Correlation between Serum Uric acid In Pre Diabetics and Diabetics: A Prospective Observational Study

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ABSTRACT

To determine the level of serum uric acid level in diabetics and pre diabetics individuals. To compare the level of serum uric acid, FPG , HBA1C in pre diabetics and diabetics. There was a significant relation between prediabetics who were younger in age compared to diabetics (almost a decade younger). The gender distribution was identical between the two groups. 53% had complaint <1 year.39% had isolated HTN; 9% had IHD whereas 19% had both. The diabetics had HbA1c significantly higher than prediabetics. Although proportionately more prediabetics had raised creatinine levels, but the difference was not significant. The difference of mean uric acid wrt HbA1c was not significant, although people with lower HbA1c values had a higher uric acid levels. The difference was not significant wrt uric acid levels with FBS values in prediabetics. The difference was not significant, although people with lower PPBS had higher uric acid levels in prediabetics. There was a significant relation of lower uric acid mean values for people with elevated HbA1c over 7g% amongst diabetics. There was no significant relation, although mean uric acid levels were raised for people with FBS<110 amongst diabetics. There was no significant relation but uric acid levels were higher in people with PPBS <140 amongst diabetics Younger age in India is predisposed to prediabetes and diabetes. Often patients are silent, without symptoms and detected only by investigations, so investigations for prediabetes and diabetes should be mandatorily routine. Lower uric acid levels have correlation with impaired glycemic control and should be part of check ups for metabolic syndromes. Hypertension and heart disease commonly coexist with diabetes and should be tackled together. Uric acid monitoring should have a role in guiding glycemic goals.

Keywords: Serum uric acid, FBS, PPBS , Pre diabetics , Diabetics

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INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. \(^1\) It is considered a disorder of ageing, but can affect any age group. The effect of diabetes mellitus includes long term damage, dysfunction and failure of various organs, eyes, kidneys, nerves and heart, and blood vessels. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories - those having little or no endogenous insulin secretory capacity (IDDM or type 1 diabetes mellitus) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM or type 2 diabetes mellitus). \(^2\) Both the diseases are widely prevalent across the globe and adding to morbidity and mortality.

Without concerted action to prevent diabetes, in less than 25 years’ time there will be 592 million people living with the disease. \(^3\) Most of those cases would be preventable with lifestyle changes, dietary habits and health education i.e. primordial and primary prevention. In the year 2013, there were 382 million people living with diabetes. \(^4\) By the end 2013, diabetes had caused 5.1 million deaths. \(^5\) Type 2 diabetes accounts for approximately 90 to 95% of all diagnosed cases of diabetes. \(^6\) Studies suggest that at the time of diagnosis, the typical patient with type 2 diabetes mellitus have diabetes for at least 4 to 7 years. \(^7\)

Among patients with type 2 diabetes mellitus, 25% are believed to have retinopathy, 9% nephropathy and 8% neuropathy at the time of diagnosis. \(^8\) Often the presenting symptoms of Type 2 diabetes may be the end organ complication, and diabetes detected subsequently on investigation for this end organ complication.

Micronutrients have been investigated as potential, preventive and therapeutic agents for type 2 diabetes mellitus and their complications. In particular, diabetes has shown to be associated with abnormalities in the metabolism of zinc, chromium, copper, magnesium and manganese. \(^9\)

IFG is defined as FPG levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) \(\text{(24, 25)}\) and IGT as 2-h PG during 75-g OGTT levels between 140 and 199 mg/dL (between 7.8 and 11.0 mmol/L) \(\text{(10)}\). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L). \(\text{(10)}\)

Uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. \(\text{(11)}\) Serum urate levels vary with age and sex. Most children have serum urate concentrations of 180 to 240 μmol/l (3.0 to 4.0 mg/dl). \(\text{(12)}\)

Levels begin to rise in males during puberty but remain low in females until menopause.
Mean serum urate values of adult men and premenopausal women are 415 and 360 µmol/L (6.8 and 6.0 mg/dl), respectively. After menopause, values for women increase to approximate those of men. In adulthood, concentrations rise steadily over time and vary with height, body weight, blood pressure, renal function, and alcohol intake. Several epidemiological studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease. Population-based studies have shown that hyperuricemia is an independent risk factor for cardiovascular disease (CVD). This association has been found to be particularly robust among individuals at high risk for CVD, including those with obesity, hypertension, diabetes and renal disease. With the above background, this study was done to examine the serum level of uric acid in diabetics and pre-diabetics.

**Lacunae in Existing Literature**

On meticulous review of published literature wrt hyperuricemia and dysglycemia, it is seen that there is no Indian study observing this correlation, and existing studies have conflicting outcomes with no uniform consensus.

**RATIONALE OF THIS STUDY & DEFINING THE RESEARCH QUESTION**

The research question stands as is there any relation in Indian population between hyperuricemia and dysglycemia? This study aims to address this question in Indian population derived from Mumbai and allied areas.

**Aims and Objectives**

1) To determine the level of serum uric acid level in diabetics and pre diabetics individuals.

2) To compare the level of serum uric acid, FPG, HBA1C in pre diabetics and diabetics.

**MATERIALS AND METHOD**

**Study Design**

A single Centre, hospital based prospective observational study.

**Study site**

Department of Medicine, Saifee Hospital, Mumbai including both Indoor, OPD and emergency

**STUDY PERIOD**

JANUARY 2019- JANUARY 2020

**Study subjects**

50 pre diabetics and 50 diabetics, admitted or visiting OPD in Department of Medicine, Saifee Hospital, Mumbai.
Inclusion criteria

1. Patients with Diabetes Mellitus (ADA criteria for diabetes)
2. Pre-diabetes (Impaired Fasting Glucose/Impaired Postprandial Glucose)
3. Non diabetics.
4. All age groups & both sexes.

Exclusion criteria

1. Patients with serum creatinine > 1.3 mg/dl
2. Subjects with any diagnosed malignancy.
3. Individuals diagnosed as suffering from gout.
4. Patients on drugs which alters serum uric acid levels (diuretics, levodopa, Pyrazinamide.)
5. All other conditions which increase or decrease serum uric acid levels

SAMPLE SIZE CALCULATION

The sample size for observational studies is given as

\[ N = \frac{Zp(1-p)}{d^2} \]

Where \( N \) = sample size
\( Z = 1.96 \)
\( p = \) maximum expected prevalence = 0.5
\( d = \) acceptable error = 10%

From simple calculation, sample size = 100

There were 50 subjects in each group i.e. pre diabetic and diabetic

Sampling method

Every consecutive patient fulfilling diagnostic criteria and inclusion and exclusion criteria, giving informed and written consent were enrolled to complete the sample size in the stipulated duration ie convenience sampling.

Method of collection of data

This was hospital based observational study involving 100 patients (50 each in each group). Detailed history was taken including duration of diabetes, treatment mode, followed by physical examination. Postprandial blood sugar was measured two hours after a standard meal.

Hexokinase/G6PDH enzymatic method for measuring blood glucose as per American Diabetes Association, 2017. Fasting blood glucose of <100 mg/dL was taken as normal glucose tolerance, 100-125 mg/dL as impaired glucose tolerance and >126 mg/dL as abnormal glucose tolerance. Postprandial blood sugar of <140 mg/dL was taken as normal glucose tolerance, 140-199 mg/dL as impaired glucose tolerance and >200 mg/dL as
abnormal glucose tolerance. HbA1c estimation was done by enzymatic method measuring N-terminal fructosyl dipeptides of the β peptide chain.

**Statistical Analysis**

The data was entered into Microsoft excel data sheet and analyzed using SPSS software. Categorical data has been represented in the form of frequencies and proportions. Chi-square test has been used as test of significance. Continuous data has been represented as mean and standard deviation. Independent t-test has been used as test of significance to identity the mean difference between two groups, p-value <0.05 considered as statistically significant.

**RESULTS AND DISCUSSION**

This study was performed in department of medicine, Saifee hospital Mumbai, where patients who were pre diabetics and diabetics were selected as per inclusion and exclusion criteria and the following findings were observed

<table>
<thead>
<tr>
<th>Table 1: for age distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>&lt;50yrs</td>
</tr>
<tr>
<td>&gt;=50yrs</td>
</tr>
<tr>
<td>Mean +- SD</td>
</tr>
</tbody>
</table>

There was a significant relation between prediabetics who were younger in age compared to diabetics (almost a decade younger)

**Figure 1: Bar diagram**

**Table 2: For gender distribution**

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

The gender distribution was identical between the two groups
Figure 2: Bar diagram

Table 3: Table for duration of complaints

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1yr</td>
<td>53</td>
</tr>
<tr>
<td>&gt;=1yr</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

53% had complaint <1 year

Figure 3: Pie chart

Table 4: Table for type of treatment

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>Insulin +oha</td>
<td>44</td>
</tr>
<tr>
<td>Oha</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

49% were on only OHAs, whereas 44% received both Insulin and OHAs. 7% did not receive any medicines for diabetes prior to this study.
39% had isolated HTN; 9% had IHD whereas 19% had both. 33% did not have any comorbidity.

There was a significant relation of FBS<110 in prediabetics compared to diabetics >126
Table 6: Relation between PPBS between pre-diabetics and diabetics

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetics</th>
<th>Diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;140</td>
<td>39</td>
<td>8</td>
<td>0.00001</td>
</tr>
<tr>
<td>140-200</td>
<td>9</td>
<td>19</td>
<td>0.045</td>
</tr>
<tr>
<td>&gt;200</td>
<td>2</td>
<td>23</td>
<td>0.00001</td>
</tr>
<tr>
<td>Mean± SD</td>
<td>113.14±33</td>
<td>216.86±83.57</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

There was a significant relation of PPBS <140 between prediabetics compared to diabetics >200.

Table 7: Relation of HbA1c between pre-diabetics and diabetics

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c&lt;6.4</td>
<td>46</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>HbA1c≥6.4</td>
<td>4</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>5.96±0.223</td>
<td>8.52±2.11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The diabetics had HbA1c significantly higher than prediabetics.
Although proportionately more prediabetics had raised creatinine levels, but the difference was not significant.

<table>
<thead>
<tr>
<th></th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (male&lt;7; female&lt;6)</td>
<td>36</td>
<td>40</td>
<td>0.482</td>
</tr>
<tr>
<td>Raised</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean+- SD</td>
<td>6.04+-1.37</td>
<td>5.56+-1.79</td>
<td>0.135</td>
</tr>
</tbody>
</table>

The difference of mean uric acid wrt HbA1c was not significant, although people with lower HbA1c values had a higher uric acid levels.
Table 10: Relation of Uric acid with FBS for pre diabetics

<table>
<thead>
<tr>
<th>FBS &lt; 110</th>
<th>FBS &gt;= 110</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +SD (Uric Acid)</td>
<td>5.98+1.35</td>
<td>6.24+1.46</td>
</tr>
</tbody>
</table>

The difference was not significant wrt uric acid levels with FBS values in prediabetics.

Table 11: Relation of Uric acid with PPBS for pre diabetics

<table>
<thead>
<tr>
<th>PPBS&lt;140</th>
<th>PPBS&gt;=140</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +SD (Uric Acid)</td>
<td>6.11+1.46</td>
<td>5.83+0.99</td>
</tr>
</tbody>
</table>

The difference was not significant, although people with lower PPBS had higher uric acid levels in prediabetics.
Figure 12: Bar Diagram

Table 12: Relation of Uric acid with HbA1c for diabetics

<table>
<thead>
<tr>
<th>HbA1c &lt; 7</th>
<th>HbA1c &gt;= 7</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean+SD(Uric Acid)</td>
<td>6.67+1.52</td>
<td>5.31+1.77</td>
</tr>
</tbody>
</table>

There was a significant relation of lower uric acid mean values for people with elevated HbA1c over 7g% amongst diabetics.

Figure 13: Bar Diagram

Table 13: Relation of Uric acid with FBS for diabetics

<table>
<thead>
<tr>
<th>FBS &lt;110</th>
<th>FBS &gt;=110</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean+SD(Uric Acid)</td>
<td>5.59+1.77</td>
<td>5.55+1.81</td>
</tr>
</tbody>
</table>

There was no significant relation, although mean uric acid levels were raised for people with FBS<110 amongst diabetics.
Table 14: Relation of Uric acid with PPBS for diabetics

<table>
<thead>
<tr>
<th></th>
<th>PPBS&lt;140</th>
<th>PPBS&gt;=140</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +SD (Uric Acid)</td>
<td>5.68+-1.77</td>
<td>5.53+-1.81</td>
<td>0.83</td>
</tr>
</tbody>
</table>

There was no significant relation but uric acid levels were higher in people with PPBS <140 amongst diabetics

DISCUSSION

Uric acid usually has an antioxidative effect; however, uric acid becomes a strong oxidant in the environment of metabolic syndrome. This phenomenon of the urate redox shuttle may explain the paradoxical effects of uric acid on oxidative stress. Inflammation and oxidative stress induced by metabolic syndrome and hyperuricemia may predispose individuals to a higher risk for diabetes. This study was designed to see the relation of uric acid with glycemic levels in both diabetics and prediabetics.
There was a significant relation between prediabetics who were younger in age compared to diabetics (almost a decade younger). The gender distribution was identical between the two groups. 53% had complaint <1 year. 49% were on only OHAs, whereas 44% received both Insulin and OHAs. 7% did not receive any medicines for diabetes prior to this study. 39% had isolated HTN; 9% had IHD whereas 19% had both. 33% did not have any comorbidity. There was a significant relation of FBS<110 in prediabetics compared to diabetics >126. There was a significant relation of PPBS <140 between prediabetics compared to diabetics>200. The diabetics had HbA1c significantly higher than prediabetics. Although proportionately more prediabetics had raised creatinine levels, but the difference was not significant. There was no relation between the groups wrt creatinine.

The difference of mean uric acid wrt HbA1c was not significant, although people with lower HbA1c values had a higher uric acid levels. This correlated with the findings by Selvin E et al. Serum uric acid levels showed a similar bell-curved relation with fasting glucose levels. The baseline serum UA level has also been found to independently predict the 2hPG levels during 13.5 years follow-up in a Swedish male population, with a low regression coefficient of 0.01 (p=0.026).

The difference was not significant wrt uric acid levels with FBS values in prediabetics. This correlated with the findings by Choi HK et al. In comparison, serum uric acid levels and frequency of hyperuricaemia monotonically increased with increasing fasting C-peptide levels, as with increasing serum insulin levels and insulin resistance. These associations were independent of other risk factors for hyperuricaemia such as age, sex, BMI, dietary factors, alcohol intake, renal function, hypertension and diuretic use. A 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.

The difference was not significant, although people with lower PPBS had higher uric acid levels in prediabetics. This correlated with the findings by Chien et al. A biological mechanism underlying the bell-shaped relation between blood glucose levels and serum uric acid levels is thought to be due to the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than ~10 mmol/l (180 mg/dl). The positive association between uric acid concentration and diabetes may be explained by at least 3 potential mechanisms. First, metabolic syndrome, as a precursor of diabetes, induces high oxidative stress, which is worsened by the accompanying hyperuricemia.

There was a significant relation of lower uric acid mean values for people with elevated HbA1c over 7g% amongst diabetics. This correlated with the findings by Strasak et al. This level of blood glucose was consistent with that of HbA1c that corresponded to the peak of serum uric acid in our data, further supporting this notion. Correspondingly, history of
diabetes was significantly associated with lower levels of serum uric acid in this study as well as in previous studies. A recent study showed that hyperuricemia was associated with the severity of carotid plaque among Japanese men.49

There was no significant relation, although mean uric acid levels were raised for people with FBS<110 amongst diabetics. This correlated with the findings by Nan H et al.36 Their extended multivariate analyses showed that this inverse association became larger and stronger after adjusting for C-peptide, but became smaller and insignificant after adjusting for HbA1c, suggesting that the inverse link was due to average blood glucose levels. Collectively, these results indicate that individuals with pre-diabetes may be at a higher risk of developing gout, but once they develop diabetes their risk may drop to a lower level than that of normal individuals. This potential impact on the eventual risk of gout was also supported by these results with hyperuricaemia as a dichotomous outcome using various definitions.

The mechanism behind these apparent gender differences remains unclear, although the role of female sex hormones has been suspected. A study among Chinese in Taiwan revealed that among non-diabetic subjects, FPG increased with increasing UA levels in women, but not in men.36

There was no significant relation but uric acid levels were higher in people with PPBS <140 amongst diabetics. A population-based cross-sectional study revealed that serum UA was strongly correlated with 2hPG in non-diabetic Mauritian men (r=0.15) and women (r=0.22) (p<0.001 for both).36

This study shows that there exists a relation between uric acid and inverse glycemic control, although due to small sample size, the relation was only proportional and not statistically significant. The implications are the recognition of a very inexpensive and readily available biochemical marker to target the treatment of diabetes and prediabetes, in clinically asymptomatic and occult cases. Starting early would be starting right, mitigating lots of complications and end organ damage, translating into saving of expenditure in health and economic impacts of the same. The study needs to be followed up by a multicentric larger sized study to identify closer relation between these two variables.

CONCLUSION

This study was performed in department of medicine, Saifee hospital Mumbai, where 50 patients each who were pre diabetics and diabetics were selected as per inclusion and exclusion criteria and the following findings were observed.

1. There was a significant relation between prediabetics who were younger in age compared to diabetics (almost a decade younger)
2. The gender distribution was identical between the two groups
3. 53% had complaint <1 year
4. 49% were on only OHAs, whereas 44% received both Insulin and OHAs. 7% did not receive any medicines for diabetes prior to this study.
5. 39% had isolated HTN; 9% had IHD whereas 19% had both. 33% did not have any comorbidity.
6. There was a significant relation of FBS<110 in prediabetics compared to diabetics >126
7. There was a significant relation of PPBS <140 between prediabetics compared to diabetics>200
8. The diabetics had HbA1c significantly higher than prediabetics.
9. Although proportionately more prediabetics had raised creatinine levels, but the difference was not significant.
10. There was no relation between the groups wrt creatinine
11. The difference of mean uric acid wrt HbA1c was not significant, although people with lower HbA1c values had a higher uric acid levels
12. The difference was not significant wrt uric acid levels with FBS values in prediabetics
13. The difference was not significant, although people with lower PPBS had higher uric acid levels in prediabetics
14. There was a significant relation of lower uric acid mean values for people with elevated HbA1c over 7g% amongst diabetics
15. There was no significant relation, although mean uric acid levels were raised for people with FBS<110 amongst diabetics
16. There was no significant relation but uric acid levels were higher in people with PPBS <140 amongst diabetics

Recommendations
1. Younger age in India is predisposed to prediabetes and diabetes
2. Often patients are silent, without symptoms and detected only by investigations, so investigations for prediabetes and diabetes should be mandatorily routine
3. Lower uric acid levels have correlation with impaired glycemic control and should be part of checkups for metabolic syndromes
4. Hypertension and heart disease commonly coexist with diabetes and should be tackled together
5. Uric acid monitoring should have a role in guiding glycemic goals

Limitations
1. Small sample size
2. Single hospital based study

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