

Research Article

Quantitative analysis of Serum Uric Acid and C-reactive protein level in North Indian Pre-diabetic and Diabetic subjects

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Abstract

Background: Diabetes is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate, and lipid metabolism. In the present study, we have estimated the Level of serum Uric Acid and C-reactive protein in pre-diabetic and diabetic patients from northern India.

Method: This is a Prospective observational study and total 79 subjects were enrolled on the basis of American Diabetic Association (ADA) Guidelines 2010. Out of 79 subjects, 16 subjects were Pre-Diabetic and 63 subjects were Diabetic. Serum uric acid was estimated by using MERK Kit with the help of semi-automated analyzer. Estimation of C-reactive protein was done by the commercially available Kit with the help of MISPA instrument base on nephelometry method.

Result: The Serum uric acid level of Diabetic group was ($p < 0.001$) lower as compared to Pre diabetic group, but we did not find any significant difference of C - reactive protein level between the two groups and the diagnostic accuracy of Serum uric acid was significantly higher than the C - reactive protein level.

Conclusion: The present study suggests that that low Serum uric acid level and high CRP levels may play a significant role in progression of diabetes.

Keywords: Diabetes, Serum Uric Acid, C-reactive protein

1. Introduction

Diabetes is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. It is also associated with disturbances concerned with protein, carbohydrate and lipid metabolism. The decreased uptake of glucose into muscle and adipose tissue leads to chronic extra cellular hyperglycemia which results in tissue damage and chronic vascular complications in both type I and II Diabetes Mellitus.^{1,2} International Diabetic Federation data shows that world Diabetes & Pre-diabetes prevalence in 2007 is 5.7% and 7.5% respectively. In India Diabetes Mellitus prevalence ranges from 0.4 to 3.9% in rural areas and from 9.3 to 16.6% in urban areas.³

There has been an increasing interest in the involvement of low grade inflammation in the pathogenesis of type 2 diabetes.⁴ C-reactive protein (CRP) is an inflammatory marker produced and released by the liver under the stimulation of cytokines such as tumor necrosis factor- α and interleukins 1 and 6. It might affect the process of the atherothrombosis.^{5,6} It has emerged as a powerful risk marker for cardiovascular disease.^{7,8,9} Inflammation has also been postulated to play a role

in the pathogenesis of type 2 diabetes. Recent prospective studies have suggested that an elevated level of CRP is associated with an increased risk of developing type 2 diabetes.¹⁰⁻¹³

It was first time reported in Japan that CRP progressively increased as fasting or post load glucose levels increased.¹⁴ A number of studies have shown that plasma CRP level predicts the development of type 2 diabetes in middle-aged Caucasian men and women and in elderly subjects.^{10,15-18} Plasma CRP concentration is increased in patients with impaired glucose tolerance (IGT) and in newly detected type 2 diabetic patients compared with subjects with normal glucose tolerance (NGT), and the increase in inflammatory parameters is parallel to the stages of glucose intolerance.¹⁹⁻²¹

Uric acid is formed by the breakdown of purins and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine. Serum urate levels vary with age and sex.^{22,23} Several epidemiologic 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, hypertension, and renal disease.²⁴

An elevated level of uric acid was found in pre-diabetic individuals, and in offspring of conjugal diabetic parents. However, conflicting results on uric acid concentrations have been reported in diabetic patients.²⁵⁻²⁷ Although some studies have demonstrated the role of Uric Acid in the progression of pre-diabetes to diabetes. The conflicting data exist about the uric acid levels in type 2 diabetes mellitus, which are associated with risk factors and complications.^{28,29} Thus, the role of Uric Acid in the pathogenesis and the development of the diabetic complications are controversial.

Therefore, the present study was first time designed to look for any association of serum uric acid and C - reactive protein in pre-diabetic and diabetic patients, taking into the consideration of relevant clinical and biochemical data in North Indian population.

2. Material and Method

This is a Prospective observational study conducted in the department of physiology in collaboration with department of pathology at King George's Medical University, Lucknow. Total 79 subjects were enrolled in study based on well defined inclusion and exclusion criteria. Out of 79 subjects, 16 subjects were Pre-Diabetic and 63 subjects were Diabetic. Subjects with conditions, which may affect metabolic parameters (such as polycystic ovary syndrome or thyroid dysfunctions in history or present), pregnancy, chronic diseases, infection, and coronary artery disease, were excluded from study.

2.1. Definition

Pre-diabetic and diabetic patients were defined as per the American Diabetic Association (ADA) Guidelines 2010. The subjects having impaired fasting blood glucose level 100-125mg/dl or 2 hours oral glucose tolerance test with 75 gm of glucose, 140-199 mg/dl were defined as Pre-diabetic patients. Diabetic patients were defined as those having fasting blood glucose ≥ 126 mg/dl or 2 hours oral glucose tolerance test with 75 gm of glucose, ≥ 200 mg/dl.

2.2. Biochemical analysis

After taking the ethical approval from institutional ethical committee of King George's Medical University, Lucknow and obtaining informed consent total 5 ml. venous blood sample was drawn from each participant. 2 ml. blood was collected in fluoride vial and 3 ml. blood was taken in plain vial. Serum and plasma was separated, aliquoted and stored at -80 C. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) estimation was done by glucose oxidase-peroxidase method (Merck Kit). Serum uric acid was estimated by using MERK Kit with the help of semi automated analyzer (Microlab 300, Merck) on the same day of sample collection. Estimation of C-reactive protein was done by the commercially available Kit (Agappe Diagnostics Ltd. India) with the help of MISPA instrument base on nephelometry method.

2.3. Statistical Analysis

Continuous data were summarized as Mean \pm SD (standard deviation). Groups were compared by independent Student's t test and the results were also validated with non parametric Mann-Whitney U test. Discrete (categorical) observations were summarized in % and compared by chi-square (χ^2) test. Pearson correlation analysis was used to assess association between the variables. Diagnostic of S. uric acid and C-RP levels were done by ROC (receiver operating characteristic) curve analysis. A two-sided ($\alpha=2$) $p < 0.05$ was considered statistically significant. SPSS (version 18.0) and STATISTICA (version 6.0) statistical software were used for the analyses.

3. Result

The age of Pre-diabetic and diabetic groups were ranged from 28-66 yrs and 32-77 yrs respectively with Mean \pm SD 49.50 ± 11.57 yrs and 55.14 ± 10.79 yrs, respectively. The mean age of Diabetic group was comparatively higher than Pre diabetic group. Further, in both the groups, the age (%) of males was higher than females. The mean level of both FBS and PPBS were comparatively higher in Diabetic group than Pre diabetic group. On comparing, the mean age and % age of males and females were found similar between the two groups. (**Table 1**) The mean Serum uric acid level of Diabetic group was significantly ($p < 0.001$) lower as compared to Pre diabetic group (**Table 2**). However, mean CRP levels did not differed between the two groups but it was comparatively higher in Diabetic group than Pre diabetic group (**Table 2**). The diagnostic accuracy (cut off value) of S. uric acid and C-RP levels for pre diabetics and diabetics were summarized in **Table 3** and shown graphically in **Fig. 1 and 2** respectively. The cut off value (criterion) of S. uric acid was ≤ 7 mg/dl and at this value it is discriminating diabetics with 77.78% sensitivity (95% CI=65.5-87.3) and 100.00% specificity (95% CI=79.2-100.0). Similarly, the cut off value (criterion) of C-RP level was >6.1 Mg/l and at this value it is discriminating diabetics with 66.67% sensitivity (95% CI=53.7-78.0) and 81.25% specificity (95% CI=54.3-95.7). However, the diagnostic accuracy of S. uric acid was significantly higher than the C-RP levels (AUC: 0.947 vs. 0.656, $Z=3.80$; $p < 0.001$) (**Fig. 3**).

Table 1: Distribution of age, gender, FBS and PPBS in pre-diabetic and diabetic patients

Characteristics	Pre diabetic (n=16)	Diabetic (n=63)	χ^2/t value	p value
Age (yrs)	49.50 ± 11.57	55.14 ± 10.79	1.84	0.069
Gender:				
Male	11 (68.8%)	49 (77.8%)	0.57	0.451
Female	5 (31.3%)	14 (22.2%)		
FBS (mg/dl)	111.50 ± 10.56	142.66 ± 44.39	2.77	0.007*
PPBS (mg/dl)	168.75 ± 17.34	216.04 ± 52.89	3.51	0.001*

*- $p < 0.01$, values are in % (Categorical data) and mean \pm SD (Continuous data),

FBS (Fasting Blood Sugar), PPBS (Postprandial Blood Sugar)

Table 2: Distribution of Serum uric acid and CRP levels in pre-diabetic and diabetic patients

Characteristics	Pre diabetic (n=16)	Diabetic (n=63)	t value	p value
Serum uric acid (mg/dl)	10.84 ± 2.84	5.79 ± 1.87	8.60	$p < 0.001^{**}$
CRP (mg/dl)	6.76 ± 5.95	10.51 ± 8.98	1.58	0.117

** - $p < 0.001$, values are in mean \pm SD, C-RP (C - reactive protein)

Table 3: Diagnostic accuracy of Serum uric acid and CRP levels for diabetic from pre diabetic

Variables	Criterion (cut off value)	Sensitivity (95% CI)	Specificity (95% CI)	AUC	p value	+LR	-LR	+PV	-PV
Serum uric acid	≤ 7 mg/dl	77.78 (65.5-87.3)	100.0 (79.2-100.0)	0.947	$p < 0.001^{**}$	-	0.22	100.0	53.3
C-RP	>6.1 (Mg/l)	66.67 (53.7-78.0)	81.25 (54.3-95.7)	0.656	0.029	3.56	0.41	93.3	38.2

$p < 0.001$, +LR: Positive likelihood ratio, -LR- Negative likelihood ratio, +PV: Positive predictive value, -PV: Negative predictive value

Fig. 1: Diagnostic accuracy of Serum uric acid for pre diabetics and diabetics

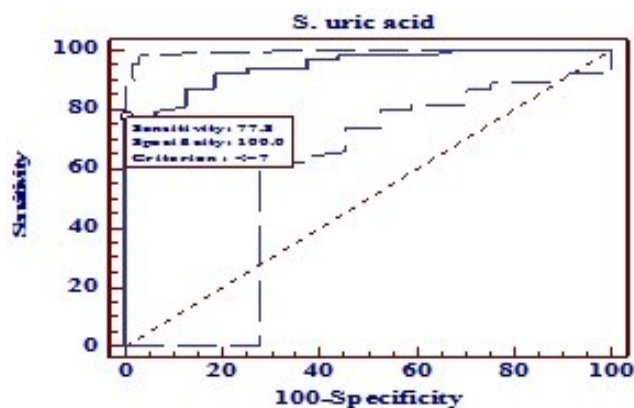


Fig. 2: Diagnostic accuracy of CRP levels for pre diabetics and diabetics

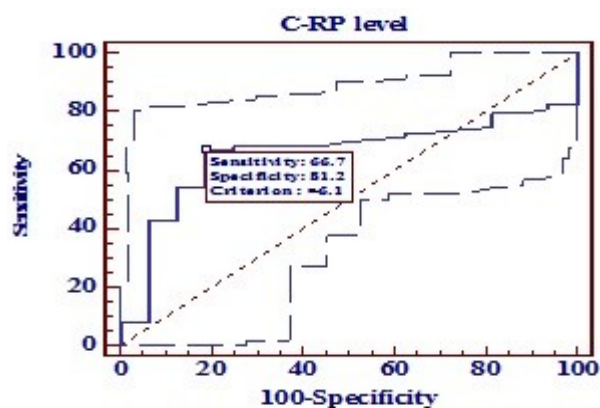
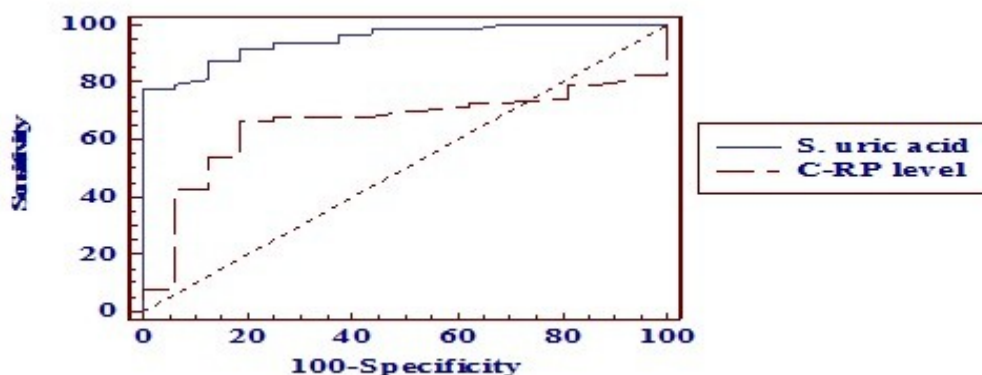


Fig. 3: Comparative diagnostic accuracy of Serum uric acid and CRP levels for pre diabetics and diabetics.



4. Discussion

Diabetes is a complex metabolic disorder. Hyperuricemia has been attributed to biochemical abnormalities found in obesity-hypertension-hypercholesterolemia-hyperuricemia syndrome as part of both diabetic and pre-diabetic conditions.³⁰ The findings of our study were consistent with the previous study, demonstrated that diabetics have lower serum uric acid levels and that prediabetics have higher levels than non-diabetics.^{25, 31-35} In the present study S. uric acid level of diabetic group was significantly lower than prediabetic ($p < 0.001$). The reduced urate level in severe hyperglycemia has been attributed to the uricosuric effect of glycosuria, which might be an explanation of the low uric acid concentration among overt diabetic patients.³⁶ Furthermore, uric acid concentration might be influenced by the changes in plasma glucose and insulin concentrations.³⁷ Thus, uric acid fluctuations during prediabetes and diabetes have so far been regarded as a secondary metabolic phenomenon. In other previous study it was also reported that serum uric acid has been shown to be associated with oxidative stress and production of tumor necrosis factor- α , both of which are related to development of diabetes.³⁸ Elevated serum uric acid levels may reflect prediabetes status particularly at the renal level. Higher insulin level associated with prediabetes can reduce renal excretion of uric acid.³⁹ Insulin can stimulate urate anion exchanger and it increases renal urate reabsorption.⁴⁰

Our results are compatible with the hypothesis that CRP and uric acid may have a role in the pathogenesis of diabetes. In our study the CRP level did not differ significantly between the diabetic and pre-diabetic but it was comparatively higher in diabetic group than pre diabetic group. However we do not included the obesity as a variable in our

study but diabetes is more common in obese individuals and thus, an association is expected between serum CRP, diabetes and obesity. Because the CRP is produced by hepatocytes, and its gene expression is regulated by tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which are secreted by adipocytes,⁴¹ as a result the obese individuals who have more and larger adipocytes also have higher baseline serum CRP. However, some studies found that obesity does not explain the association of CRP with diabetes completely, suggesting an independent role for CRP in the development of diabetes.^{42,43} It has been reported that CRP levels were significantly higher in both diabetic men and women as compared to their non-diabetic counterparts.⁴⁴ Increased CRP levels have been described in people with type-2 diabetes,¹⁰ as well as in type-1 diabetes.⁴⁵

The cut off value of Serum uric acid in our study was ≤ 7 mg/dl and at this value it is discriminating diabetics with 77.78% sensitivity and 100.00% specificity. Result of the study supports the previous report based on 475 overweight or obese individual with impaired glucose tolerance, they found that having a serum uric acid level within the top tertile (≥ 6.4 mg/dl) was associated with two-fold increase in the risk of type-2 diabetes compared with the lower tertile (< 5.2 mg/dl) [46]. The cut off value (criterion) of CRP level in our study was > 6.1 mg/l and at this value it is discriminating diabetics with 66.67% sensitivity and 81.25% specificity. However, the diagnostic accuracy of Serum uric acid was significantly higher than the CRP levels.

There are some limitations in our study such as the sample size was small and some other important risk factors like obesity and metabolic syndrome were not included in the study. Although it was multifactorial cause but as per our study findings, it may be concluded that low Serum uric acid and high CRP levels may play a significant role in progression of diabetes. The findings may used as a predictor of diabetes at its earlier stage, but the further studies with large sample size are required to establish the serum uric acid and CRP levels as a predictor for diagnostic purpose.

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