-value
I	40	0.88 ± 0.28	0.000
II	60	1.09 ± 0.29	

- Values presented as Mean + SD
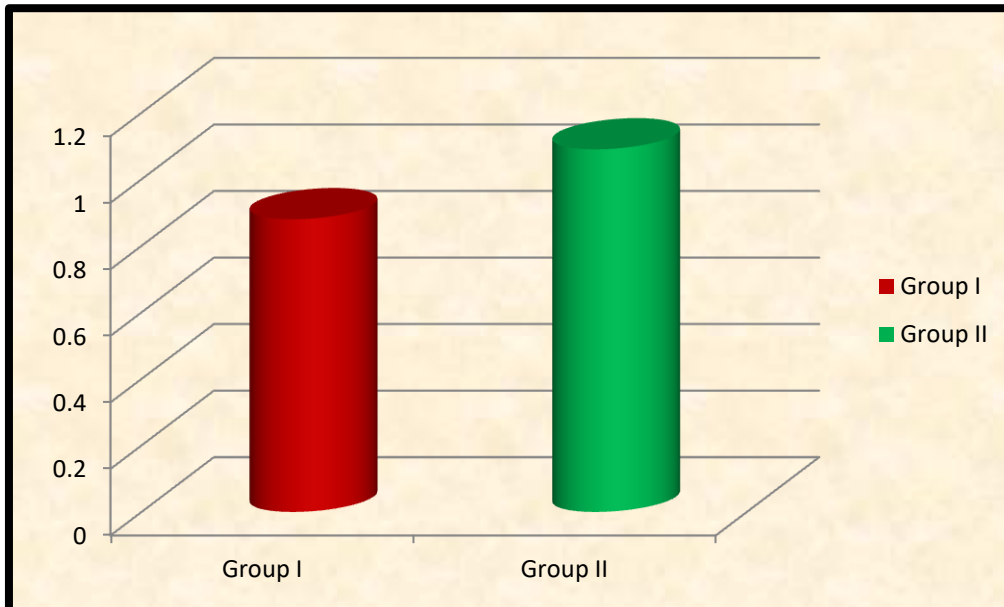- P-value as obtained on applying **z-test**

Figure 3: Level of S. Creatinine in T2D patients in the groups based on Glycemic control

Table 4: Level of B. Urea in T2D patients in the groups based on Glycemic control

Group	No. of cases (n)	B. Urea (mg/dl)	P-value
I	40	33.03 ± 13.94	NS
II	60	31.49 ± 8.71	

- Values presented as Mean + SD
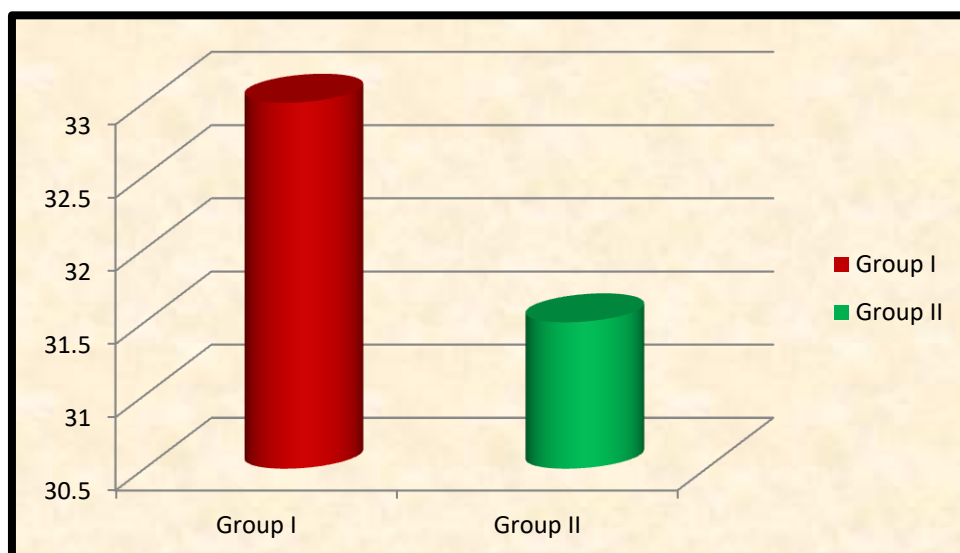- P-value as obtained on applying **z-test**

Figure 4: Level of B. Urea in T2D patients in the groups based on Glycemic control

Table 5: The correlation coefficient for different factors.

Factors	Correlation coefficient (r)	P-value
HbA1c vs Fasting Sugar	0.766	0.000
HbA1c vs Uric Acid	0.211	0.032
HbA1c vs MA	0.381	0.000
HbA1c vs Creatinine	0.278	0.004
HbA1c vs Duration	0.250	0.011
MA vs Fasting sugar	0.379	0.000
MA vs Uric Acid	0.340	0.000
MA vs Creatinine	0.357	0.000
MA vs Duration	0.037	NS

- **r** and **P**-value as obtained on applying **Pearson correlation**
- **MA - Microalbuminuria**

III. Result & Discussion

In a recent study by Naveen et al 2012[9], urinary microalbuminuria levels were reported to be 121.0 ± 49.89 mg/24 hrs. in poor glycemic control group as compared to 47.14 ± 39.15 mg/24 hrs. in the good glycemic control group. The results of the present study were quite close to the above mentioned finding. Diabetic Nephropathy is said to be a common consequences of long standing DM. Elevated glucose levels in blood lead to binding of glucose to protein resulting in excessive protein glycosylation which in turn leads to elevated glycated end products. Incresaed deposition of these glycated end products on the glomerulus resulting in renal & glomerulohypertrophy and thickening of glomerular basement membrane. This allows leakage of low molecular weight protein [Albumin] [Naveen et al.][9]. This condition is turned as incipient nephropathy [microalbuminuria].

Further, in the present study a linear correlation was observed between glycemic controls [HbA1c levels] and microalbuminuria [r = 0.381] (Table 5). This above finding was similar to the finding of Naveen et al. 2012[9] and Kundu et al. 2013[10].

Table 3, shows the mean $\pm$ SD levels of serum creatinine in the groups based on glycemic control. On applying Z- test it was observed that serum creatinine levels were significantly higher in group 2 [poor glycemic control] as compared to the poor control group [p = 0.004] similar findings have been reported by Naveen et al who observed elevated levels of serum creatinine in patients with poor glycemic control (figure 3).

Table 4, shows the level of serum urea in poor & good glycemiccontrol groups. No significant variation was observed in the urea levels in the two groups. As such no study has quoted a significant association in the serum urea levels with hyperuricemia, proteinuria or HbA1c levels (figure 4).

Table 5, shows the correlation coefficient for the various lists. It was observed that HbA1c levels showed a strong correlation with microalbuminuria, serum uric acid and creatinine in type 2 DM. A statistacally significant positive correlation was also observed between HbA1c levels and duration of diabetes [r = 0.250].

A significant correlation between microalbuminuria and serum uric acid as well as microalbuminuria and serum creatinine was also observed. A positive correlation of serum uric acid and microalbuminuria in type 2 DM was shown in a study conducted by Fukui et al [Fukui M et al. 2008][11]. Similarly Fu et al reported that hyperuricemia was significantly associated with abnormal albuminuria in chinese diabetics.

IV. Conclusion

The present study reported that a poor glycemic control in type 2 diabetics may lead to development of microalbuminuria and hyperuricemia which in turn may bring about changes resulting in progressive renal disease and also 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 Sr. uric acid in type 2 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. The effect of uric acid lowering drugs and HbA1c variability on risk factors of DN and other cardiovascular complications may be interesting to explore further.

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