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A STUDY TO ASSESS SERUM URIC ACID LEVEL AND ITS ASSOCIATION WITH GLYCEMIC PARAMETERS ININDIVIDUALS WITH PREDIABETES AND DIABETES MELLITUSIN A NORTH INDIAN TERTIARY CARE HOSPITAL

(URIC ACID AND PREDIABETES)

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Abstract

Uric acid is considered to be an important risk factor for the development of type 2 diabetes mellitus (T2D) and a determinant of incidence of T2D in adults with glucose intolerance. There is conflicting finding regarding the trend of serum uric acid level in different glycemic status. Therefore this study has been aimed to investigate the association of serum uric acid level with glycemic parameters in prediabetic and diabetic individuals attending the tertiary care hospital in Uttarakhand,

An observational study was conducted in 721 individuals based on data collected from Biochemistry log book of AIIMS Rishikesh maintained from October 2014 to September 2016. The enzymatic method was carried out for measurement of Serum uric acid [(Uricase) and blood glucose (BG) (Hexokinase)] level, and HbA1c was determined by immune inhibition method.

Out of 721 individuals (410 male and 311female) 118 and 504 individuals belonged to prediabetes and T2D respectively. Prediabetic individuals have higher uric acid level (5.408±1.7747 vs 5.639±1.7881) and diabetic individuals have significantly (p= 0.005) lower level of uric acid compared to healthy individuals (5.40±1.77 vs 5.12±1.53). Glycemic parameters showed positive association in normoglycemic individuals whereas significantly negative association in prediabetic and diabetic individuals. The ROC scatter plot revealed the area under the curve created by uric acid was 0.464 with 95% CI 0.399 - 0.530.

From this study it could be concluded that serum uric acid may be a determinant of altered glucose metabolism but not a potential predictor of prediabetes in north Indian populations residing in Uttarakhand.

Keywords: Uric acid, Prediabetes, diabetes, glycated haemoglobin, Uttrakhand, Uricase

Introduction:

Diabetes mellitus appears to be an epidemic in India. More than 62 million people are diagnosed with diabetes and without effective intervention the number would be projected to 79.4 million by 2030.(1). A recent local study conducted by Uttarakhand health department revealed an increasing incidence of diabetes mellitus among teen agers and more than 2 lakhs individuals are diagnosed with diabetes. Moreover more than 100 people are dying every year due to diabetes(2).

Uric acid is the end product of purine metabolism which occurs primarily in the liver from diet or endogenous purine containing molecules. It can act as a strong reducing agent as well as an antioxidant with free radical scavenging property.Specific enzyme defect and diseases such as cancer and psoriasis having enhanced tissue turnover may contribute to the manifestation of hyperuricemia.(3) . Uric acid is considered to be an important risk factor for the development of type 2 diabetes mellitus (T2D). It can also be used as a predictor of incidence of T2D in adults with glucose intolerance(4). A Finnish diabetes prevention study conducted on obese individuals with impaired glucose tolerance, reported that baseline uric acid level could be a good predictor of the risk of diabetes mellitus even after adjustment of modifiable and non modifiable risk factors for metabolic disorders such as age, gender, blood pressure, lipid profile, physical activity etc(5). It has also been documented that irrespective of other risk factors, individuals with history of gout are more prone to develop diabetes in near future(6).

Serum uric acid in healthy individuals is reported to be positively associated with plasma glucose(7, 8). However, this association between healthy and diabetic individuals are not consistent(9, 10).A meta-analysis of 11 cohorts reported that serum uric acid level is associated with increased risk of developing diabetes (11). However, a recent prospective study have reported that diabetes is related to a lower risk of incident gout in the UK general population (12) and in Chinese population (13).One study has shown a declining trend of serum uric acid level in hyperglycemic state (14) and in some cases there was no significant association between serum uric acid and glycemic state(15).
It is imperative to know the actual trend of uric acid level in prediabetics and diabetics since hyperuricemia is increasingly found to be significantly associated with various modifiable risk factors contributing to cardiovascular disease such as centralobesity,glucoseintolerance,highbloodpressure and dyslipidemia(16).
Therefore this study has been aimed to assess the serum uric acid level in prediabetic and diabetic individuals and to evaluate its relationship with various glycemic parameters in populations of Uttarakhand.

Methods:
An observational study was conducted in 721 individuals. Data were collected from Biochemistry log book of AIIMS Rishikesh maintained from October 2014 to September 2016 in order to observe the uric acid level and glycemic parameters of individuals visited AIIMS Rishikesh during that time. . Ethical clearance was obtained from the Institute Ethical Committee prior to the commencement of the research (Ref. Number: AIIMS/IEC/15/140). Based on ADA classification study subjects were divided into three groups.

Inclusion criteria:
Adult with Prediabetes and Diabetes more than 18 years of both gender enrolled in AIIMS, Rishikesh and blood test reports were recorded in the AIIMS biochemistry department.
Control was defined as a subject who had a fasting serum glucose level lower than 100 mg/dl and PPBS <140mg/dl
The diagnosis of T2DM is based on ADA 2015
Fasting blood glucose>126 mg/dl or 2 hour Post prandial blood glucose> 200 mg/dl or both or HbA1c ≥6.5%
Criteria for prediabetes: based on ADA 2015
Fasting blood glucose≤126 mg/dl or 2 hour Post prandial blood glucose ≤ 200 mg/dl or both or HbA1c 5.7-6.4%
The enzymatic method was carried out for measurement of Serum uric acid [(Uricase) and blood glucose (BG) (Hexokinase)] level, and HbA1c was determined by immune inhibition method

Statistical analyses
Statistical analyses were carried out using SPSS , version 23.0 (SPSS,
Chicago, IL). Normal distribution of all parameters was validated by Kolmogorov-Smirnov test..Baseline characteristics of the groups were compared using ANOVA . Data are given as mean± SD. A p-value < 0.05indicated statistical significance. Pearson's correlation coefficients were calculatedbetween selected variables. The receiver-operating characteristic (ROC) curves analysis was used toestimate the predictive value of uric acid for identifying prediabetic individuals .It also determines the sensitivity and specificity of the diagnostic procedure. The curves arebetween the limits 0 and 1 and the area under the curve will give the idea of theaccuracy of the tests. ROC curves were created by plotting the sensitivity on the yaxisand the false-positive rate (1-specificity) on the x-axis. The peak of the curverepresents the optimal cut-point.

Results:
General characteristics of study population
Out of 721individuals (410 male and 311female) 118 and 504 individuals belonged to prediabetes and T2D respectively (according to ADA classification). The mean age of Prediabetic and diabetic individualsis almost same (55.23±13.09 vs 54.71±10.94 p=>0.05) while healthy reference s were little bit of younger age (49.05±16.01). Among these 3 study groups, there is a significantly (p<0.001) increasing trend in fasting plasma glucose (91.96±13.84mg/dl , 107.06±18.12 mg and 193.80±87.10 mg/dl in healthy , prediabetes and diabetes respectively) and postprandial plasma glucose level (129.18 ±6.05 mg/dl, 167.33±48.25 mg/dl, and 307.06±121.49 mg/dl in healthy, prediabetes and diabetes respectively). Moreover, HbA1c also showed the similar trend (p= 0.001) 5.322±.2659, 6.038±.2425, 9.395±2 in healthy, prediabetes and diabetes respectively. Interestingly, Prediabetic individuals have higher uric acid level compared to the healthy individuals (5.408±1.7747 vs 5.639±1.7881).On the other hand diabetic individuals have significantly (p= 0.005) lower level of uric acid compared to prediabetes (5.63±1.78 vs 5.12±1.53) as well as healthy (5.40±1.77 vs 5.12±1.53). Demographic and biochemical parameters are presented in table 1(A,B,C).

Association between uric acid and glycemic parameters among study participants

The correlation coefficients for the indicated parameters are presented in Table 2(A,B,C,D). In case of normoglycemicsall glycemic parameters showed a nonsignificant positive association with uric acid while in diabetic individuals they (FBS, PPBS, HbA1c)showed a significant ($p<0.001$) negative associationwith uric acid. Out of these three glycemic parameters PPBS ($r= -0.309$) showed a slightly better correlation with uric acid compared to FBS($r=-0.240$) and HbA1c ($r= -0.255$). These associations remain significant even after adjustment with age and sex.

Effect of gender on association between uric acid and glycemic parameters

In order to observe the effect of gender on association between uric acid and glycemic parameters , the study participants are divided into two groups (Male and Female) and pearson's correlation coefficients are calculated in each group. The correlation coefficients for the indicated parameters of different genders are presented in Table 3(A and B). There is a significant ($p<0.001$) negative association between uric acid and glycemic parameters in both male and female. However this association is stronger in case of male compared to female (for FBS: $r= -0.261$ vs -0.228; PPBS: $r= -0.381$ vs -0.259; HbA1c: $r= - 0.322$ vs -0.181).

Effects of age on uric acid level

Previous study revealed that glycosuria is influenced by age among diabetic individuals (17). Hence the study participants having diabetes mellitus were divided into two groups younger than 40 years and older than 40 years (Table 4). It has been found that younger individuals have significantly higher trend of glycemic parameters(FBS and PPBS= significant, HbA1c=Not Significant) compared to older age group. Interestingly, on the contrary, younger age group has lower level of uric acid compared to older age group of individuals with diabetes mellitus although it is not significant (4.700 ± 1.5983 vs5.186 ± 1.5157, $p=0.683$) .

The predictive performance of uric acid for identifying prediabetic individuals

ROC curve for study participants is shown in Fig 1. The ROC scatter plot revealed the area under the curve created by uric acid was 0.464 with 95% CI 0.399 - 0.530. The optimal cut off point of uric acid for identifying the prediabetic individuals corresponds to 4.050 with sensitivity 78% and specificity 25% which is absolutely within the normal range. Since the area under the curve is less than (0.5) , uric acid is not a good predictor for identifying prediabetic individuals in population of Uttarakhand.

Discussion:

Prediabetes is characterised by insulin resistance, impaired fasting glucose and/or glucose tolerance and 70% of them are at future risk of developing T2D within 10 years (18). Cumulative evidence suggest a differential association of various degrees of hyperglycemia and level of uric acid in diabetic patients (19, 20). While the plasma glucose test reflects glycemic status at the moment of the test, glycatedhaemoglobin or haemoglobin A1c (HbA1c) reflects an average blood glucose level over the past 3 months. Thus, HbA1c levels provide a long-term picture of blood glucose status as an exposure variable. The mutual interdependent effect of higher incidences between T2D and Gout could be partially explained by the common genetic factors shared by these two disorders(21).However the other modifiable and nonmodifiable confounding factors may influence the out come of these metabolic disorders as a function of race and ethnicity. Hence this study was carried out to observe the association between serum uric acid level and glycemic parameters including HbA1c in prediabetic and diabetic individuals in North Indian population attending a tertiary care hospital.

General characteristics of our study participants revealed that male participants have higher level of serum uric acid level compared to female individuals irrespective of glycemic status. This is in line with the previous studies(22) carried out to observe the impact of sex on uric acid level. Moreover in diabetic individuals have significantly lower level of uric acid level compared to healthy and prediabetic individualsand showed a negative association with glycemic parameters (FBS, PPBS and HbA1c). This is in agreement with previous studies (17, 23) where a decreasing trend of uric acid level was demonstrated with increasing HbA1c. This may be due to the uricosuric effect.On the other hand Gill et al(24) have demonstrated a rising trend of both HbA1c and uric acid level in diabetic individuals. This may be because of the difference in duration of diabetes mellitus among study participants. They have also documented an increase in the level of insulin secretion which may be the reason of increase in uric acid level in the newly diagnosed diabetic individuals.

According to this study, in prediabetic individuals there is higher level of uric acid compared to the healthy individuals. Prediabetes is commonly associated with insulin resistance andcompensatory hyperinsulinemia which produces antiuricosuric effect through increase in reabsorption of uric acid along with water and electrolytes from the renal tubules(25).

On the contrary, female diabetic individuals have slightly higher level of uric acid compared to healthy individuals. This may be due to the fact that diabetic individuals (55.139±9.6756) compared to the healthy counterpart (47.592±14.9205) are of higher age group since menopause is known to cause rise in the uric acid level(17).
Moreover younger diabetics have lower level of uric acid compared to the older diabetics which is endorsed by the previous study conducted by Whitehead et al(1992)(17)and can be explained by increased glycosuria leading to declining trend in uric acid level in younger individuals.
Normal metabolic reactions in human being is associated with generation of substantial amount of toxic free radicals. However body's antioxidant mechanism play a crucial role to get rid of these free radicals. Various disease conditions such as cancer, diabetes, atherosclerosis , rheumatoid arthritis are found to be associated with increased circulating free radicals. However there is controversy whether the increased productions of free radicals or the weakening of defensive mechanism is actually responsible for this increase in free radical concentration. It has been found that features related to T2D are partially contributed by increased free radical damage. It has also been reported that diabetes melltus is associated with decrease in various free radical scavenger such as ascorbic acid(26). The present study result showing the significant fall of uric acid, an important free radical scavenger, may have an implication in weakening of defensive mechanism in diabetic individuals leading to the development of dreadful complications in T2D.
Limitation: Lack of history whether the patients were taking any medicine which could influence uric acid metabolism was a great limitation in interpreting the results of this study. There is no evidence whether the participating individuals were having any other associated metabolic disorders which could influence the study results. Moreover, there is absence of direct assessment of modifiable and non modifiable risk factors which may influence the outcomes of uric acid levels. Since data were collected from old records of the institute it is difficult to ensure that the study participants constituted the ideal cohort. Hence the study limits the generalizability of this result and warrants a further study with proper history taking to select the appropriate cohort.

In brief, Prediabetic individuals have higher uric acid level whereas diabetic individuals have significantly lower level of uric acid compared to the healthy or normoglycemic individuals living in Uttarakhand. Diabetic individuals showed a significant negative correlation with glycemic parameters and this association persists even after adjustment with age and sex. From this study it could be concluded that serum uric acid may be a potential determinant of altered glucose metabolismin north Indian populations residing in Uttarakhand.

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Table 1A General characteristics of all study participants

Ser No	Varibles	Normal	Prediabetes	Diabetes	Sig
1.		99	118	504	
2.	Age	49.051±16.0111	55.237±13.0951	54.718±10.9430	<0.001
3.	FBS	91.960±13.8471	107.061±18.1209	193.800±87.1084	<0.001
4.	PPBS	129.180 ±6.0542	167.332±48.2509	307.063±121.493	<0.001
5.	HbA1c	5.322±.2659	6.038±.2425	9.395±2.2434	<0.001
6.	Uric acid	5.408±1.7747	5.639±1.7881	5.125±1.5334	0.005

Table 1B General Characteristics of Male participants

Ser No	Varibles	Normal	Prediabetes	Diabetes
1.		50	66	291
2.	Age	50.480±17.0417	56.894±13.5523	54.509±11.7709
3.	FBS	92.389±15.5770	109.900±20.2881	191.285±88.2720
4.	PPBS	130.208±41.3227	183.854±49.0237	309.481±126.6440
5.	HbA1c	5.314±.2893	6.053±.2438	9.386±2.3684
6.	Uric acid	5.952±1.4403	5.727±1.7833	5.318±1.4682

Table 1C General Characteristics of Female participants

Ser No	Varibles	Normal	Prediabetes	Diabetes
1.		49	52	208
2.	Age	47.592±14.9205	53.135±12.29	55.139±9.6756
3.	FBS	91.564±12.2298	103.844±14.8767	197.642±86.4117
4.	PPBS	128.231±31.2235	150.811±41.9112	302.521±114.0844
5.	HbA1c	5.331±.2426	6.019±.2418	9.389±2.0856
6.	Uric acid	4.853±1.9211	5.527±1.8052	4.889±1.5892

Table 2A Pearson's Correlation coefficients for all participants

	Variables	r	significance
Uric acid	FBS	-.240**	<0.001
	PPBS	-.309**	<0.001
	HbA1c	-.255**	<0.001

Table 2B Correlations Pearson's for Normoglycemic

	Variables	r	significance
Uric acid	FBS	.131	.261
	PPBS	.225	.117
	HbA1c	.069	.495

Table 2CPearson's Correlation coefficients for individuals with Prediabetes

	Variables	r	significance
Uric acid	FBS	-.009	.932
	PPBS	.018	.880
	HbA1c	-.021	.821

Table 2D Pearson's Correlation coefficients for individuals with diabetes

	Variables	r	significance
Uric acid	FBS	-.263**	<0.001
	PPBS	-.334**	<0.001
	HbA1c	-.311**	<0.001

Table 3A Pearson's Correlation coefficients for female participants

	Variables	r	significance
Uric acid	FBS	-0.228	<0.001
	PPBS	-0.259	<0.001
	HbA1c	-0.181	=0.001

Table 3B Pearson's Correlation coefficients for male participants

	Variables	r	significance
Uric acid	FBS	-0.261	<0.001
	PPBS	-0.381	<0.001
	HbA1c	-0.322	<0.001

Table 4: Effects of Age on Diabetic individuals younger than 40 years and Older than 40 years

Variables	Younger ≤ 40 years (56)	Older> 40 years (380)	Significance
FBS	218.071±108.0320	190.224±83.1595	0.004
PPBS	345.692±167.5599	301.388±112.3682	<0.001
HbA1c	10.309±2.6237	9.263±2.1539	0.137
Uric acid	4.700±1.5983	5.186±1.5157	0.683

Fig 1 ROC curve for prediction of prediabetes defined by HbA1c >2.8 among young apparently healthy individuals by Uric acid.