



A Cross Sectional Study Showing Association of Serum Uric Acid in Pre-Diabetic and Diabetic Indian Population

Authors

Pushpalata Sachan¹, Dr R.S. Gangwar², Dr M.L. Patel³, Dr M.M.Khan⁴,
Dr Indu Pisharody⁵

¹Assistant Professor, Department of Physiology, Career Institute of Medical Sciences and Hospital,
Lucknow, U.P., India

Email: sachandrpushpalata@gmail.com

²Assistant Professor, Department of Anaesthesiology, K.G.M.U., Lucknow, U.P., India

³Associate Professor, Department of Medicine, K.G.M.U., Lucknow, U.P., India

⁴Professor and Head, department of Physiology, Career Institute of Medical Sciences and Hospital,
Lucknow, U.P., India

⁵Associate Professor, Department of Physiology, Career Institute of Medical Sciences and Hospital,
Lucknow, U.P., India

Corresponding Author

Dr M.L.Patel

Associate Professor, Department of Medicine, K.G.M.U., Lucknow, U.P., India

Email: raddy.kgmc@gmail.com, Ph: 917839317837

Abstract

Background: Diabetes is a huge burden worldwide and India is only second to China in prevalence of Diabetes. Recent studies showed that the prevalence of Diabetes and Pre-diabetes (IGT) is rapidly increasing, especially in urban population. Serum uric acid level varies in various stages of glucose homeostasis. The present study is coined to show the association of serum uric acid level with Diabetic and Pre-diabetic stage of glucose homeostasis.

Methods: This is a cross sectional observational study and enrolled total 79 subjects from medicine OPD during one year duration. On the basis of American Diabetic Association (ADA) guidelines 2010 among 79 subjects, 16 subjects were assigned as pre-diabetic and 63 as diabetic. Estimation of Serum uric acid was done by using MERK Kit with the help of semi-automated analyzer. The quantitative parametric datas were analysed by student "t" test whereas non parametric datas by Mann- whitney U test. The categorical datas were analysed by Chi square test.

Results: The Serum uric acid level in diabetic group was 5.79 ± 1.87 mg/dl (mean \pm SD) whereas in pre-diabetic group was 10.84 ± 2.84 mg/dl (mean \pm SD). So it is significantly lower in diabetics as compared to pre-diabetic. ($p < 0.001$)

Conclusion: The present study suggests that that serum uric acid level is significantly higher in pre-diabetic group and may play a significant role in progression of Diabetes.

Keywords: Diabetes, Pre-diabetes, Serum Uric Acid.

Introduction

Diabetes, a disorder of glucose homeostasis, is a massive burden in both developing and developed world. International Diabetes Federation (2013) reported the worldwide prevalence of Diabetes and India is 2nd leading country (65.1 million) just after the China (98.4 million).¹ A study conducted in India by ICMR (2011) reported that in India, 77.2 millions are pre-diabetics and 62.4 million are diabetics.² Pre-diabetes, an intermediate stage of glucose homeostasis characterized by impaired fasting glucose and/or impaired glucose tolerance. It is a reversible stage and provides increased risk of type II Diabetes mellitus. Therefore early identification of this intermediate stage of glucose homeostasis can contribute to prevention of type II Diabetes mellitus.

The uric acid is a byproduct of human purine catabolism and play a key role in the pathogenesis of Diabetes mellitus.³ As shown by previous studies, high level of serum uric acid is associated with increased risk of hypertension⁴ and cardiovascular disease.⁵ It also increases the risk for insulin resistance, and other components of the metabolic syndrome.⁶ However conflicting results have been obtained between serum uric acid levels and spectrum of glucose homeostasis. According to many previous studies, elevated serum uric acid level increases the risk of Diabetes.⁷⁻¹⁰ However study conducted by S. Kodama et al (2009) reported no association of serum uric acid for development of Diabetes.¹¹ Furthermore few studies reported an inverse relationship of uric acid with development of Diabetes.^{12,13} In this context, further analysis deserves to establish association. So this study is coined to show the association of serum uric acid with pre-diabetic and diabetic stage of glucose homeostasis.

Material and Method

Study Population

This is a cross sectional observational study carried out in the department of Physiology with association with the department of Pathology and

department of Medicine. Total 79 subjects were selected from the patients attending Medicine outward department during one year duration. As per ADA guidelines (2010), among 79 subjects, 16 were assigned as pre-diabetic and 63 as diabetic. The necessary information were obtained about the age, sex, history about diabetes mellitus, hypertension, cardiovascular diseases, chronic kidney disease, drug history, habits including alcohol intake, smoking and diet.

Inclusion criteria

All diabetic and pre-diabetic subjects of both sex as per ADA guidelines (2010)

Exclusion criteria

Patients having systemic inflammation/inflammatory diseases, patients with hypothyroidism or vit.B12 deficiency, chronic alcoholic, liver disease, chronic kidney disease and coronary artery disease and other conditions and drugs affecting serum uric acid level were excluded.

Definitions of Pre-diabetes and Diabetes

Pre-diabetic and diabetic patients were defined as per the American Diabetic Association (ADA) Guidelines 2010.

The pre-diabetic subjects were defined as those having impaired fasting blood glucose level 100-125mg/dl and/or 2 hours oral glucose tolerance test with 75 gm of glucose (OGTT), 140-199 mg/dl. Whereas diabetic subjects were defined as those having fasting blood glucose \geq 126 mg/dl or 2 hours oral glucose tolerance test with 75 gm of glucose (OGTT) \geq 200 mg/dl.

Biochemical analysis

After the approval from ethical committee of institute, informed consent was obtained from the patients. 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 oxide-peroxidase method (Merck Kit). Serum uric acid was estimated on the same day of sample collection by using MERK Kit with the help of semi automated analyzer (Microlab 300, Merck).

Statistical Analysis

The continuous data were summarized as Mean ± 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 accuracy of S. uric acid was 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.

Results

The age of pre-diabetic and diabetic groups were ranged from 28-66 yrs and 32-77 yrs respectively with mean± SD, 49.50± 11.57 yrs and 55.14± 0.79 yrs, respectively. The mean age of diabetic group was comparatively higher than pre-diabetic group but statistically similar. Further, statistically male and female distribution in both the groups was similar. (p value= 0.451) The mean level of both FBS and PPBS were comparatively higher in diabetic group than pre-diabetic group. ($P<0.05$) On comparing, the mean age and percentage 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) 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). (Fig. 1)

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%)	0.57	0.451
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*

*Significant ($p<0.05$), values are in % (Categorical data) and mean± SD (Continuous data), FBS (Fasting Blood Sugar), PPBS (Postprandial Blood Sugar)

Table 2: Distribution of Serum uric acid 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	$p<0.001^{**}$

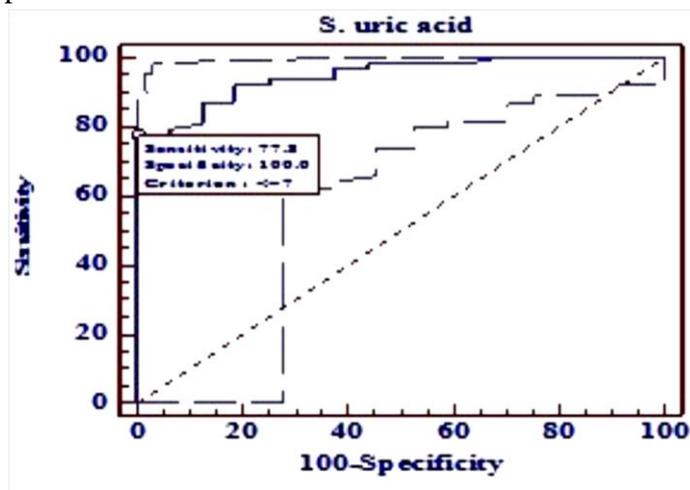
**Significant ($p<0.05$), values are in mean ± SD

Table 3: Diagnostic accuracy of Serum uric levels for pre-diabetics and diabetics

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	$<0.001^{**}$	-	0.22	100.0	53.3

**Significant ($p<0.05$), +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



Discussion

Diabetes and Pre-diabetes are disorder of inappropriate hyperglycemia either due to deficiency of insulin secretion or decreased effectiveness of it or both. Hyperuricemia has been attributed to biochemical abnormalities found in obesity-hypertension-hypercholesterolemia-hyperuricemia syndrome as part of both diabetic and pre-diabetic conditions.¹⁴

In our study serum uric acid level of diabetic group was significantly lower than pre-diabetic group. ($p < 0.001$) Similar results were reported by many previous studies conducted by K.L.Chien⁸, Krishnan E¹⁵, Sudhindra RM¹⁶ and Feig DI.¹⁷ They had demonstrated that diabetics have lower serum uric acid levels and that pre-diabetics had higher level than non-diabetics. Gotfredson A (2008)¹⁸ concluded that low level of uric acid 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. Furthermore, uric acid concentration might be influenced by the changes in plasma glucose and insulin concentrations.¹⁰ Thus, uric acid fluctuations during Pre-diabetes and Diabetes have so far been regarded as a secondary metabolic phenomenon. A previous study conducted by Koenig W (2008)¹⁹ 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. Elevated serum uric acid levels may reflect Pre-diabetes status particularly at the renal level. Higher insulin level associated with Pre-diabetes can reduce renal excretion of uric acid.²⁰ Insulin can stimulate urate anion exchanger and it increases renal urate reabsorption.²¹

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).²² 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.

Conclusion

Although it was multifactorial cause but as per our study findings, it may be concluded that serum uric acid is significantly higher at pre-diabetic stage and 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 as a predictor for diagnostic purpose.

Acknowledgement

I am very thankful and would like to appreciate each and everyone including doctors, health practitioners in the department of Physiology, Medicine and Pathology in KGMU, Lucknow who took care of the subjects.

Conflict of Interest: None

References

1. L. Guariguata, D.R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp, J.E. Shaw. Global

- estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes research and clinical practice*. 2014;103:137- 149.
2. Anjana, R.M., Pradeepa, R., Deepa, M., Datta, M., Sudha, V. and Unnikrishnan, R. Prevalence of diabetes and Pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results ICMR-INDIAB study. *Diabetologia*. 2011; 54:30, 22-7.
 3. Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. *Arterioscler Thromb Vasc Biol*. 2005; 25: 1038–44.
 4. A. Shankar, R. Klein, B. E. K. Klein, and F. J. Nieto, “The association between serum uric acid level and long-term incidence of hypertension: population-based cohort study,” *Journal of Human Hypertension* 2006; 20 : 937–45
 5. R. Klein, B. E. Klein, J. C. Cornoni, J. Maready, J. C. Cassel, and H. A. Tyroler, “Serum uric acid. Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia,” *Archives of Internal Medicine*.1973; 132:401–10.
 6. T. W. Yoo, K. C. Sung, H. S. Shin et al., “Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome.” *Circulation Journal*. 2005; 69: 928–33.
 7. A. Dehghan, M. Van Hoek, E. J. G. Sijbrands, A. Hofman, and J. C. M. Witteman, “High serum uric acid as a novel risk factor for type 2 diabetes,” *Diabetes Care*. 2008; 31: 361–2.
 8. K. L. Chien, M. F. Chen, H. C. Hsu et al., “Plasma uric acid and the risk of type 2 diabetes in a Chinese community,” *Clinical Chemistry*. 2008; 54: 310–6.
 9. S. Kodama, K. Saito, Y. Yachi et al., “Association between serum uric acid and development of type 2 diabetes,” *Diabetes Care*. 2009; 32: 1737–42.
 10. M. Modan, H. Halkin, A. Karasik, and A. Lusky, “Elevated serum uric acid—a facet of hyperinsulinaemia,” *Diabetologia*. 1987; 30: 713–8.
 11. Y. Taniguchi, T. Hayashi, K. Tsumura, G. Endo, S. Fujii, and K. Okada, “Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men: the Osaka health survey,” *Journal of Hypertension*. 2001; 19: 1209–15.
 12. E. Oda, R. Kawai, V. Sukumaran, and K. Watanabe, “Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men,” *Internal Medicine*. 2009; 48: 1785–91.
 13. H. Nan, Y. Dong, W. Gao, J. Tuomilehto, and Q. Qiao, “Diabetes associated with a low serum uric acid level in a general Chinese population,” *Diabetes Research and Clinical Practice*. 2007; 76: 68-74.
 14. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, et. al. Hyperinsulinemia. a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985; 75 : 809-17.
 15. Krishnan E, Pandya B J, Chung L, Hariri A and Dabbous O. Hyperuricemia in young adults and risk of insulin resistance, Pre-diabetes and diabetes: A 15 year follow up study. *Am J Epidemiol*.2012; 176: 108-16.
 16. Sudhindra RM, Sahayo BJ. A study of serum uric acid in diabetes mellitus and Pre-diabetes in a south Indian Tertiary care hospital. *NUJHS*. 2012; 2: 18-23.
 17. Feig DI, Mazzali M, Kang DH, Nakagawa T, Price K, Kannelis J, et. al. Serum uric acid: a risk factor and a target for treatment, *J. Am. Soc. Nephrol*. 2006; 17 : 69-73.
 18. Gotfredsen A, McNair P, Christiansen C, Transbol I. Renal hypouricaemia in insulin treated diabetes mellitus. *Clin Chim Acta* 1982; 20: 355-61.
 19. Koenig W, Meisinger C. Uric acid, type 2 diabetes, and cardiovascular diseases: fueling

the common soil hypothesis? Clinical Medicine 2008; 54 : 231-3.

20. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, et.al. Effects of insulin on renal sodium and uric acid handling in essential hypertensio. Am J Hypertens. 1996; 9 : 746-52.
21. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Ho Cha S, et.al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature. 2002; 417: 447-52.
22. Niskanen L, Laaksonen DE, Lindstrom J, Eriksson JG, Keinanen-Kiukaanniemi S, Ilanne-Parikka P, et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. Diabetes Care. 2006; 29 : 709-11.