Hypouricemia in type 2 diabetes mellitus without nephropathy: A case control study

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Abstract

Introduction: Some previous studies and our recent study had shown low serum uric acid (UA) in Diabetic patients compared to Non diabetics and it was suggested that low serum UA levels in Diabetics are probably due to uricosuric effect of urinary Glucose. This study was conducted to have an insight regarding the pathophysiology of low serum UA levels in Diabetics.

Materials And Methods: Fasting blood glucose (FBG), Post lunch blood glucose (PLBG), serum UA and 24 hr urinary excretion were estimated in Type 2 Diabetics without nephropathy (Cases) and in Nondiabetic inpatients (Controls) who got admitted into various Departments of KIMS hospital. The comparison of serum UA and 24 hr urinary excretion between cases and controls and correlation between 24 hr urinary excretion, FBG and serum UA in cases was tested using SPSS 19 version.

Result: Serum UA Mean is low in Diabetics compared to Non diabetics and this difference is significant whereas 24 hr urinary excretion is significantly higher in Diabetics compared to Nondiabetics. Significant negative association between FBG and serum UA and positive association between 24hr urinary UA and FBG and negative association of 24 hr urinary excretion with serum UA in Diabetics which is nonsignificant.

Summary and Conclusions: At high concentrations of FBG there is increase in 24 hr urinary excretion providing an objective evidence to hypothesis that low UA levels in diabetics are probably due to inhibition of UA reabsorption in the proximal convoluted tubule of kidney by glucose.

Keywords: Type 2 Diabetics, Fasting blood glucose, serum UA, 24 hr urinary excretion.

Introduction

Several studies had shown that serum uric acid (UA) levels are associated with an increased risk of insulin resistance,¹ chronic kidney disease,² hypertension,³ cardiovascular disease,⁴ and for peripheral arterial disease.⁵ Studies have shown conflicting results regarding the levels of serum UA levels in Diabetic patients. Some studies had shown high serum UA levels in Diabetics⁶-¹¹ and some low serum UA levels in Diabetics.¹²-¹⁶ So to explore serum UA levels in Diabetics we had conducted a study to compare serum UA levels in diabetic patients and Nondiabetics and to correlate fasting blood glucose (FBG) with serum uric acid (UA).¹⁷ In that study we had shown that UA Mean is low in Diabetics whose FBS is >126mg/dl compared to Nondiabetics whose FBS is <100mg/dl and this difference is statistically significant. FBG is positively correlated with serum UA in Nondiabetics & negatively correlated in Diabetics. The conclusion of that study was at high concentrations of FBG there is decrease in Serum UA level probably due to inhibition of UA reabsorption in the proximal convoluted tubule of kidney by urinary Glucose. There are very few studies which objectively prove that low serum UA levels in Diabetics are due to uricosuric effect of Glucose in urine. So this study was carried out to analyze the pathophysiology of low serum UA levels in Diabetic patients i.e whether the low serum UA levels in Diabetics are probably due to inhibition of UA reabsorption in the proximal convoluted tubule of kidney by Glucose or alternate metabolic abnormalities result in low serum UA levels in Diabetics compared to Nondiabetics. The objectives of present study are to estimate and compare serum UA and 24 hr urinary excretion in Type 2 Diabetics (FBG > 126mg/dl) and Nondiabetics (FBG<110mg/dl) and also to correlate between 24 hr urinary excretion, FBG and serum UA levels in Diabetics.

Materials and Methods

The study was conducted in Kamineni institute of medical sciences, Narketpally, Nalgonda (District), Telangana, India. Institutional ethics committee clearance and valid informed consent from subjects was taken. Subjects for the study were screened from inpatients who admitted into the various Departments.

Inclusion criteria:

Cases: 50 Type 2 Diabetic Male subjects of age group 45 – 60years whose FBG is >126mg/dl
BMI between 25–30

Controls: 50 Male Nondiabetics of age group 45-60yrs whose FBG is between <100mg/dl
BMI between 25–30

Exclusion criteria: Subjects with history of smoking, alcoholism, hypertension, hyperlipidemia.
Patients with diseases that can cause altered uric acid levels such as obesity, renal disease were excluded.

Diabetic Male subjects on insulin treatment.

Subjects detail was taken. Their name, age, sex, occupation, history of Diabetes, Hypertension, other comorbid conditions and treatment history was taken by standard proforma.

Subjects Height and Weight were recorded.

Sample collection:

**Serum:** 5 ml of venous blood was drawn after an overnight fasting into a sterile disposable syringe under aseptic conditions. Samples are centrifuged at 3000 rpm for 5 mins. Plasma and serum were separated within two hours of collection of blood. Care was taken to prevent hemolysis of the samples. Lipaemic and icteric samples were discarded. The following parameters were estimated in BS380 autoanalyzer

- Fasting Blood Glucose by GOD – POD method
- Serum Uric acid by Uricase method
- Urea by Berthelot reaction
- Creatinine by Jaffes kinetic method
- Triacylglycerol by GPO-POD method
- Total cholesterol by CHOD - PAP – Colorimetric Method
- LDL by Direct enzymatic method
- HDL by Cholesterol oxidase method

**Urine:** All patients provided 24 Hr urinary samples.

The statistical analysis was performed using SPSS software 19.00 version. The descriptive results are expressed as Mean ± S.D. significance of difference between cases and control group observed and assessed by using the unpaired student t’ test. The ‘p’ values are expressed along with mean values and S.D. The ‘p’ value < 0.05 was considered statistically significant.

Pearson correlation ‘r’ was used to assess the correlation between different parameters in the groups analyzed. The results were represented in the form of tables.

### Results

#### Table 1: Age and BMI distribution of cases and controls

| Parameter      | Cases (Type 2 Diabetics) N=50 Mean±S.D | Controls (Non Diabetics) N=50 Mean±S.D | ‘t’ value | ‘p’ value |
|----------------|----------------------------------------|----------------------------------------|-----------|-----------|
| Age (in years) | 48±5.24                                | 49±4.81                                | 0.99      | 0.32      |
| BMI (Kg/m²)    | 24.5±2.6                                | 24±2.4                                 | 0.99      | 0.32      |

Age and BMI distribution among cases and controls is comparable.

#### Table 2: Mean± S.D values of parameters in serum of cases and controls

| Parameter (Serum) | Cases (Type 2 Diabetics) N=50 Mean±S.D | Controls (Non Diabetics) N=50 Mean±S.D | 't' value | 'p' value |
|-------------------|----------------------------------------|----------------------------------------|-----------|-----------|
| FBG (mg/dl)       | 179.54±31.62                           | 100.12±11.2                            | 16.74     | 0.00      |
| PLBS (mg/dl)      | 207.93±56.45                           | 116.2±26.06                            | 10.29     | 0.00      |
| Uric acid (mg/dl) | 4.90±1.22                              | 5.92±1.41                              | 4.6       | 0.00      |
| Urea (mg/dl)      | 20.58±3.52                             | 19.67±1.91                             | 1.60      | 0.11      |
| Creatinine (mg/dl)| 0.81±0.4                               | 0.72±0.21                              | 1.40      | 0.16      |
| TAG (mg/dl)       | 129.42±24.24                           | 124±16.34                              | 1.31      | 0.19      |
| Total Cholesterol (mg/dl) | 170±16.12                     | 166±11.12                              | 1.44      | 0.15      |
| VLDL (mg/dl)      | 21.24±8.26                             | 22.47±4.92                             | 0.90      | 0.36      |
| LDL (mg/dl)       | 100.2±20.32                            | 98.62±14.1                             | 0.45      | 0.65      |
| HDL (mg/dl)       | 40.56±5.21                             | 41.11±2.92                             | 0.65      | 0.51      |

FBG and PLBG are significantly more in cases compared to controls. Serum UA is significantly less in cases compared to controls. Serum Urea, Creatinine, TAG, Total cholesterol, VLDL, LDL, HDL are comparable among cases and controls.

#### Table 3: Mean & S.D values of parameters in 24 hour urinary samples of cases and controls
24hr excretion of UA is more in cases compared to controls and it is statistically significant. 24hr excretion of creatinine and albumin are normal in cases and controls and they are comparable.

Table 4: Correlation between FBS and PLBS in controls and cases

| Parameter | Controls (Non diabetics) N=50 FBS | Cases (Type 2 Diabetics) N=50 FBS |
|-----------|-----------------------------------|-----------------------------------|
| Non diabetics PLBS | r=0.631 p=0.000 | |
| Diabetics PLBS | r=0.750 p=0.000 | |

There is significant positive correlation between FBG and PLBG in Diabetics and Nondiabetics.

Table 5: Correlation of 24hr urinary UA with FBG and serum UA in Type 2 Diabetics without nephropathy

| Group Type 2 Diabetics | 24hr Urinary UA | FBG |
|------------------------|-----------------|-----|
| FBG                    | r= -0.254 p=0.113 | 1   |
| Serum UA               | r= -0.160 p=0.323 | p=.382 |

There is statistically significant negative association between FBG and serum UA and statistically not significant positive association between urinary UA and FBG. Statistically not significant negative association between urinary UA and serum UA.

Discussion

In the present study in Type 2 Diabetics without nephropathy (FBG > 126 mg/dl) there is decrease in Serum UA levels compared to Nondiabetics (FBG <110mg/dl). Difference in mean serum UA levels between Diabetics and Nondiabetics is statistically significant (‘p’<0.05) as shown in Table 2. In Type 2 diabetics FBG showed significant negative correlation with Serum UA as shown in Table 5. These results are similar to our previous study and few other studies.12,17

To know the pathophysiology of low serum UA levels in Type 2 Diabetic patients we have estimated 24 hr Urinary UA excretion rate in Type 2 Diabetics without nephropathy and Nondiabetics. Previous studies had shown that hyperinsulinemia increases serum UA in diabetics by increasing the rate of synthesis of UA through activation of the hexose phosphate shunt which results in more production of purines than needed by cell and also insulin may stimulate the urate anion transporter in the proximal convoluted tubule increasing reabsorption of uric acid from the kidneys. So we excluded from our study diabetics on insulin treatment18,19. We found that 24 hr Urinary UA excretion rate is significantly higher in Type 2 Diabetics whose FBG is >126mg/dl compared to Nondiabetics with normal FBG. These findings of significantly low serum UA levels and significantly high Urinary UA excretion rate in Type 2 Diabetics without nephropathy compared to individuals with normal FBG suggests uricosuric effect of glucose .This finding is in agreement with study conducted by NS Neki*, Himanshu Gupta**. They showed that in Diabetic patients without nephropathy low serum UA and high urinary UA excretion rate.20 Boner G and Rieselback study has shown that in normal individuals urinary UA excretion is positively associated with urinary Glucose if serum glucose levels are more than renal threshold causing glycosuria.21

Serum UA levels are determined by reabsorption of UA by PCT and rate of excretion of UA by kidneys.22 After filtration, UA undergoes both re-absorption and secretion in the proximal convoluted tubules and this process is mediated by urate/anion exchanger and a voltage sensitive urate channel. Reabsorption of UA by
PCT is by urate transporters which includes URAT1 transporter and two sodium-coupled monocarboxylate transporters (SMCT1 and SMCT2), situated in apical membrane. SLC2A9 transporter which is previously known as GLUT9 transports UA from lumen of PCT cells into blood. This reabsorption of UA into blood by PCT is affected by several factors, such as inorganic and organic anions and several uricosuric agents like Glucose. As shown in Table 4, Diabetic patients with higher FBG levels are recognized to have more post-prandial blood glucose levels with greater Glucose loading of the kidneys resulting in Glucosuria. High levels of excretion of Glucose in Diabetic patients results in high UA excretion rate and low levels of serum UA levels.

To explore the association between 24 hr urinary excretion, Fasting blood glucose levels and serum UA correlation study was done in Type 2 Diabetics as shown in Table 5. In this study we found that serum UA has significant negative association with FBG and no significant positive association with urinary UA. We also found out that there is no significant positive association of urinary UA with serum UA. The probable reason for statistically not significant weak association of urinary UA with FBG and serum UA is FBG and serum UA are single time estimates whereas urinary UA is 24-hour estimate and relatively small sample size to extrapolate the findings to general population. Though the sample size is small it is a positive step in the direction to establish the cause for low serum UA levels which is an antioxidant in Diabetics.

Conclusion

At high concentrations of FBG there is increase in 24 hr urinary excretion providing an objective evidence to hypothesis that low UA levels in Type 2 diabetics are probably due to inhibition of uric acid reabsorption in the proximal convoluted tubule of kidney by glucose in urine.

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