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Correlation among Biochemical Profile Markers and Diagnostic Value of Uric Acid Level to Differentiate between Glucose Abnormalities

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EK and BI designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Author KT managed the analyses of the study. Author MA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The current study aims to compare the relationship among uric acid level, fasting blood glucose, 2-hour glucose, HbA1C and diagnostic value of uric acid level with diabetes and Pre-diabetes in healthy people and patients with pre-diabetes and diabetes.
Study design: It is a descriptive – analytical study.
Methodology: This study composed of a total of 1080 participants classified into three groups (n = 360) including healthy people (HbA1C<5.6 and fasting plasma glucose<100 mg/dl), prediabetic (5.7%≤ HbA1C<6.5% and 100 mg/dl < fasting plasma glucose < 126 mg/dl) and diabetic patients (HbA1C≥6.5 and fasting plasma glucose ≥126 mg/dl) presented at Endocrinology and Metabolism Research Center in Isfahan, during 2008 – 2013. The parameters including gender, BMI, blood pressure, fat level, fasting plasma glucose, 2-hour postload glucose, HbA1C and serum uric acid

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were recorded and analyzed with SPSS (Ver. 20).
Results: Mean uric acid levels of healthy, prediabetic and diabetic groups were 4.89±1.37 mg/dl , 5.21±1.29 mg/dl and 5.01±1.44 mg/dl respectively, indicating a significantly higher level in prediabetic group (P<0.001). Blood sugar levels had a significant increase in healthy people (P<0.001) compared to other groups. Serum uric acid was positively correlated with fasting plasma glucose and HbA1C in general but weak in prediabetic and healthy subjects versus a negative correlation in the diabetic group. In addition, serum uric acid cut-off (≥4.75 mg/dl) can be a good diagnostic criterion for pre-diabetes prediction compared with normal people (P<0.05).
Conclusion: Although serum uric acid is not a target for the treatment of asymptomatic hyperuricemia and not a risk marker of clinical activities, it may be considered as a new therapeutic target for prevention of diabetes or its progression.

Keywords: Pre Diabetes; diabetes; serum uric acid; 2-hour Post load Glucose; fasting plasma Glucose; HbA1C.

1. INTRODUCTION

Hyperglycemia is called Pre-diabetes when it does not meet the criteria to be diagnosed as diabetes mellitus [1]. Pre-diabetic patients are at high risk for developing diabetes in the future based on impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or impaired HbA1c (IHbA1C), so that 70 percent of them develop type II diabetes within 10 years [2]. On the other hand, Pre-diabetes condition express no clear clinical sign and with respect to content, early diagnosis is required.

In this regard, laboratory methods, such as Fasting Plasma Glucose (FPG), oral glucose tolerance test (OGTT) and recently HbA1C are used to diagnose diabetes [3-7]. The most common method is to measure blood sugar. Increased 2-hour Postload Glucose (2-h PG) usually occurs before FPG and it has been used as a Gold-Standard for diagnosis of diabetes for many years [7].

Also, to diagnose Pre-diabetes and diabetes status, measuring HbA1C is used; The results of some studies suggest that using HbA1C alone has low sensitivity and high specificity to diagnose diabetes and Pre-diabetes compared to glucose level measurement, but there are problems to diagnose Pre-diabetes condition by HbA1C [8].

Some recent studies have shown that there is a significant correlation between the two-hour blood glucose and serum uric acid (SUA) to detect Pre-diabetes condition. Uric acid is the oxidation (breakdown) end product of purine metabolism and potentially benefits from both oxidant and antioxidant properties depending on the surrounding microchemical environment [9,10]. Increased uric acid levels is a risk factor for arterial complications [11,12], metabolic syndrome components, and insulin resistance [13].

On the other hand, type II diabetes is strongly associated with hyperuricemia and low levels of SUA is associated with a lower incidence of type II diabetes [14]. According to some studies, up to 7 mmol increase in FPG was associated with increased SUA levels. But the reduced SUA was observed in 2-h PG concentrations of ≥10 mmol/l. There is an upward trend in SUA concentration in the concentration of 2-h PG <10 mmol/l. Reduction in SUA concentration has been observed in concentrations of 2-h PG ≥10 mmol/l [14]. In Pre-diabetic patients (IFG or IA1C), the SUA is directly associated with 2-h PG and independently with FPA, HbA1c and the other risk factors. SUA is directly associated with 2-h PG and it is dependently in association with FPA, HbA_1c and another risk factors in Pre-diabetic patients (IFG or IA_1C). SUA levels have a clear impact on the development of diabetes in patients with IFG or IA_1C so that 1SD (1.53 mg / dl) increase in SUA is a warning for 36 percent increase in the risk of diabetes [9].

Taking into account abovementioned studies and what was stated in this respect, The current study attempts to determine the strength of existing relationship between uric acid and blood sugar levels, in healthy subjects, Pre-diabetic (including IFG, IGT and IA1C) and diabetic patients by eliminating uric acid-lowering agents (such as Allopurinol, diuretics, corticosteroids, warfarin) as well as uric acid-increasing agents (such as alcohol, aspirin, levodopa, phenothiazines), and evaluate the predictive value of uric acid levels for diabetes and Pre-diabetes.

2. MATERIALS AND METHODS

This descriptive – analytical study conducted on a population composed of all people presenting at Endocrinology and Metabolism Research Center in Isfahan during 2008 – 2013. Sample size was calculated as 360 using sample size formula for correlation studies with %95 of confidence interval, test power of 80% and the correlation coefficient of 0.13 between SUA and FPG. Subjects were divided into three groups (n = 360) of healthy people, Pre-diabetes and diabetes.

Inclusion criteria in healthy subjects were as follows: FPG <100 mg/dl, 2-h PG <140 mg/dl, HbA_1A <5.6% and it was considered in Pre-diabetic group as 100 mg / dl <FPG <126 mg / dl and 5.7% ≤ HbA_1A <6.4%. Exclusion criteria were hyperuricemia (women SUA≥6 mg/dl and men SUA≥7 mg/dl) and taking uric acid level modifiers such as anti-hypertensives, allopurinol, aspirin, corticosteroids, levodopa, phenothiazines, Nicotinic acid, and Clofibrate, history of alcohol consumption (once in the past year) or smoking (at least once a day).

All subjects were weighted by Seca weight scales with a precision of 100 gr. Height was calculated with Secastodiometer in anatomy standing positions and BMI was calculated by dividing weight in terms of kg per height in meters (kg/m^2). Blood pressure was specified after measurement by expert from the right hand after 5 minutes of rest using a Japanese Rester mercury sphygmomanometer in case of 140 mmHg <SBP or 90 mm Hg <DBP and the use of anti-hypertensive. History of smoking (at least once a day) and alcohol consumption (once a week over the past year) were recorded through a written questionnaire that was given to the subjects.

History of drugs that affect SUA such as aspirin, nicotinic acid, Levodopa, corticosteroids, allopurinol and Clofibrate were asked via phone calls.

Lipid Profile was defined after 12 hours of fasting including TG, Total Cholesterol, LDL and HDL that was measured using Pars Azmoon kit.

SUA and blood glucose levels were measured with Pars Azmoon kits as SUA<7 mg/dl for male and SUA<6 mg/dl for female, and FPG <100 mg/dl, 2-h PG <140 mg/dl, and HbA_1C<5.7%.

2.1 Statistical Analysis

The collected data were analyzed with SPSS software (Ver. 20). Statistical tests including one way ANOVA, independent samples t test, Pearson correlation coefficient, multiple linear regression, Logistic regression and ROC analysis were used. A p-values of less than 0.05 were considered.

3. RESULTS AND DISCUSSION

The present study was conducted on 1080 individuals in three groups of healthy subjects (n = 360), diabetes (n = 360) and Pre-diabetes (n = 360).It showed that the three groups are matched in gender and age (P value> 0.05). On the other hand, a significant difference was found among the three groups in the factors of HbA_1C, 2-h PG, FPG, Triglycerides, HDL, SBP, DBP, BMI (P <0.001) , cholesterol (P value = 0.026) and SUA (P value = 0.007). The levels of HbA_1C, blood glucose and fasting plasma glucose in healthy subjects showed the lowest values, while the highest values was observed in diabetic group, but uric acid levels in normal group with the mean of 4.89 ± 1.37 mg/dl was at the lowest level, and it was at the highest level in Pre-diabetic group with the mean of 5.21 ± 1.29 mg/dl (P value = 0.007) (Table 1).

In addition, as shown Fig. 1, the mean value of uric acid in women was higher than men in three groups. So, in both genders, the uric acid levels increased from healthy group to pre-diabetic group, and reduced from Pre-diabetes to diabetes. This difference was statistically significant (P value in Female: 0.030 and Male: 0.006).

In addition, estimating the predictive value of uric acid levels for diabetes and Pre-diabetes using ROC analysis showed uric acid is not proper diagnostic criterion (Comparing with normal: Area = 0.536, P value = 0.348, Comparing with Pre-diabetes: Area = 0.536, P value = 0.359), but it can be good diagnostic criterion to predict Pre-diabetes compared to normal screens (area = 0.574, P value = 0.001. The critical point (Cut off) was considered as >4.75 mg/dl with sensitivity and specificity of 0.640 and 0.536, respectively (Fig. 2).

Results of regression analysis (Multiple linear regression) showed the role of factors influencing blood glucose (2- h PG) in each group. It showed that the gender plays a critical role in variations

in the blood glucose (2- h PG) levels. Hence, the risk of developing diabetes is higher in women than men (in each group; P value = 0.001). The age also plays an important and direct role in changes in blood glucose levels among Pre-diabetics (β±SE = 0.275 ± 0.095; P value = 0.004). It leads to a negative but not significant effect on blood glucose levels in the two groups of healthy and diabetic (P value> 0.05). Also in the diabetic group, factors such as BMI (β±SE=3.010±0.960) and HbA_1C (β±SE=25. 105±3.616) had significant positive impact on blood glucose levels (2-h PG) (P value <0.05), but negative insignificant effect in other two groups (P value> 0.05). On the other hand, the effect of uric acid on blood glucose (2- h PG) in three groups of healthy, Pre-diabetes and diabetes negative but statistically insignificant (P value> 0.05) (Table 2).

Table 1. Demographic and biochemical characteristics of the study population

Variables	Normal (n=360)	Pre Diabetes (n=360)	Diabetes (n=360)	P value
Male gender (%)	203(56.4%)	163(45.3%)	114(31.4%)	0.573
Age, years	43.24±6.05	44.21±6.40	45.92±5.57	0.053
BMI, kg/m^2	28.04±4.44	29.43±4.11	29.86±4.88	<0.001
SBP, mmHg	110.79±1.49	110.85±1.54	120.74±1.63	<0.001
DBP, mmHg	70.87±0.98	70.91±1.04	80.42±0.92	<0.001
HDL, mmol/L	46.38±12.70	42.78±11.83	43.08±10.56	<0.001
LDL, mmol/L	124.21±31.91	124.71±30.71	130.81±34.59	0.297
Triglycerides, mmol/L	142.71±94.93	177.66±101.17	185.83±88.22	<0.001
Cholesterol, , mmol/L	198.41±37.50	202.29±38.25	211.88±41.71	0.026
SUA, mg/dl	4.89±1.37	5.21±1.29	5.01±1.44	0.007
FPG, mg/dl	90.63±6.21	104.34±9.50	149.83±48.66	<0.001
2-h PG, mg/dl	101.94±20.52	136.78±32.11	246.69±74.99	<0.001
HbA_1C(%)	5.11±0.56	5.39±0.73	6.60±1.41	<0.001

Data were expressed as mean ± SD or frequency (%). Means and proportions were compared by ANOVA and Chi Square test, respectively. P values testing the overall difference among normal, Pre-diabetic and diabetic groups

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; FPG: Fasting Plasma Glucose; 2-h PG: 2-Hour Postload Glucose; SUA: serum uric acid

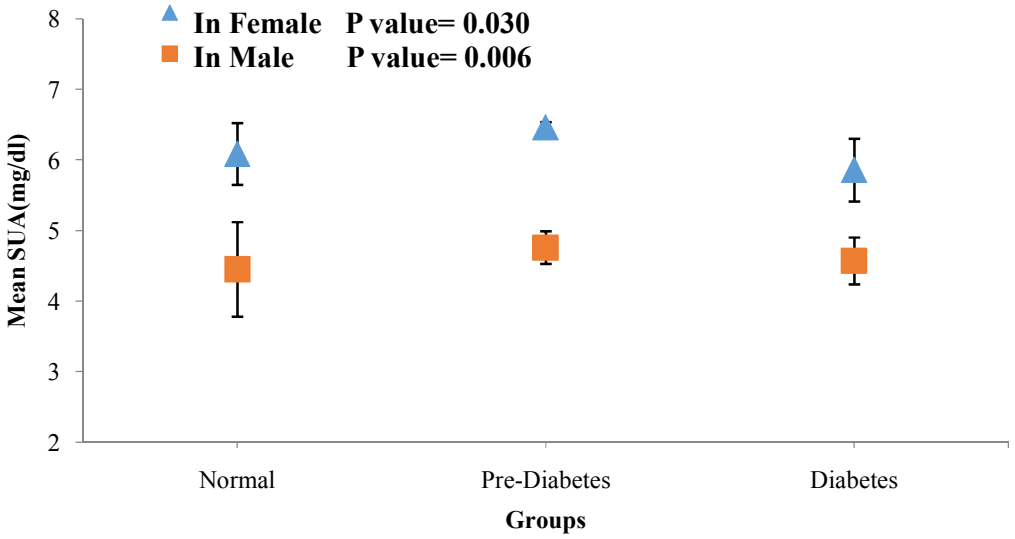

Fig. 1. Comparing the mean serum level of uric acid based on gender in three groups

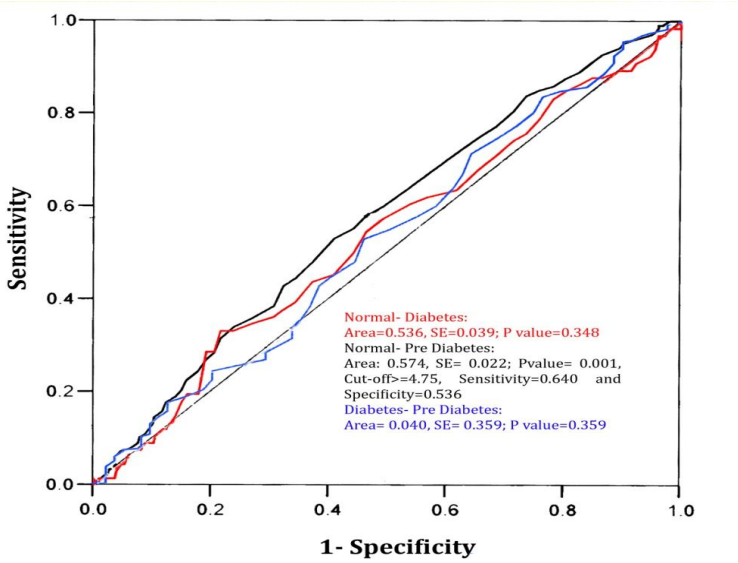

Fig. 2. ROC curves illustrating the diagnostic capability of uric acid to predict diabetes and Pre-diabetes

Table 2. Multiple linear regression analysis between 2-h PG and different covariates in three groups

Factors	Normal (n=360)		Pre-Diabetes (n=360)		Diabetes (n=360)	
	β±SE	P	β±SE	P	β±SE	P
Sex	3.23±0.984	0.001	5.872±1.756	0.001	7.460±13.240	0.001
Age, years	-0.010±0.061	0.876	0.275±0.095	0.004	0.484±0.837	0.566
BMI, kg/m^2	0.171±0.052	0.052	0.272±0.143	0.059	3.010±0.960	0.003
Smoking	2.134±1.208	0.078	2.31±2.370	0.331	7.768±18.029	0.669
SBP, mmHg	0.273±0.355	0.442	0.089±0.592	0.881	1.109±4.714	0.815
DBP, mmHg	0.508±0.548	0.355	0.246±0.869	0.777	0.759±8.290	0.927
SUA, mg/dl	-0.306±0.307	0.319	-0.001±0.565	0.999	-0.964±3.732	0.801
HbA_1C(%)	0.860±0.616	0.164	1.427±0.773	0.066	5.105±3.616	<0.001

Multiple linear regression analysis was performed to investigate the determinants of 2-h PG, after adjustment for gender, age, smoking, BMI, SBP, DBP, SUA, and HbA1c. Values were regression coefficient (β) ± standard error (SE). Abbreviate shown BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; SUA: serum uric acid.

Table 3. Association between serum uric acid level and diabetes

Groups	SUA*	Totally odds ratio (95% confidence interval)	Age, Sex and BMI adjusted odds ratio (95% confidence interval)	Multivariable adjusted odds ratio(95% confidence interval)ϒ
Normal	Q1	Referent	Referent	Referent
versus	Q2	0.866(0.453, 1.657)	0.689(0.343, 1.383)	0.763(0.299, 1.944)
Diabetes	Q3	1.359(0.726, 2.546)	0.998(0.467, 2.135)	0.789(0.271, 2.293)
Normal	Q1	Referent	Referent	Referent
versus Pre-	Q2	1.576(0.814, 3.051)	1.364(0.936, 1.986)	1.262(0.832, 1.915)
diabetes	Q3	1.302(0.691, 2.453)	1.118(1.323, 3.390)	1.021(1.150, 2.767)
Pre-diabetes	Q1	Referent	Referent	Referent
versus	Q2	1.688(0.853, 3.338)	1.460(0.655, 3.256)	1.841(0.781, 4.339)
Diabetes	Q3	1.837(0.858, 3.088)	1.667(0.667, 4.164)	1.975(0.752, 5.185)

*Used of Logistic regression; *Serum uric acid quartiles: <4.4 mg/dL, 4.40–5.50 mg/dL, >5.50mg/dL.*
ϒAdjusted for age, sex, BMI, TG, Chol, LDL, HDL, SBP, DBP, HbA_1C

Table 3 has been suggested the association between increased serum uric acid levels and diabetes in the three study groups. As shown, compared to the first quartile of uric acid (referent), with increasing levels of uric acid the risk of diabetes decreased, and risk of pre-diabetes increased, so that OR was reported as 1.118% with adjustment of age, sex and BMI and as 1.021% with multivariable adjusted (P value <0.05).Pre-diabetes with higher levels of uric acid has more chances of diabetes compared to diabetes, but expressed relationships were not statistically significant (P value> 0.05) (Table 3).

3.1 DISCUSSION

The results of the study on three groups of normal, Pre-diabetes and diabetes showed that on average, higher levels of factors including blood pressure, HDL, LDL, triglycerides, cholesterol, blood glucose and HbA1C were observed in diabetic patients than Pre-diabetes and Pre-diabetes than normal subjects. In contrast, serum uric acid levels in prediabetic patients were higher than normal and diabetic subjects. In other words, uric acid levels were significantly higher in Pre-diabetics than diabetics. In line with this study, Sadhindra Rao et al. (2012) showed SUA levels were higher in Pre-diabetics than healthy group [15]. Also, some studies reported lower levels of uric acid in diabetic subjects [16,17], whose levels were higher in Pre-diabetes than to normal subjects [18].

Moreover, the study of 1080 cases indicated that SUA was positively correlated with HbA_1C and FPG while SUA was negatively correlated with 2-h PG. With medical condition adjustment of diabetes, in Pre-diabetic patients, a significant positive correlation between SUA and FPG, an insignificant positive between SUA and HbA_1C, as well as an insignificant negative correlation between SUA and 2-h PG were found whereas in diabetic group, SUA was weakly and negatively correlated with FPG, 2-h PG and HbA_1C.

Although the assumed relationship between serum uric acid and diabetes has not been proven, some studies have reported a positive correlation between high levels of uric acid and diabetes [19-21]. While others reported no relationship [16] or have reported inverse negative correlation [17,22]. The precise reason why previous studies have found a positive correlation between uric acid and diabetes is unclear. The majority of these studies were limited by small sample size, or participation of just males or females (not both genders) in the study and/or existing unadjusted confounders such as the uric acid-increasing and lowering drugs, which have been especially considered in the current study. Observation of acceptable negative correlation between SUA and diabetes in this study may be due to the possible mechanism to prevent reabsorption of uric acid from proximal tubule in high levels of glucose in people with diabetes [23,24].

SUA status in terms of gender suggested that uric acid levels were generally higher in women than men and the highest levels of SUA were observed in the Pre-diabetic group in both genders. Consistent with the current study, many studies identified the lower level of SUA in men compared to women, although these differences have not been proved by all studies [9,19].

On the other hand, identification of risk factors affecting 2-h PG in three study groups showed such factors as smoking and blood pressures play no significant role in 2-h PG variations, but the risk of high 2 h PG could be increased with BMI in diabetic group, and higher 2-h PG levels were observed among older Pre-diabetic patients. In addition, SUA had an inverse weak effect on 2-h PG in three groups, and HbA_1C had a direct effect on 2-h PG, which is considerable and significant in diabetes group (with higher blood glucose levels). Also, gender is an effective factor on 2-h PG, so that women had higher 2-h PG level compared to men. In this regard, Fan et al. (2013) found consistent results in identifying risk factors affecting 2-h PG showing that blood pressure, smoking history, blood fat and triglycerides play no significant role in the 2-h PG, but inconsistent with the current study, they found a strong significant role of SUA in 2-h PG [9].

For instance, in the Qingdao study [22], SUA was negatively and significantly correlated with 2-h PG at the higher range of the 2-h PG distribution (2-h PG ≥144 mg/dl), but not at the normal range of 2-h PG. However, in another clinical study, SUA was significantly and positively correlated with 2-h PG at the normal range of 2-h PG in non-diabetics Mauritian subjects [25].

On the other hand, uric acid classification and investigation of diabetes or Pre-diabetes chance in the current study showed that chance of diabetes reduced in the third and second quartiles of SUA with adjusting age, sex, BMI,

and other confounding factors, so that the more confounding variables are controlled by chance of diabetes is more reduced. In addition, SUA increase in the third quartile compared to first quartile increase Pre-diabetes chance compared to normal people, and chance is increased in Pre-diabetes with increasing SUA compared to diabetes. Overall control of confounding factors substantially decreases the chance and which was not significant. In line with these findings, some studies suggest that lowering serum uric acid in patients in the highest quartile reduces the incidence of diabetes by 24 percent [26]. Another study on middle-aged men showed that relationship between uric acid and the risk of diabetes was not significant after the adjustments for BMI, alcohol consumption, smoking, physical activity, fasting blood sugar and diabetes history of parents.

Evaluation of SUA diagnostic criterion in diagnosing diabetes and Pre-diabetes showed SUA factor cannot be a suitable diagnostic criterion for identifying diabetes in comparison with healthy or Pre-diabetic people, but it can be acceptable diagnostic criterion for predicting Pre-diabetes compared to normal people, so that uric acid level in pre-diabetes incidence compared to diabetes with Cut off>4.75 and high sensitivity and average specificity. Consistent with the current study, Zhang et al. reported proposed cut-off for SUA in the diagnosis of metabolic syndrome in women as 4.9 mg/dl and as 6.3 mg/dl in men with low sensitivity and high specificity [27].

It has previously been reported that using SUA ≥7.0 mg/dl as a cut-off point for the diagnosis of the Metabolic Syndrome, the sensitivity would be 58.0% and the specificity would be 55.3% in men [28].

As previously stated, OGTT method is not so suitable for prediction of Pre-diabetes or diabetes due to lack of repeatability and heavy cost [7]. But the evaluation methods by uric acid, are widely available at a lower price. In addition, xanthine oxidase inhibitors, which recently are used to reduce serum uric acid, are safe and inexpensive. As a result, our findings in association with the other results of previous studies indicate that lowering uric acid may be a novel therapeutic target for prevention of diabetes.

Now, SUA is significantly correlated with 2-h PG directly and with HbA_1C indirectly (with the intermediary of 2-h PG), this can affect the results. In other words, the diagnostic value of SUA may be influenced by HbA_1C which could not be controlled in this study. The further studies may be required to evaluate the diagnostic value of this parameter or a combination of abovementioned parameters to achieve a proper model differentiating between Pre-diabetes and diabetes.

4. CONCLUSION

Overall the results indicated that SUA could not be an appropriate diagnostic to detect diabetes. However, its capability to detect Pre-diabetes could be more highlighted. The SUA>7.45 mg/dl could be considered as a cutoff point to differentiate between Pre-diabetes and diabetes.

CONSENT

As per international standard or university standard, patients' consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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