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Evaluation of the relationship between glycemic parameters and serum uric acid level in type 2 diabetes mellitus patients

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Abstract

Introduction: Previous studies have demonstrated that serum uric acid (SUA) is an independent predictor of incident type 2 diabetes mellitus (T2DM) and have shown the positive association of hyperglycemia with increased serum uric acid. While some have reported lower serum uric acid levels in patients with severe hyperglycemia. The relationship between SUA and diabetes is controversial. Hence, present study was designed to establish the association of serum uric acid with different glycemic state.

Objectives

1. To evaluate serum uric acid levels in patients of Type 2 Diabetes Mellitus.
2. To correlate serum uric acid levels with glycemic parameters in patients of Type 2 Diabetes Mellitus.

Materials and Methods: 50 cases and 50 controls were included. Fasting blood sugar (FBS), HbA1c and SUA were measured. Based on FBS levels cases were divided into 4 groups i.e., Group I (126mg/dl to 175mg/dl), II (176mg/dl to 225mg/dl), III (226mg/dl to 275mg/dl) and IV (≥276mg/dl) and based on HbA1c levels cases were divided into 3 groups i.e., Group A (6% to 7.9%), B (8% to 9.9%) and C (≥10%). Data was statistically analyzed using SPSS–17.

Results: Based on FBS levels classification significant positive difference to serum uric acid was observed among Group I Vs II ($p<0.05$) & Group I Vs III ($p<0.01$), No significant difference among Group II Vs III ($p>0.05$) and significant negative difference among Group I Vs IV ($p<0.0001$), Group II Vs IV ($P<0.0001$) & Group III Vs IV ($p<0.0001$). Based on HbA1c levels classification significant positive difference to serum uric acid was observed among Group A Vs B ($p<0.0001$) and negative significant difference among Group A Vs C ($p<0.01$) & Group B Vs C ($p<0.0001$).

Conclusion: We found increase in serum uric acid in cases compared to controls. Serum uric acid initially increased with increase in FBS and HbA1c ranging from 126 mg/dl to 275 mg/dl and 6% to 9.9% respectively and thereafter decreased with further increase in FBS and HbA1c.

Keywords: Fasting blood sugar; HbA1c; Serum uric acid, Type 2 Diabetes Mellitus.

Introduction

Type 2 diabetes is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production[1]. The chronic complications of Diabetes Mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease[1]. Identifying the risk factors for the development of type 2 diabetes is essential for primary prevention[2].

In humans, uric acid is the final breakdown product of purine degradation[2]. UA can act as a pro-oxidant depending upon the surrounding environment such as timing (early or late in the disease process), location of the tissue and substrate, acidity, the surrounding oxidant milieu, depletion of other local antioxidants, the supply and duration of oxidant substrate and its oxidant enzyme[3]. Recent studies have shown that hyperuricemia is associated with impaired renal function[4], stroke[5], cardiovascular risk[4], hypertension[4] and myocardial infarction[6] mediated by endothelial dysfunction and pathologic vascular conditions. A population based study conducted by Abbas Dehghan et al[7] proposed that Serum Uric Acid is a strong and an independent risk factor for diabetes. It has been shown in middle aged Japanese men by Nakanishi et al[8] that serum uric acid level is significantly associated with the risk of diabetes. Several studies have shown that a moderate degree of hyperglycemia is associated with higher SUA levels, while a higher degree of hyperglycemia is related with lower SUA levels[9,10]. Hence there is a need to study the significance of serum uric acid in Type 2 Diabetes mellitus by systematic evaluation of the relationship between glycemic parameters and serum uric acid levels at different glucose tolerance statuses.

Objectives of the study

1. To Evaluate Serum Uric acid levels in patients of Type 2 Diabetes Mellitus and its comparison with controls.
2. To Correlate Serum Uric acid levels with Glycemic parameters in patients of type 2 Diabetes Mellitus

Materials and Methods

The present study was conducted at Khaja Banda Nawaz Teaching & General Hospital attached to KBNIMS, Karnataka. Observational Cross Sectional Study was performed. Period of Study was from September 2015 to January 2016. Sample Size was of

100 Subjects, which includes 50 cases and 50 controls. The present Study was approved by the Ethical committee.

Inclusion Criteria

1. Individuals in the age group 30-70 years suffering from type 2 diabetes mellitus, which is defined as fasting blood sugar ≥ 126mg/dL irrespective of the duration of diabetes.
2. Includes both men and women.
3. Diagnosed type 2 diabetes mellitus patients taking oral hypoglycaemic medications or insulin for treatment.

Exclusion Criteria: Individuals having type 1 diabetes mellitus, diagnosed hypertensive, cardiovascular disease, stroke, pre-existing renal disease, dyslipidemia, gout, drugs (e.g.: thiazide diuretics, probenecid, allopurinol, etc.) which alter serum uric acid levels were excluded.

The nature of study was explained to the subjects and written informed consent was taken. Subjects were instructed to have overnight 10-12 hours fast. Under aseptic conditions 6 ml of venous blood sample was collected from anticubital vein of which 2ml was collected in fluoride tubes for fasting blood glucose estimation, 2ml in EDTA tubes for HbA1c estimation and 2ml in plain tube for uric acid estimation.

Grouping of Cases: Based on fasting blood sugar level, 50 cases were arbitrary divided into 4-groups i.e., Group-I comprising of patients having FBS 126-175 mg/dL, Group-II having FBS 176-225 mg/dL, Group-III having FBS 226-275 mg/dL & Group-IV having FBS ≥276 mg/dL. Based on HbA1c level, 50 cases were arbitrary divided into 3-groups i.e., Group-A comprising of patients having HbA1c 6.0-7.9%, Group-B having HbA1c 8.0-9.9% & Group-C having HbA1c ≥10%. Estimation of Fasting Blood Glucose was done by Glucose oxidase peroxidise method[11], HbA1c by Turbidimetric inhibition immunoassay method[12] and Serum Uric Acid by Uricase method[13]. Statistical analysis of data was done by applying independent t test, chisquare test, z test and karl pearson's correlation. Statistical software SPSS 17 was used.

Results

No significant difference (p>0.05) was observed in relation to Age in cases compared to controls, significant positive difference (p<0.0001) was observed in relation to Fasting Blood Sugar, HbA1c and Serum uric acid in cases compared to controls **(Table 1 & Fig. 1, 2 & 3)**. No Statistically Significant difference (p>0.05) was observed in comparison of distribution of cases and controls in relation to different age groups (**Table 2)**. No statistical significant difference (p>0.05) was observed with respect to sex distribution among age groups in Cases compared to Controls **(Table 3)**. No statistical significant difference (p>0.05) was observed in Serum Uric acid levels in cases with different age groups **(Table 4 & Fig. 4)**. No statistical significant difference (p>0.05) was observed in cases of Serum Uric acid levels in relation to Gender **(Table 5 & Fig. 5)**. Significant Positive difference to Serum Uric acid were observed among Group I Vs Group II (p<0.05) and Group I Vs Group III (p<0.01) and no Significant difference to Serum Uric acid was observed among Group II Vs Group III (p>0.05), But Significant Negative difference to Serum Uric acid were observed among Group I Vs Group IV (p<0.0001), Group II Vs Group IV (p<0.0001) and Group III Vs Group IV (p<0.0001) **(Table 6 & Fig. 6)**. **Graph 1, 2 & 3** depicts Positive correlation between serum uric acid and fasting blood sugar in Group-I, Group-II and Group III (r= 0.16, r= 0.37 & r= 0.54 respectively) whereas **Graph 4** depicts Negative correlation between serum uric acid and fasting blood sugar in group-IV (r= -0.09). Significant Positive difference to Serum Uric acid was observed among Group A Vs Group B (p<0.0001), But Significant Negative difference to Serum Uric acid were observed among Group A Vs Group C (p<0.01) and Group B Vs Group C (p<0.0001) **(Table 7 & Fig. 7)**. **Graph 5 & 6** depicts Positive correlation between serum uric acid and HbA1c in Group-A and Group B (r= 0.11 & r= 0.16 respectively) but **Graph 7** depicts Negative correlation between serum uric acid and HbA1c in group-C (r= -0.06).

Table 1: Details of Subjects included in Study

Parameters	Type 2 Diabetes Mellitus Cases	Normal Healthy Controls	p-value
Total Number	50	50	
Age Range (years)	30-70	30-70	
Age (Mean±SD)	50.64±10.41	49.78 ±10.94	p>0.05
Mean±SD Fasting Blood Sugar (mg/dl)	228.6±76.29	84.5±9.59	p<0.0001
Mean±SD HbA1c (%)	9.45± 2.06	4.784±0.58	
Mean±SD Serum Uric acid (mg/dl)	6.68 ±1.50	4.124±1.01	

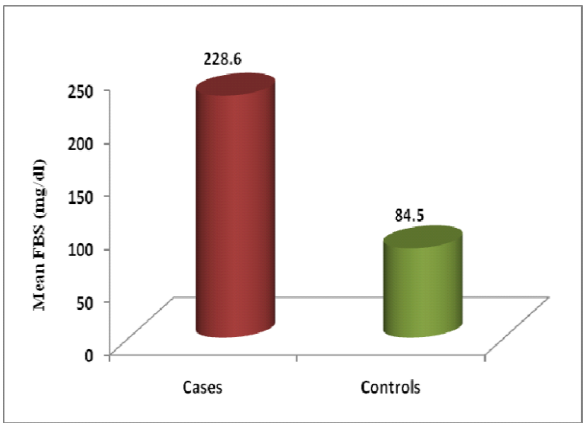


Fig. 1: Mean FBS in cases and control

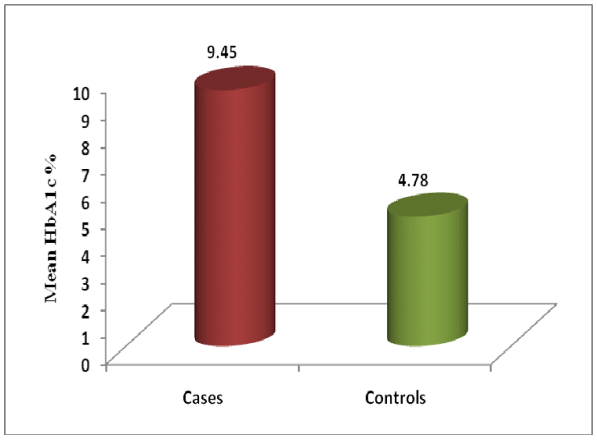


Fig. 2: Mean HbA1c in cases and controls

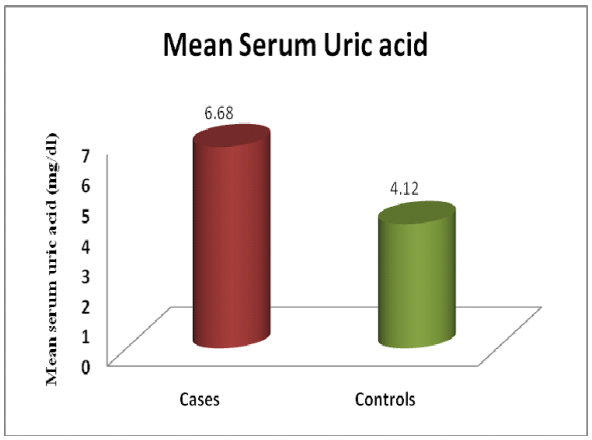


Fig. 3: Mean SUA in cases and controls

Table 2: Distribution of Cases and Controls in relation to different Age groups

Age Group (years)	Cases		Controls	
	No	%	No	%
30-40	10	20%	11	22%
41-50	17	34%	17	34%
51-60	13	26%	11	22%
61-70	10	20%	11	22%

Table 3: Sex distribution within age groups in cases and controls

Age Group	Male		Female	
	Control	Cases	Control	Cases
30-40 years	6	6	5	4
41-50 years	8	9	9	8
51-60 years	6	8	5	5
61-70 years	5	6	6	4

Table 4: Mean serum uric acid levels in cases with different age groups

Age Group (years)	Mean±SD Serum Uric acid (mg/dl)
30 – 40	6.63±2.57
41 – 50	6.7±2.58
51 – 60	6.5±2.56
61 -70	6.8±2.61

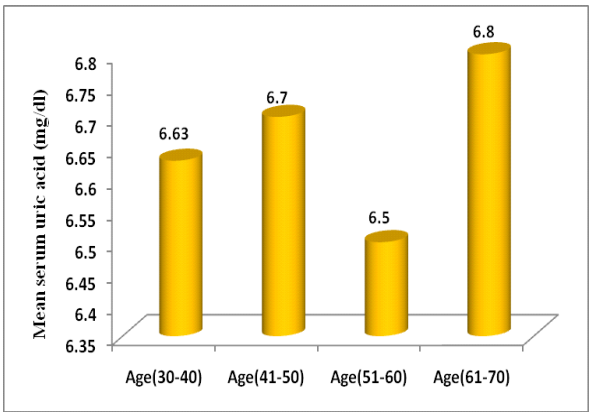


Fig. 4: Mean Serum Uric acid level in cases with different Age groups

Table 5: Serum Uric acid level in Cases in relation to Gender

	Cases	
	Male	Female
Serum Uric acid	6.8±2.6	6.6±2.56

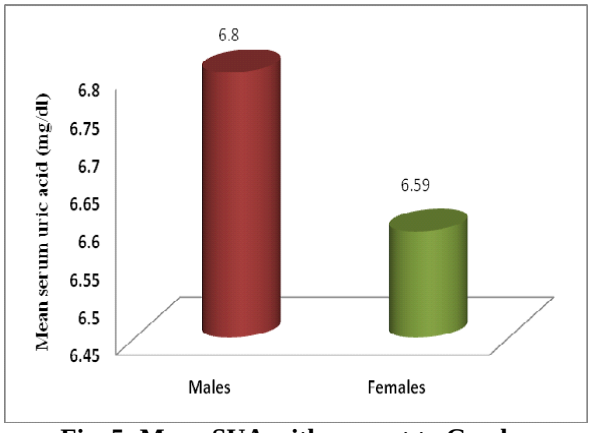


Fig. 5: Mean SUA with respect to Gender

Table 6: Serum Uric acid level in cases at different levels of Fasting Blood Sugar

Group	Fasting Blood Sugar Range (mg/dl)	Fasting Blood Sugar (mg/dl)		Serum Uric acid (mg/dl)	
		Mean	S.D.	Mean	S.D.
I	126-175 (n=13)	152.23	13.39	6.79	0.63
II	176-225(n=13)	190.46	14.63	7.28	0.53
III	226-275(n=12)	247.42	15.86	7.84	0.97
IV	≥276(n=12)	333.83	64.55	4.75	1.54

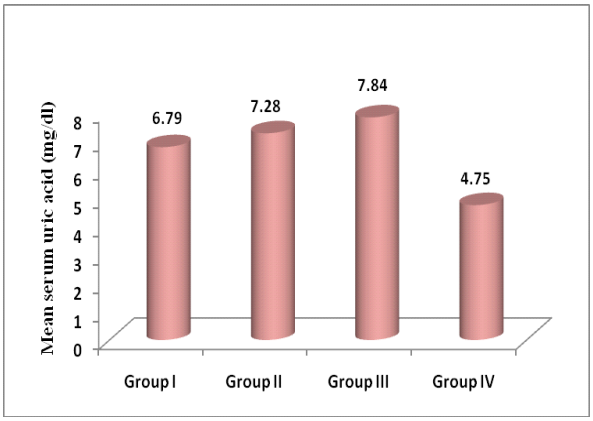
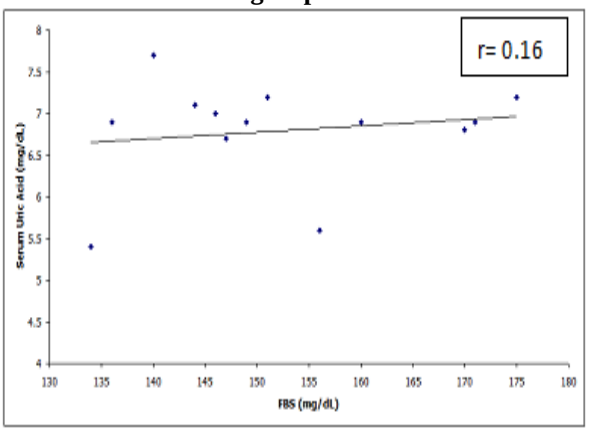
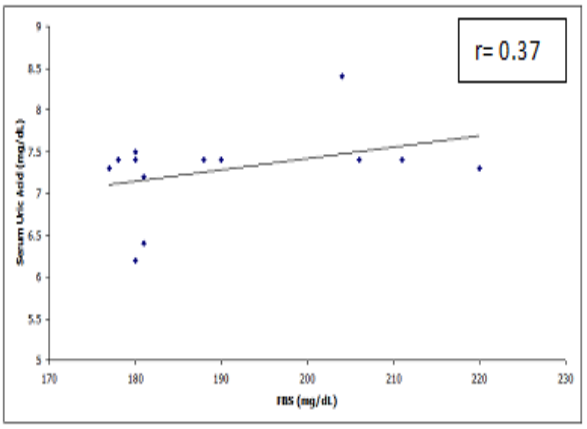


Fig. 6: SUA in cases at different levels of FBS

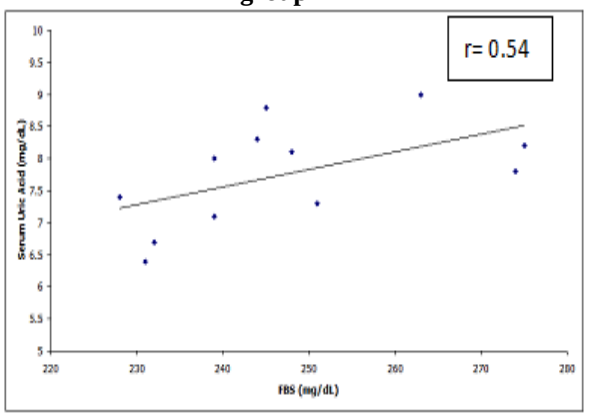
Graph 1: Correlation of serum uric acid with FBS in group-I



Graph 2: Correlation of serum uric acid with FBS in group-II



Graph 3: Correlation of serum uric acid with FBS in group-III



Graph 4: Correlation of serum uric acid with FBS in group-IV

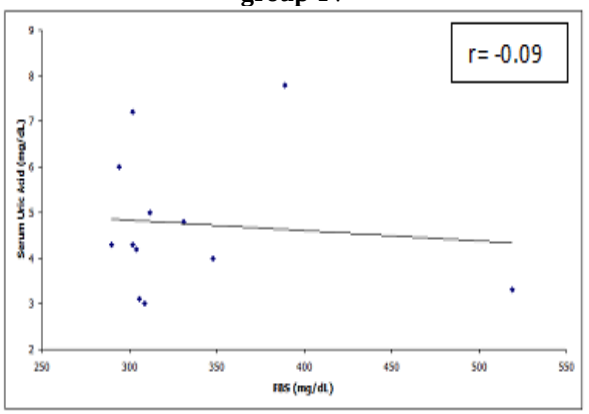


Table 7: Serum Uric acid levels in cases at different levels of HbA1c

Group	HbA1c Range (%)	HbA1c (%)		Serum Uric acid (mg/dl)	
		Mean	S.D.	Mean	S.D.
A	6-7.9 (n=12)	6.90	0.54	7.41	1.11
B	8-9.9(n=21)	7.09	0.80	9.16	0.50
C	10 and above (n=17)	11.60	1.59	5.67	1.89

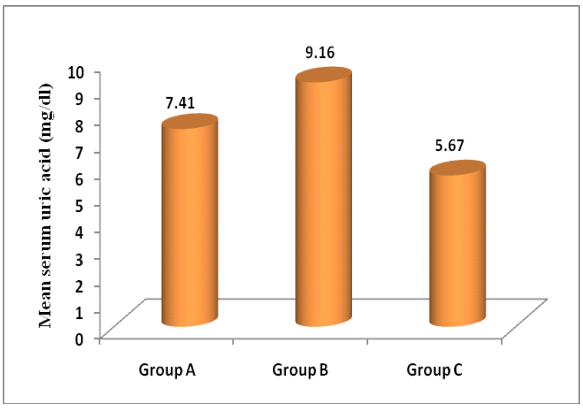
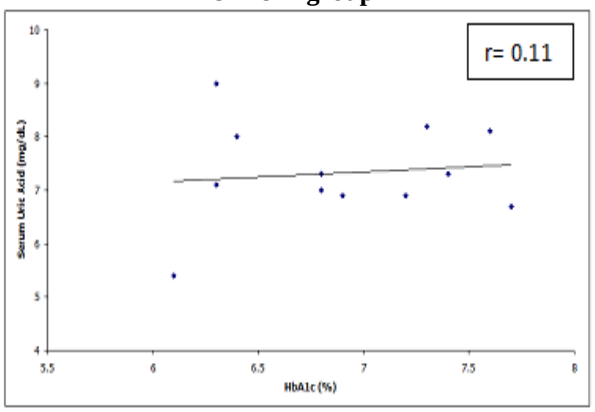
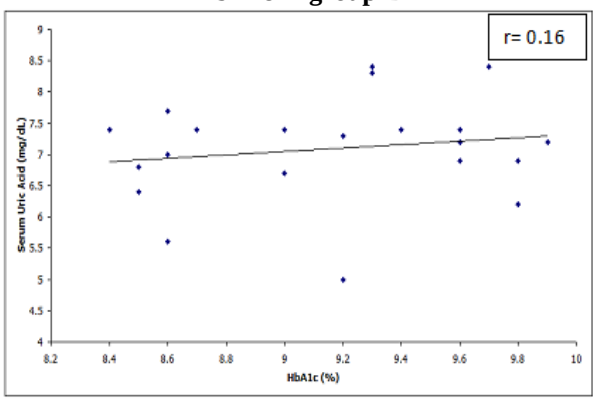


Fig. 7: SUA in cases at different levels of HbA1c

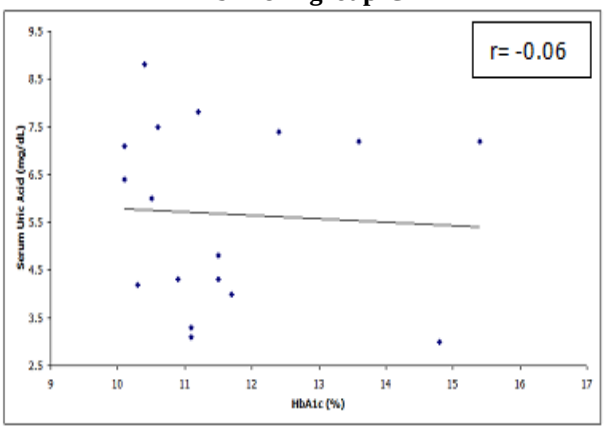
Graph 5: Correlation of serum uric acid with HbA1c in group-A



Graph 6: Correlation of serum uric acid with HbA1c in group-B



Graph 7: Correlation of serum uric acid with HbA1c in group-C



Discussion

There is a need for sensitive serum markers that are associated with diabetes and its complications. Estimation of these parameters helps in early intervention, thereby delaying/ reverting the microvascular complications (retinopathy & nephropathy) of diabetes in the early stages[1]. In our study there were no statistically significant difference ($p>0.05$) observed in distribution of cases and controls within different age groups and gender distribution. Significant positive difference ($p<0.0001$) were observed in relation to FBS, HbA1c and SUA levels among cases and controls. No statistically significant difference ($p>0.05$) was observed in serum uric acid levels in cases with different age groups and in relation to gender. When Serum Uric acid levels were compared in different FBS and HbA1c groups we observed very interesting results. We observed positive correlation between fasting blood sugar and serum uric acid in group-I, group-II and group-III and negative correlation in group-IV. Serum Uric acid initially increased to 7.84$\pm$0.97 mg/dl (Mean$\pm$2SD) with increase in Fasting Blood Sugar from 126mg/dl to 275mg/dl range in cases and thereafter decreased to 4.75$\pm$1.54 mg/dl (Mean$\pm$2SD) with further increase in Fasting Blood Sugar levels. We observed positive correlation between HbA1c and serum uric acid in group-A and group-B and negative correlation between HbA1c and serum uric acid in group-C. Serum Uric acid initially increased with increase in HbA1c from 6% to 9.9% range in cases and thereafter decreases with further increase in HbA1c levels.

The reason for initial increase in serum uric acid may be due to the effect of insulin on the metabolism of uric acid and glucose. Hyperinsulinemia could increase the activation of the hexose phosphate shunt, which would promote the biosynthesis and transformation of purine, thus increasing the rate of uricogenesis[14]. At the same time, insulin may increase reabsorption of uric acid from the kidneys by stimulating the urate anion transporter and/or Na^+ -dependent anion co-transporter

on the brush border membrane in the proximal tubular brush[15]. Type 2 DM is associated with microvascular injuries resulting in local tissue ischemia. Ischemia with associated increased lactate production that blocks urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA-DNA (purine) breakdown, which increases uric acid and ROS through the effect of xanthine oxidase (XO). Ischemia itself causes increased generation of XO[16]. Hyperglycemia induces both an oxidative stress [glucose autoxidation and advanced glycosylation end products (AGE) – ROS oxidation products] and a reductive stress through pseudohypoxia with the accumulation of NADH and NAD(P)H in the vascular intima. This redox stress consumes the natural occurring local antioxidants such as: Superoxide dismutase, Glutathione peroxidase and catalase. Once these local intimal antioxidants are depleted uric acid can undergo the paradoxical antioxidant – prooxidant switch or the urate redox shuttle[3]. Collectively, these data provide a strong mechanism underlying the close link of the initial positive correlation between glycemic parameters and SUA.

The decrease in serum uric acid level at high levels of glycemic parameters may be accounted due to subsequent development of glycosuria in diabetic patients leading to uricosuria and lower uric acid levels[10]. Also glycosuria causes sodium concentration in the fluid to falls resulting in limitation of sodium reabsorption in proximal tubules. This leads to further decrease in the Serum Uric acid levels due to decreased in proximal reabsorption of sodium and urate.

A cross sectional study such as ours cannot provide a definitive answer (such as cut off point for paradoxical shuttle); further longitudinal studies are indicated. However, uric acid can be considered as a reliable marker which is less expensive and helps clinicians in controlling the progression of Diabetes mellitus to microvascular complications like diabetic retinopathy and diabetic nephropathy.

The public health impact of high serum uric acid may be larger than currently thought. Estimation of Serum Uric acid is simple and cost effective test. Even today uric acid is neither a target for treatment in asymptomatic hyperuricemia nor a risk marker in clinical practice. This study shows that there is initial increase in Serum uric acid in Type 2 Diabetes Mellitus. So Xanthine oxidase inhibitors which are safe and inexpensive can be used in initial hyperuricemia in Type 2 Diabetes Mellitus to prevent further microvascular complications.

Conclusion

Serum Uric acid initially increased with increase in Fasting Blood Sugar and HbA1c from 126mg/dl to 275mg/dl range and 6%-9.9% range respectively and thereafter decreased with further increase in Fasting Blood Sugar and HbA1c. Initial increase in Serum Uric acid with hyperglycemia can be due to hyperinsulinemia, paradoxical urate redox shuttle, microvascular injury and/or increase generation and activity of Xanthine oxidase. Decrease in Serum Uric acid with advancing hyperglycemia can be due to glycosuria causing uricosuria and decrease in sodium reabsorption. Hence periodic evaluation of Serum Uric acid can help in early detection and prevention of microvascular complications in Type 2 Diabetes Mellitus.

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References

1. Fauci, Braunwald, Kasper, Hauser, Longo, Jameson et al. Harrison`s Principles of internal medicine.18th edition; Mc Graw Hill medical publishing division; 2012.
2. Schulze MB and Hu FB. Primary prevention of Diabetes: What can be done and how much can be prevented? Annual Rev Public health 2005;26:445-467.
3. Hayden MR and Tyagi SC. Uric acid: A new look at an old risk marker for cardiovascular disease, metabolic syndrome and type 2 diabetes mellitus: The urate redox shuttle. Nutrition and Metabolism 2004;1:10.
4. Johnson RJ, Kang DH, Daniel Feig et al. Is There a Pathogenetic Role for Uric Acid in Hypertension and Cardiovascular and Renal Disease? Hypertension 2003;41:1183-1190.
5. Seppo Lehto, Leo Niskanen, Tapani Rönnemaa and Markku Laakso. Serum Uric Acid Is a Strong Predictor of Stroke in Patients With Non-Insulin- Dependent Diabetes Mellitus. Stroke 1998;29:635-639.
6. Nadkar MY, Jain VI. Serum Uric Acid in Acute Myocardial Infarction. JAPI 2008;56:759-762.
7. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetic Care 2008;31:361-362.
8. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or type 2 diabetes in Japanese male office workers. Eur J Epidemiol 2003;18:523-530.
9. Yuan HJ, Yang XG, Shi XY, Tian R and Zhao ZG. Association of serum uric acid with different levels of glucose and related factors. Chinese Medical Journal 2011;124(10):1443-1448.
10. Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relationships in a population study. Postgrad Med J 1986;62:1001-1006.
11. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor. Ann Clin Biochem 1969;6:24-27.
12. Little RR, Wiedmeyer HM, England JD, Wilke AL, Rohlfing CL, Wians FH, et al. Interlaboratory standardization of measurements of glycohemoglobins. Clin Chem 1992;38:2472-2478.
13. Trivedi R, Berta E and Rebar L. Enzymatic uric acid determination at 500nm by Trinder method. Clin. Chem 1976;22:1223.
14. I. H. Fox. "Metabolic basis for disorders of purine nucleotide degradation", Metabolism, vol. 30, no. 6, pp 616-634;1981.

15. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 2005;143:499-516.
16. Leyva F, Anker S, Swan JW, Godsland IF, Wingrove CS, Chua TP, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. Eur Heart J 1997;8:858–865.