

Serum uric acid level and its association with cardiometabolic risk factors in prediabetic subjects

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Background: Excess serum uric acid (UA) accumulation can lead to various diseases. Increasing evidences reveal that UA may have a key role in the pathogenesis of metabolic syndrome. Little is known about the associations of UA levels with cardiometabolic risk factors in prediabetic individuals. This study was designed to evaluate the association between UA and cardiometabolic risk factors in prediabetic subjects with family history of diabetes compared with those with normal glucose tolerance (NGT). **Materials and Methods:** In a cross-sectional setting, a sample containing 643 (302 prediabetic subjects and 341 normal) of the first-degree relatives of diabetic patients aged 35-55-years old were investigated. Samples were assessed in prediabetic and normal groups using glucose tolerance categories. Prediabetes was defined based on American Diabetes Association (ADA) criteria. Body weight and height, systolic and diastolic blood pressure (SBP and DBP), UA, creatinine (Cr), albumin (Alb), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and lipid profiles were measured and compared between two groups. **Results:** Prediabetic persons were older and obese than normal persons. Also, prediabetic persons (5.2 ± 1.3 mg/dl) had significantly higher UA than normal persons (4.9 ± 1.4 mg/dl) ($P < 0.05$). FBG after 0, 30, 60, and 120 min in prediabetic were higher than normal persons ($P < 0.001$). With respect to metabolic parameters, the patients in the higher UA quartiles exhibited higher levels of body mass index (BMI), SBP, FBG and triglycerides (TG). The higher quartiles of UA tended to be associated with higher BMI and higher total cholesterol (TC) in females prediabetic persons. Based on logistic regression analysis in different models, UA was positively (odds ratio (OR) >1 , $P < 0.05$) associated with glucose tolerance categories. This association remained statistically significant after adjusting the effects of age and BMI. Also, the association between glucose tolerance categories and UA were positively significant in both genders. **Conclusion:** High UA level was associated with some cardiometabolic risk factors in prediabetic individuals compared with normal person. UA level was also a significant predictor for prediabetes condition.

Key words: Cardiometabolic, glucose tolerance, prediabetic, uric acid

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INTRODUCTION

A main worldwide public health problem is a clustering of cardiovascular risk factors such as insulin resistance, hypertension, glucose intolerance, hypertriglyceridemia, and low high-density lipoprotein cholesterol levels.^[1,2]

Prediabetes, which is defined as impaired fasting glucose and/or glucose tolerance,^[3] is an important risk factor for the development of overt diabetes as well as cardiovascular disease (CVD).^[4,5] Patients with prediabetes are at high risk of future type 2 diabetes, and within 10 years, 70% of them tend to develop type 2

diabetes.^[6] More importantly, patients with prediabetes seem to share the similar associated damage to end target organs, as patients with diabetes.^[7]

The final oxidation product of human purine metabolism is uric acid (UA) and excess serum accumulation can lead to various diseases.^[8,9] Increasing evidences reveal that UA may have a key role in the pathogenesis of metabolic syndrome^[10] and suggested that increased UA is used clinically as a marker of metabolic syndrome and is a risk factor for CVD in the general population.^[11,12] The associations between increased UA levels with components of metabolic syndrome and often accompanied by obesity, raised BP,

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hyperlipidemia, glucose intolerance, and CVD clustering are reported in many previous studies.^[13-15] Also, pathogenetic and epidemiological rationale for a role of serum UA in the development of diabetes is provided in current studies.^[16,17]

Despite prospective clinical cohorts that suggested UA could predict the development of vascular-related diseases like hypertension, diabetes, and metabolic syndrome, the association of UA levels in metabolic syndrome and prediabetes is still unclear.^[18] Also, little is known about the associations of UA levels with cardiometabolic risk factors in prediabetic individuals. Therefore, this study was designed to evaluate the association of UA levels with cardiometabolic risk factors in prediabetic individuals.

MATERIALS AND METHODS

Study design and participants

This population-based cross-sectional study was performed in accordance with the principles of the Declaration of Helsinki, and the ethics committee of School of Medicine in Isfahan University of Medical Sciences, Isfahan, Iran, approved the study protocol. Data collection was conducted in Isfahan Endocrine and Metabolism Research Center outpatient clinics affiliated to Isfahan University of medical sciences. The sample of patients and their first-degree relatives of diabetic patients were recruited between 2003 and 2005 during the conducting of Isfahan diabetes prevention program.^[19] An invitation letter, which described the study, was sent to the first-degree relatives of diabetic patients registered at our center to take part in the study. A total of 643 persons who were desire to participate in the study were eligible and were informed about information sessions and site visits. Inclusion criteria were first-degree relatives of diabetic patients, age of 35-55-years old, and no previous history of proteinuria and recent urinary tract infection. Participants with known systemic diseases, including diabetes mellitus, gastrointestinal disease, hypertension, CVD, pulmonary disease, renal disease or cancer, treatment with corticosteroids or spironolactone, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors and medications that affect insulin sensitivity were excluded. Written informed consent was obtained from all subjects before the start of the study.

Procedures and variables assessment

Data collection was conducted at the baseline and through follow ups according to Standard of Medical Care in Diabetes. Participants completed a standard questionnaire, which included age and sex as demographic characteristics, body weight and height as physical condition, past medical history and lifestyle risk factors, systolic blood pressure (SBP) and diastolic blood pressure (DBP), UA, creatinine (Cr), albumin (Alb), fasting blood glucose (FBG), and lipid profiles including total cholesterol (TC), triglycerides (TG),

high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C).

Serum Cr, TG, TC, HDL (measured using standardized procedures), and LDL (calculated by the Friedwald equation provided that total TG did not exceed 400 mg/dl).

An oral glucose tolerance test (OGTT) was conducted after a 12-h overnight fast. In all, 75 g of glucose solution was ingested after fasting blood sample was obtained for plasma glucose. Blood samples were obtained at baseline, 30, 60, and 120 min after ingestion and were later assayed for glucose concentrations. Then subjects were classified in two groups according to glucose tolerance status as defined by the American Diabetes Association (ADA) criteria.^[20]

1. Normal glucose tolerance (NGT) was defined as fasting plasma glucose (FPG) of less than 5.5 mmol/l (100 mg/dl) and 2-h postload glucose of <7.8 mmol/l (140 mg/dl).
2. Prediabetes was defined as FPG of 5.5-6.9 mmol/l (100-125 mg/dl) and/or impaired glucose tolerance (IGT) (2-h postload glucose of 7.8-11.0 mmol/l [140-199 mg/dl]).

Height was measured barefoot three times to the nearest 0.1 cm using a wall-mounted stadiometer and weight was measured to the nearest 0.1 kg using a calibrated beam scale. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters squared). Blood pressure was measured after subjects were seated in a chair for ≥ 10 min with their backs supported as well as their arms supported at heart level. The mean of three measurements was recorded as the blood pressure. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or usage of antihypertensive medications.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software for Windows, version 20, was used for statistical analyses. Descriptive data are reported as mean \pm standard deviation (SD), median interquartile range (IQR) for quantitative variables, and number (percent) for qualitative. Normality distribution of studied variables was investigated using one-sample Kolmogorov – Smirnov test. For positive skewed variables such as lipid profiles, UA, Alb, and Cr, log-transformation was applied to normalize the distribution. Independent sample *t*-test and chi-square test were used to compare quantitative and qualitative, respectively, studied variables between groups. One-way analysis of variance (one-way ANOVA) or Kruskal–Wallis test was considered for comparing the quantitative dependent variables across the quartiles of UA. Logistic regression and receiver operating characteristic (ROC) analysis were used to evaluate the prognostic value of UA for predicting the prediabetes. Logistic regression analysis was used in different models to examine the association between UA levels and prediabetes. In the first model, we adjusted for age. The second model was

additionally adjusted for BMI. The level of significance is considered to be less than 0.05.

RESULTS

The prevalence of prediabetes among participants was 47% (302 of 643 participants). The baseline and main characteristics of the studied participants are shown in Table 1. As can be seen from Table 1, prediabetic persons

Table 1: Demographic and main clinical characteristics in studied groups

	Prediabetic group	Normal group	P-value
Age (year)	44.4±6.2	43.1±5.8	0.005 [†]
Male/female	77/225	90/251	0.79 [*]
BMI (kg/m ²)	29.5±4.1	28±4.4	<0.0001 [†]
FBG 0 (mg/dl)	104.1±9.4	90.5±6.2	<0.0001 [†]
FBG 30 (mg/dl)	155.5±29.4	128.5±24.5	<0.0001 [†]
FBG 60 (mg/dl)	172.4±24.5	172.3±29.4	<0.0001 [†]
FBG 120 (mg/dl)	136.9±32.2	102.2±20.5	<0.0001 [†]
SBP (mmHg)	119±1.53	117.9±1.5	0.35 [†]
DBP (mmHg)	79.4±1.01	78.9±0.98	0.52 [†]
HbA1c (%)	5.4±0.74	5.1±0.56	<0.001
TG (mg/dl)	176.9±101.6	140.6±94.1	<0.0001 [†]
TC (mg/dl)	202.5±38.5	197.7±35.4	0.1 [†]
HDL (mg/dl)	43±12	46.6±12.6	<0.0001 [†]
Alb (g/dl)	11.9±9.3	10.2±8	0.017 [†]
Cr (mg/dl)	0.2±0.1	0.19±0.1	0.09 [†]
Alb/Cr	57.2±39.8	54.28±42.5	0.38
UA (mg/dl)	5.2±1.3	4.9±1.4	0.002 [†]

Data expressed as mean ± SD or number (percent). P-values calculated by †independent sample t-test and †chi-square test. SBP and DBP = Systolic and Diastolic blood pressure; HbA1c = Hemoglobin A1c; UA = Uric acid; Cr = Creatinine; Alb = Albumin, BMI = Body mass index, FBG = Fasting blood glucose; TC = Total cholesterol; TG = Triglycerides; HDL-C = High-density lipoprotein-cholesterol; LDL-C = Low-density lipoprotein-cholesterol; SD = Standard deviation

were older ($P < 0.01$) and obese ($P < 0.001$) than normal persons. Also, prediabetic persons had significantly higher UA than normal persons ($P < 0.01$). We also investigated sex-specific UA level difference in two studied groups; the results showed that in both genders the UA levels in prediabetic patients are significantly higher than normal ones (results not shown). There was no statistical group difference in terms of sex. The results showed significant difference in terms of fasting glucose after 0, 30, 60, and 120 min between groups, which in prediabetic persons were higher than normal persons ($P < 0.001$). SBP, DBP, TC, and Cr were not statistically significant between groups. TG ($P < 0.001$) and Alb ($P < 0.05$) in prediabetic persons were significantly higher than normal persons, and HDL in normal persons were significantly higher than pre-diabetic persons ($P < 0.001$).

In Table 2 some demographic and main proposed medical characteristics in our study for both groups of study's participants across UA quartiles are shown. Analyzed by quartiles of UA levels show that the subjects with higher UA were more likely to be male, in both normal and prediabetic persons ($P < 0.001$). With respect to metabolic parameters, the patients in the higher UA quartiles exhibited higher levels of FBG and TG in both normal and prediabetic persons ($P < 0.05$), an increasing trend was found between BMI and UA quartiles in prediabetic as well as normal persons ($P < 0.05$). In contrast, in prediabetic persons HDL was significantly lower in the higher UA quartile ($P < 0.05$). There were no statistically significant differences in other variables in both normal and prediabetic groups across quartile of UA.

Table 2: Comparison of investigated variables in studied groups across the UA level quartiles

UA (n)	Normal group (n = 341)				P	Prediabetic group (n = 302)				P
	Q ₁ (106)	Q ₂ (82)	Q ₃ (78)	Q ₄ (72)		Q ₁ (69)	Q ₂ (65)	Q ₃ (73)	Q ₄ (95)	
Age (year)	43.8±5.1	44.2±6.4	44.7±6.4	44.8±7.4	0.75	44.4±6.2	44.4±6.2	44.4±6.2	44.4±6.2	0.75
Male/female	2/67	2/63	13/60	60/35	<0.001	8/99	9/73	23/57	50/22	<0.001
BMI (kg/m ²)	27±4.3	27.8±4.1	28.7±4.8	28.8±4.2	0.018	29±4	28.9±4	30.1±4.3	32.9±3.9	0.016
FBG 0 (mg/dl)	89.8±6.5	91.2±6.4	90.4±5.7	91±5.9	0.44	102±9.5	103.7±8.9	106.3±9.5	104.4±9.4	0.047
FBG 30 (mg/dl)	128.6±24.7	125.9±23.7	128.2±24.6	131.7±25.1	0.57	149.4±29.7	154.7±30.8	157.2±28.1	159±29.2	0.23
FBG 60 (mg/dl)	121.2±27.6	122.8±32.5	132.2±36.8	136±30	0.008	162.7±41.3	171.5±41.9	166.5±41.2	184.1±37.9	0.006
FBG 120 (mg/dl)	101.5±20.4	105.2±20.3	102.2±20.5	99.8±21	0.42	138.1±30.1	143.1±29.7	135.8±34.8	132.6±32.9	0.24
SBP (mmHg)	117.4±14.7	116.3±14.4	117.3±14	120.8±17.1	0.001	118.1±16.5	117.7±14.9	120.6±15.5	119.4±14.5	0.64
DBP (mmHg)	78.1±9.6	77.5±9.9	79.6±9.2	80.1±10.4	0.06	78.3±10.4	78.7±10.4	80.2±9.7	80±10	0.6
HbA1c (%)	5.09±0.52	5.15±0.64	5.12±0.51	5.13±0.63	0.92	5.37±0.78	5.36±0.85	5.38±0.61	5.46±0.72	0.84
TG (mg/dl)	106.2±53.9	125.7±61	148.8±76.4	199.2±147	0.001	150.1±111.5	161.9±94.8	178.7±82.1	205.4±106.1	0.003
TC (mg/dl)	190.3±36.8	201±36.8	200.9±34.9	201.7±30.7	0.3	196.3±39.5	200.9±27.6	209.3±34.5	202.8±45.9	0.24
HDL (mg/dl)	48.3±11.7	50.7±14.7	46.4±11.8	39.6±9.4	0.15	44.9±11.2	43.7±11.1	44.3±12.3	40.2±12.7	0.044
Alb (g/dl)	10.9±10	10.3±8	10.2±6.8	9±5.3	0.52	13.4±9.9	10.7±7.8	11.2±8.2	12±10.4	0.35
Cr (mg/dl)	0.19±0.1	0.19±0.08	0.2±0.08	0.21±0.09	0.77	0.21±0.1	0.2±0.1	0.2±0.1	0.22±0.1	0.57
Alb/Cr	57.9±42.1	53.7±40.6	53±34.1	51±52.7	0.74	62.6±26.7	53.1±33.9	56.2±34.8	56.8±53.7	0.58

Data expressed as mean ± SD or number (percent). P-values calculated by ANOVA. SBP and DBP = Systolic and Diastolic blood pressure; HbA1c = Hemoglobin A1c; UA = Uric acid; Cr = Creatinine; Alb = Albumin, BMI = Body mass index; FBG = Fasting blood glucose; TC = Total cholesterol; TG = Triglycerides; HDL-C = High-density lipoprotein-cholesterol; LDL-C = Low-density lipoprotein-cholesterol; SD = Standard deviation; ANOVA = Analysis of variance

The characteristics of the prediabetic group according to the sex-specific quartile of the serum UA levels are summarized in Table 3. The age distribution was similar for males and females. The higher quartiles of UA levels tended to be associated with higher BMI in females ($P < 0.05$) but were similar in males. No significant trend of other studied variables were found across the quartile of the serum UA levels in both male and female prediabetic persons; just higher quartiles of UA levels tended to be associated with higher TC in female prediabetic persons ($P < 0.01$).

Logistic regression analysis in different models was performed with NGT or prediabetic as the dependent variable and UA as independent variable. As shown in Table 4, UA was positively (odds ratio (OR) >1 , $P < 0.05$) associated with glucose tolerance categories (NGT or prediabetic). This association remained statistically significant after adjusting the effects of age and BMI. Also, the association between glucose tolerance categories and UA in males and females are shown in Table 4, separately. As can be seen, the associations were positively significant in both genders. For evaluating the prognostic value of UA, we further conducted ROC analysis. The result is presented in Figure 1. Area under the curve (AUC) and its 95% confidence interval (CI) (AUC = 0.756, 0.532-0.620) indicated that UA is a moderately reliable prognostic index for prediabetes.

DISCUSSION

Prediabetes is one of important risk factor of CVD, which is associated with impaired fasting glucose and/or glucose tolerance.^[4,5] The growing evidence suggests that prediabetic patients have a substantially increased risk of CVD and death compared with normal patients.^[10]

Usually, individuals with prediabetes have no apparent clinical symptoms; therefore, great efforts may be needed to identify them early. Also, they needed to intervene against overweight, physical inactivity, and unhealthy diet in pediatric primary care and through public health services as the root causes of insulin resistance.^[21]

Present study was aimed to assess the associations of UA levels with cardiometabolic risk factors in prediabetic individuals with family history of diabetes mellitus. Evidence suggests that family history by itself is most useful for predicting disease when there are multiple family members affected, the relationship among relatives is close, and disease is premature, i.e. it occurs at younger ages than would be expected.^[22] Based on our results, prediabetic persons had significantly higher BMI, UA level, fasting glucose after 0, 30, 60, and 120 minutes, TG, and Alb than normal persons. Also, quartiles of UA level were associated with FBG, TG, BMI, and SBP in both normal and prediabetic persons.

The prevalence of prediabetes in study population was 47% using the ADA criteria, which was similar to 40.9% of the study subjects in a recent community-based cross-sectional study in Oman.^[20] The prevalence in our study is more than other studies in China,^[23] Malaysia,^[21] and Turkish adults.^[24] Differences between reported studies is due to different study population and diagnostic criteria, which individuals with family history of diabetes mellitus were assessed in present study compared with general population in other studies.

It is reported that in men and women from the general population, UA levels were significantly associated

Table 3: Comparison of investigated variables in UA level quartiles separately in each gender in 302 prediabetic subjects

UA (n)	Male (n = 77)				P	Female (n = 225)				P
	Q ₁ (2)	Q ₂ (2)	Q ₃ (13)	Q ₄ (60)		Q ₁ (67)	Q ₂ (63)	Q ₃ (60)	Q ₄ (35)	
Age	41±2.8	42.5±2.1	43.8±6.6	44.6±7.2	0.87	43.9±5.1	44.2±6.5	45±6.4	45.2±7.7	0.69
BMI (kg/m ²)	27	26±7.8	29.6±2.5	28.4±3	0.39	29.1±4.1	29±4	31.1±4.6	30.4±5	0.02
FBG 0 (mg/dl)	111.5±4.9	104.5±2.1	107.8±10.2	106.5±8.2	0.8	101.7±9.5	103.6±9.1	106±9.4	100.7±9.9	0.022
FBG 30 (mg/dl)	143±46.7	164.5±34.6	161.2±31.7	165.2±29	0.76	149.7±29.5	154.3±31	156.3±27.4	148.8±27	0.53
FBG 60 (mg/dl)	131±120.2	171.5±109.6	163±31.3	184.6±37.9	0.14	163.8±38.6	171.5±40.2	167.3±43.5	183.4±38.5	0.14
FBG 120 (mg/dl)	135.5±40.3	125±14.1	119.3±35.5	124±32.7	0.92	138.2±30.1	143.7±30	139.4±34	147.2±28.1	0.47
SBP (mmHg)	100	122.5±3.5	122.5±11.3	118.2±15.7	0.24	118.6±1.65	117.75±1.52	12.03±1.63	12.15±1.25	0.59
DBP (mmHg)	70	80	83.3±12.2	80.6±10.8	0.45	78.5±1.05	78.7±1.06	7.95±0.91	7.9±0.89	0.95
HbA1c (%)	5.0±0.98	5.0±0.84	5.13±0.42	5.42±0.70	0.37	5.39±0.79	5.37±0.86	5.44±0.63	5.52±0.76	0.82
TG (mg/dl)	284.5±304.8	322.5 ±293.4	170.3±54.5	214.5±115.6	0.25	146.1±104.2	156.8±83.8	180.6±87.2	189.8±86.7	0.057
TC (mg/dl)	208.5±82.7	209±42.4	198.1±37.1	194.6±48.6	0.95	195.9±38.8	200.7±27.5	211.8±33.8	217±37.5	0.007
HDL (mg/dl)	38.5±4.9	41±11.3	35.1±5.2	36.1±10.4	0.85	45.1±11.3	43.8±11.1	46.3±12.5	47.2±13.5	0.51
Alb (g/dl)	17.5±14.4	1.1	10.1±6.4	12.5±10.4	0.48	13.3±9.9	10.9±7.8	11.5±8.6	11.2±10.6	0.44
Cr (mg/dl)	0.25±0.16	0.05	0.22±0.15	0.24±0.11	0.46	0.21±0.11	0.2±0.1	0.2±0.09	0.19±0.11	0.81
Alb/Cr	64.5±17.5	22	46.7±18.9	54.5±48.9	0.82	62±6.27	53.6±34	58.3±37.3	60.7±61.7	0.61

Data expressed as mean ± SD or number (percent). P-values calculated by ANOVA or Kruskal-Wallis test. SBP and DBP = Systolic and Diastolic blood pressure; HbA1c = Hemoglobin A1c; UA = Uric acid; Cr = Creatinine; Alb = Albumin; BMI = Body mass index; FBG = Fasting blood glucose; TC = Total cholesterol; TG = Triglycerides; HDL-C = High-density lipoprotein-cholesterol; LDL-C = Low-density lipoprotein-cholesterol; SD = Standard deviation; ANOVA = Analysis of variance

Table 4: The relationship between UA and prediabetes

	All subjects	Males	Females
UA (crude model)			
OR (95% CI)	1.2 (1.07-1.36)	1.3 (1.02-1.69)	1.32 (1.12-1.58)
P-value	0.002	0.035	0.001
UA (adjusted for age)			
OR (95% CI)	1.19 (1.06-1.34)	1.29 (1.007-1.66)	1.33 (1.12-1.59)
P-value	0.004	0.044	0.002
UA (adjusted for age and BMI)			
OR (95% CI)	1.16 (1.03-1.31)	1.25 (0.95-1.62)	1.26 (1.04-1.51)
P-value	0.016	0.11	0.016

UA = Uric acid; BMI = Body mass index; OR = Odds ratio; CI = Confidence interval

with different categories of impaired glucose regulation independent of known metabolic risk factors and lifestyle variables. In women the associations were more pronounced than in men.^[21] It could be shown that prediabetic subjects had higher UA levels than normoglycemic subjects. Other study demonstrated that UA levels were higher in prediabetic subjects than in nondiabetics.^[25-28] Despite the different study population, in agreement to other studies in the present investigation, prediabetic persons with family history of diabetes mellitus had also higher UA levels than NGT persons with family history of diabetes mellitus. In a prospective, observational analysis by Krishnan *et al.*,^[28] the association between UA level and prediabetes endpoints was assessed and authors suggested that UA levels can be a useful predictor. Similarly, we find that UA level is in relation with prediabetes and can be a useful predictor.

In the present study, other biochemical parameters such as BMI, FBG after 0, 30, 60, and 120 min, TG, and Alb were also relatively higher in subjects with prediabetes. It is largely unknown whether there are gender-specific differences regarding the association between UA and prediabetic states. Our findings showed that BMI, FBG, and TC were associated with quartiles of UA level in prediabetic persons. Other study reported that in all normal and prediabetic groups, women had a significantly lower SBP than men, whereas DBP was significantly higher in men only in the normal groups.^[24] In contrast, in our study SBP and DBP were not significantly different between than prediabetic males and females. Totally, the present study is based on a cross-sectional survey, which is unable to determine causality or the temporal relationship between CVD risk factors (such as obesity and hypertension,) and prediabetes.

Meisinger *et al.*,^[11] in a multivariable adjusted multinomial regression analysis showed that UA concentration was significantly associated with glucose status of groups; also they reported that high UA levels were associated with glucose intolerance among women. However, this was not the case in men. Authors in this study believed that it

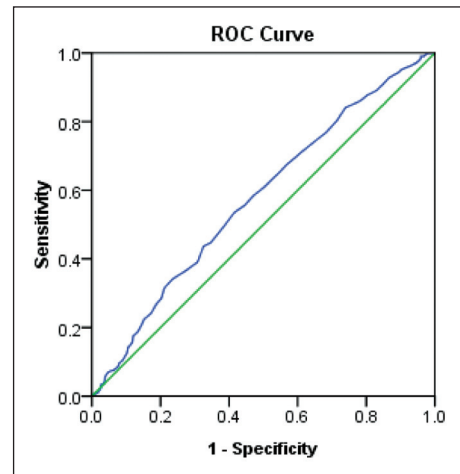


Figure 1: The ROC analysis for evaluating the prognostic value of UA. ROC = Receiver operating characteristic, UA = Uric acid

seems UA had a high specificity for men and women with prediabetic states. Our findings after logistic regression analysis, similar to Meisinger *et al.*,^[11] study revealed that UA concentration was significantly associated with prediabetes. Also our study showed UA levels were associated with prediabetes in two genders significantly after age adjustment. Our prediabetic subjects had high risk factors, also, this is not to be unexpected because prediabetes is a prelude to type 2 diabetes mellitus and is also associated with various comorbidities, which has been termed metabolic syndrome. The clustering of risk factors indicates the need of cardiometabolic risk reduction in prediabetes through primordial prevention. Recent studies showed that lowering UA level by medication such as allopurinol-improved cardiovascular risk factors and endothelial function and UA reduction contributes to attenuation of cardiovascular risk.^[29] A recent cohort study of hyperuricemic patients reported that the use of allopurinol was associated with a 23% lower all-cause mortality rate.^[30] However, larger clinical trials with longer follow-up periods are still needed to determine the safety and efficacy of urate-lowering therapy such as allopurinol in CVD.^[31]

One of the limitations of our study is that because of the cross-sectional design, the temporal and causal association cannot be assessed, and many confounding factors could affect the results despite the multivariate analysis. Further prospective population-based trials are needed to investigate the association between UA levels with cardiometabolic risk factors in prediabetic individuals.

In summary, our findings suggest that higher UA levels are associated with some cardiometabolic risk factors in prediabetic individuals compared with normal person with history of first diabetes in first-degree relatives; also, UA level was a significant predictor for prediabetic individuals.

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REFERENCES

- Esfahani MA, Jolfaii EG, Torknejad M, Etesampor A, Amiz FR. Postprandial hypertriglyceridemia in non-diabetic patients with coronary artery disease. *Indian Heart J* 2004;56:307-9.
- Yamaoka-Tojo M, Tojo T, Takahira N, Matsunaga A, Aoyama N, Masuda T, *et al.* Elevated circulating levels of an incretin hormone, glucagon-like peptide-1, are associated with metabolic components in high-risk patients with cardiovascular disease. *Cardiovasc Diabetol* 2010;9:17.
- American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35(Suppl 1):S64-71.
- Levitzyk YS, Pencina MJ, D'Agostino RB, Meigs JB, Murabito JM, Vasana RS, *et al.* Impact of impaired fasting glucose on cardiovascular disease: The framingham heart study. *J Am Coll Cardiol* 2008;51:264-70.
- Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, *et al.* Atherosclerosis Risk in Communities Investigators. Identifying individuals at high risk for diabetes: The atherosclerosis risk in communities study. *Diabetes Care* 2005;28:2013-8.
- Pour OR, Dagogo-Jack S. Prediabetes as a therapeutic target. *Clin Chem* 2011;57:215-20.
- Taba'k AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Pre-diabetes: A high-risk state for diabetes development. *Lancet* 2012;379:2279-90.
- Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, *et al.* Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: The framingham heart study. *Arterioscler Thromb Vasc Biol* 2007;27:127-33.
- Wang T, Bi Y, Xu M, Huang Y, Xu Y, Li X, *et al.* Serum uric acid associates with the incidence of type 2 diabetes in a prospective cohort of middle-aged and elderly Chinese. *Endocrine* 2011;40:109-16.
- 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.
- Meisinger C, Koenig W, Baumert J, Doring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population — The MONICA/KORA cohort study. *Arterioscler Thromb Vasc Biol* 2008;28:1186-92.
- Mankovsky B, Kurashvili R, Sadikot S. Is serum uric acid a risk factor for atherosclerotic cardiovascular disease?: A review of the clinical evidence. Part 1. Diabetes and Metabolic Syndrome. *Clin Res Rev* 2010;4:176-84.
- Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005;112:3066-72.
- McNeill AM, Katz R, Girman CJ, Rosamond WD, Wagenknecht LE, Barzilay JI, *et al.* Metabolic syndrome and cardiovascular disease in older people: The cardiovascular health study. *J Am Geriatr Soc* 2006;54:1317-24.
- Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program *et al.* Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007;30:8-13.
- Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, *et al.* Hypothesis: Could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009;30:96-116
- Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, *et al.* Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009;32:1737-42.
- Kim ES, Kwon HS, Ahn CW, Lim DJ, Shin JA, Lee SH, *et al.* Serum uric acid level is associated with metabolic syndrome and microalbuminuria in Korean patients with type 2 diabetes mellitus. *J Diabetes Complications* 2011;25:309-13.
- Amini M, Janghorbani M. Diabetes and impaired glucose regulation in first degree relatives of patients with type 2 diabetes in Isfahan, Iran: Prevalence and risk factors. *Rev Diabet Stud* 2007;4:169-76.
- Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, *et al.* Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160-7.
- Mustafa N, Kamarudin NA, Ismail AA, Khir AS, Ismail IS, Musa KI, *et al.* Prevalence of abnormal glucose tolerance and risk factors in urban and rural Malaysia. *Diabetes Care* 2011;34:1362-4.
- Yang Q, Liu T, Valdez R, Moonesinghe R, Khoury MJ. Improvements in ability to detect undiagnosed diabetes by using information on family history among adults in the United States. *Am J Epidemiol* 2010;171:1079-89.
- Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, *et al.* China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090-101.
- Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dincag N, *et al.* TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and pre-diabetes in Turkish adults. *Eur J Epidemiol* 2013;28:169-80.
- Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H. Plasma uric acid level and its association with diabetes mellitus and some biological parameters in a biracial population of Fiji. *Am J Epidemiol* 1988;127:321-36.
- Whitehead TP, Jungner I, Robinson D, Kolar W, Pearl A, Hale A. Serum urate, serum glucose and diabetes. *Ann Clin Biochem* 1992;29:159-61.
- Nan H, Qiao Q, Söderberg S, Pitkaniemi J, Zimmet P, Shaw J, *et al.* Serum uric acid and incident diabetes in Mauritian Indian and Creole populations. *Diabetes Res Clin Pract* 2008;80:321-7.
- Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168:1104-10.
- Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811-21.
- Luk AJ, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricemic patients. *Rheumatology (Oxford)* 2009;48:804-6.
- Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2010;62:170-80.

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