Original Article

Effect of Body Mass Index on the Association of Uric Acid and Glycemic Status in Diabetes in South Indian Population

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Abstract

Background and Aim: Currently, there is a need for simple yet affordable marker for monitoring cardiovascular (CV) risk, especially for the poor section of the society. Uric acid (UA) is a routine parameter which has been linked to deterioration in glucose metabolism and CV morbidity separately. However, relationship of UA with glycemic status in participants with different body mass index (BMI) has not been explored. Therefore, the present study aims at evaluation of the metabolic and CV profiles in patients with diabetes mellitus (DM) with different BMIs. **Methods:** The anthropometric, biochemical, and noninvasive CV risk markers of myocardial work stress such as rate pressure product (RPP) were assessed in patients with diabetes with normal ($n = 46$) and high BMI ($n = 80$) compared with healthy age- and gender-matched nondiabetic controls ($n = 43$). **Results:** High BMI diabetic patients alone had increased diastolic blood pressure (DBP) ($P < 0.05$) and RPP ($P < 0.05$) compared to control. Mean fasting serum glucose (FSG) was highest ($P < 0.01$) and UA ($P < 0.05$) was lowest in normal BMI DM patients. Our data show that once DM sets in UA level start rising with rise in FSG and DBP, especially in high BMI DM patients. The myocardial work stress marker RPP was highest in high BMI DM patients, and this was positively associated with increased UA level. The findings of the present study indicate the presence of increased myocardial work stress in DM in the high BMI range which is associated with a steady rise in UA level which is known antioxidant within physiological range. **Conclusion:** Patients with DM with higher BMI should monitor their CV profile more closely, and this can be achieved by monitoring of simple markers such as UA and RPP even in a rural setting in developing countries.

Keywords: Body mass index, myocardial work stress, oxidative stress, rate pressure product

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Introduction

The current load of diabetes in India is 62.4 million as per the Indian Council of Medical Research (ICMR)-Indian diabetic study.[1] Cardiovascular disease (CVD) and diabetes mellitus (DM) are two major health problems in India.[2,3] Several factors such as insulin resistance, dyslipidemia, hypertension, and inflammation have been cited as the mechanisms linking diabetes with CVD.[3] It is a major cause of mortality and morbidity worldwide, and DM is one of its well-established risk factors.[4] However, as CVD is a multifactorial disease affecting people from all strata of the society, one has to look at various other parameters other than the worsening glycemic status alone in a patient with diabetes.[3] DM being a strong risk factor for CVDs requires adequate monitoring of these patients.

There are several traditional as well as newer biomarkers for the assessment of cardiac health profile. However, the poor and underdeveloped section of the society and the rural health-care services may not be able to afford them routinely. Therefore, despite revolution in the cardiac health care, there still remains the need of simple yet cost-effective markers for routine health monitoring. Recently, a simple biochemical parameter such as serum uric acid (UA) has been cited as a potential biomarker of deterioration in glucose metabolism.[5] It was also associated with CV morbidity, and the underlying mechanism was proposed as inflammation.[6,7] However, the relationship of UA with glycemic status is not a linear one, and results are also controversial.[5,8] Therefore, higher UA in case

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of patients with Type 2 DM even within normal range can be more harmful compared to nondiabetic individual. There is a high prevalence of DM among South Indians.[9] Thus, in our study, we wanted to revisit this relationship in patients with diabetes in South Indian population.

Rate pressure product (RPP) is a derived parameter calculated from systolic blood pressure (SBP) and heart rate. Increased resting heart rate and RPP have been established as CV risk.[10] UA was strongly linked in conditions with high body mass index (BMI) such as obesity and metabolic syndrome.[11] However, the effect of BMI on this relation has not yet been explored in the previous reports. As noninsulin-dependent diabetes mellitus is characterized by hyperinsulinemia, obesity, and vascular abnormalities, we may deduce that the risk of CVD in patients with diabetes may increase when both hyperglycemia and obesity coexist and altered UA level might be a reflection of this risk.

To the best of our knowledge, no work has been done to analyze the effect of BMI on the interrelationship among UA and fasting glucose in patients with diabetes of India. Therefore, in the present study, we evaluated the metabolic and CV profiles in patients with DM with different BMIs. We also wanted to analyze the link of UA with CV risks in patients with DM and compare with age- and gender-matched healthy nondiabetic controls.

Materials and Methods

Subjects

In this cross-sectional study, after obtaining the approval of Institute Scientific and Ethics Committees, we screened the population of 200 participants within the age range of 30–65 years using consecutive sampling process. The study setting was in the Medicine Outpatient Department (OPD), PIMS. The patients were identified and recruited in the OPD. The participants were divided into three groups based on fasting serum glucose (FSG) and BMI. Group 1 consisted of healthy nondiabetic controls with normal BMI and fasting glucose (BMI <23 kg/m^2 and fasting blood sugar [FBS] <100 mg/dL), Group 2 consisted of patients with DM with normal BMI (BMI <23 kg/m^2 and FBS ≥100 mg/dL), and Group 3 consisted of DM patients with high BMI (BMI ≥23 kg/m^2 and FBS ≥100 mg/dL). The BMI cutoff was decided based on the new criteria of BMI for Asians (WHO expert consultation, 2004).[12]

Healthy volunteers who consented to be a participant in our study were enrolled into our control group. After obtaining their height, weight, BP, and heart rate, their BMI was calculated. Those volunteers whose BMI was <23 kg/m^2 were selected by us. Later, based on their FSG, we chose only those participants whose serum glucose was <100 mg/dL.

Individuals with a history of smoking, alcoholism, DM, CVD, renal disorder, inflammatory diseases, and pregnant or lactating women were excluded from the study. The participants were asked to report to the laboratory after 8–12 h of fasting for fasting blood sample collection. The study protocol was explained to all the participants in their vernacular and informed written consent was obtained from all before starting the study procedures.

Anthropometric measurements and blood collection

Participants were asked to report to the medicine OPD, Pondicherry Institute of Medical Sciences, following overnight fasting. The participants were asked to sit in a chair comfortable for 5 min. Height and weight of the participants were measured to calculate BMI. Their SBP and diastolic BP (DBP) and heart rate were recorded using a standard protocol. Fasting blood was collected by venipuncture from all the venipuncture under aseptic conditions. The serum was separated and sent for routine biochemical analysis.

Estimation of glucose was done using commercial kits adapted to clinical chemistry autoanalyzer by Hexokinase method (Roche Diagnostics, Roche) in the autoanalyzer (Integra 400 plus, Roche Diagnostics). UA was estimated by Uricase/peroxidase method (Beacon Diagnostics Pvt. Ltd.,) in the semi-autoanalyzer (Merck 300, Merck).

Measurement of blood pressure and rate pressure product

The participant was asked to sit comfortably down on a couch inside laboratory of Medicine Department. Their SBP and DBP and basal heart rate (BHR) were measured using an automated BP monitor. The SBP and DBPs and heart rate were noted from the display monitor of the equipment, and RPP was calculated using the formula, RPP = Systolic pressure × BHR × 10^{-2}.[10]

Statistical analysis

SPSS version 16 (SPSS Software Inc., Chicago, IL, USA) software was used for statistical analysis. All the data were presented as a mean ± standard deviation. Normality of data was tested by Kolmogorov–Smirnov test. Comparison between the difference in continuous variables test and control groups was done by Student's *t*-test for parametric data and by Mann–Whitney test for nonparametric data. The association of quantitative data of anthropometric, biochemical, and physiological parameters was done by Pearson correlation analysis. All statistical analyses were performed at 5% level of significance and $P < 0.05$ was considered statistically significant.

Results

There was no significant difference in the distribution of number and gender among the participants in the three groups [Table 1]. There was no difference in the mean age between nondiabetic controls, patients with diabetes with normal and high BMI in our study [Table 2]. As the glucose value was not a criterion to differentiate between Group 2 and 3, the difference between normal and high BMI diabetes groups was noteworthy. We found that the mean FSG was higher, but it did not achieve any statistical significance in Group 2 (Normal BMI DM patients) compared to Group 3 (High BMI

Table 1: Gender distribution analysis by Chi-square test

	Value	Df	Asymp significance (2 sided)	Exact significance (2 sided)	Exact significance (1 sided)	Point Pro-bability
Pearson Chi square	4.021	2	0.134	0.146		
Likelihood ratio	4.058	2	0.131	0.137		
Fisher's exact test	3.987	1	0.399	0.143		
Linear by linear association	0.711			0.439	0.227	0.054
N for valid cases	169					

Table 2: Comparison of various parameters in participants of Group 1 consisting of control subjects (fasting blood glucose <100 mg/dL; body mass index <23 kg/m^2) and test Group 2 (fasting blood glucose <100 mg/dL; body mass index ≥23 kg/m^2) and test Group 3 (fasting blood glucose ≥100 mg/dL; body mass index ≥23 kg/m^2)

Parameters	Group 1 Control (*n*=43)	Group 2 DM with normal BMI (*n*=46)	Group 3 DM with high BMI (*n*=80)	*P*
Age (years)	48.44±16.93	54.30±11.39	49.66±10.22	0.060
BMI (kg/m^2)	20.60±2.30	20.30±2.58	27.62±3.81***,###	0.000
SBP (mmHg)	119.12±14.91	125.26±17.73	126.24±17.73	0.080
DBP (mmHg)	77.42±9.81	80.13±12.14	82.90±9.44*	0.010
RHR (beats/min)	82.65±6.76	84.33±10.83	85.75±10.76	0.260
FSG (mg/dL)	82.53±12.48	194.81±86.52***	166.86±77.52***	0.000
UA (mg/dL)	4.90±2.05	3.91±1.39**	4.04±1.21*	0.004
RPP (bpm × mmHg)	98.93±15.03	105.53±20.28	108.43±21.97*	0.045

Data expressed as mean±SD. Analysis done by one-way ANOVA followed by *post hoc* test by Bonferroni. *P*<0.05 was considered significant; the level of significance between Group 1 and 2 is depicted by the sign *, between Group 2 and 3 by #. RPP=SBP × HR/100. RPP: Rate pressure product, SBP: Systolic blood pressure, SD: Standard deviation, BMI: Body mass index, DBP: Diastolic blood pressure, HR: Heart rate, RHR: Resting heart rate, FSG: Fasting serum glucose, UA: Uric acid, DM: Diabetes mellitus

DM patients). There was a significant decrease in serum UA levels in Group 2 and 3 compared to control group.

Both SBP and resting heart rate (RHR) showed no significant difference among the three groups. However, RPP which is a calculated product of RHR, and SBP was significantly higher in patients with diabetes with high BMI [Table 2]. The DBP of the patients with DM with high BMI was significantly higher than healthy controls. However, it was not different from DM with normal BMI.

The correlation of UA with FSG and various other parameters is shown in Tables 3 and 4. Table 3 shows the correlation in control group and in all patients with DM taken together (Group 2 and 3), whereas Table 4 shows a correlation in all three groups separately.

UA was positively associated with serum SBP and RPP in the patients with diabetes (n = 126). It was statistically more evident in the diabetes patients with higher BMI (Group 3) where UA was linked to SBP, DBP, FSG, and RPP [Table 3].

Table 3: Correlations of serum uric acid with other anthropological and biochemical parameters between healthy control (Group 1), and patients with diabetes (Group 2 and Group 3) by Pearson correlation analysis

Parameters (*n*=43)	*r* (*n*=126)	*P*	*r*	*P*
Age	0.12	0.424	0.08	0.330
BMI	0.05	0.748	0.05	0.573
SBP	0.11	0.462	0.33	0.000
DBP	0.12	0.430	0.14	0.104
RHR	−0.25	0.100	−0.08	0.366
FSG	0.12	0.437	0.12	0.160
RPP	−0.02	0.894	0.18	0.040

P<0.05 was considered significant. RPP: Rate pressure product, SBP: Systolic blood pressure, BMI: Body mass index, DBP: Diastolic blood pressure, HR: Heart rate, RHR: Resting heart rate, FSG: Fasting serum glucose

Discussion

There is a high prevalence of DM among South Indians.[9] Among all the comorbidities associated with diabetes, CVD is the most fatal one considering the fact that it is the cause of more than 50% of mortality incidence among the patients with diabetes.[13] Serum UA has been associated with deterioration in glucose metabolism and[5] CV morbidity.[6,7] However, despite correlating UA level with glucose level or glycated hemoglobin levels, previous authors did not explore the implication of this relation in the absence and presence of BMI higher than the normal range.

This gap in review of literature, led us to our study design where we considered two parameters, namely, FSG and BMI as the basis for grouping of our participants. Therefore, Group 2 and 3 had a higher FSG and BMI than control. In our study, we have considered the Asian criteria for BMI cutoff (23 kg/m^2).[12] However, it was interesting to note that there was no statistically significant difference between the two test

Table 4: Correlations of serum uric acid with other anthropological and biochemical parameters in Group 1, Group 2, and Group 3 by Pearson correlation analysis

Parameters	*r* (*n*=46)	*P*	*r* (*n*=80)	*P*	*r*	*P*
(*n*=43)						
Age	0.12	0.424	0.18	0.227	0.03	0.747
BMI	0.05	0.748	0.03	0.819	0.01	0.872
SBP	0.11	0.462	0.22	0.140	0.41	0.000
DBP	0.12	0.430	0.03	0.844	0.23	0.036
RHR	−0.25	0.100	−0.15	0.301	−0.03	0.740
FSG	0.12	0.437	0.01	0.929	0.22	0.041
RPP	−0.02	0.894	0.04	0.762	0.26	0.018

P<0.05 was considered significant. RPP: Rate pressure product, SBP: Systolic blood pressure, BMI: Body mass index, DBP: Diastolic blood pressure, HR: Heart rate, RHR: Resting heart rate, FSG: Fasting serum glucose

groups that is DM with and without high BMI [Table 3]. This shows that once DM has settled in, the glycemic status may not be influenced much by BMI.

UA was significantly lower in Group 2 and 3 patients [Table 2]. However, there was a more decreasing trend in Group 2 compared to Group 3. Previously, Kukreja *et al*.[14] and Rao *et al*.[15] showed that among prediabetes and diabetes, the UA level was higher in the former group despite lower mean glycated hemoglobin[14] and FSG,[15] respectively. Hence, among their two test groups, the UA was inversely proportional to FSG level. In our study, we found that among normal BMI and high BMI DM patients, UA was more decreased in the former group, but mean FSG was more increased. Therefore, despite having a different study design with previous authors, our findings match in terms of inverse relationship of UA with FSG level for people with FSG ≥100 mg/dL.

UA is considered as the most abundant aqueous phase antioxidant. It can cover up to 60% of free radical scavenging capacity. Therefore, the sharp decrease in mean UA level in contrast to sharp rise in mean FSG level in Group 2 may indicate the oxidative stress load in this group leading to depletion of aqueous phase antioxidants such as UA. On the other hand, UA may not be allowed by the body to cross its normal range. This is so because, above the normal range, UA also can act as a pro-oxidant adding to oxidative stress due to hyperglycemia.[16] Therefore, cells may deplete UA and increase the production of other antioxidants to fight the hyperglycemia-mediated oxidative stress.

Conversely, in Group 3 where the body faces a metabolic challenge in terms of both higher FSG and higher BMI, there was a steady increase in UA level parallel to FSG level. This could be due to increased antioxidant action of UA in the aqueous phase of plasma.

Previously, the effect of BMI on the relation between UA and FSG was not reported.[17-19] This is the first time we are reporting from our study that UA positively correlated with FSG ($r = 0.22$; $P = 0.041$) in patients with DM with high BMI [Table 4]. According to previous reports, UA was strongly linked in conditions with high BMI such as obesity and metabolic syndrome.[20] However, in our study, there was no statistical correlation between UA and BMI.

Despite no significant rise in SBP, it was significantly correlated ($r = 0.18$; $P = 0.04$) with UA among all patient with DM [Table 3]. The strength of association grew stronger ($r = 0.26$; $P = 0.018$) when analyzed the Group 3 alone [Table 4]. DBP also correlated ($r = 0.23$; $P = 0.036$) with UA. Previous reports state that UA may play a causative role in hypertension.[21] Therefore, our present finding showing UA correlating with SBP and DBP levels in DM patients with high BMI is important. It reemphasizes the fact that patients with DM with high BMI are at high CVD risk which can be mediated through inflammation or oxidative stress (high UA) or through sympathovagal imbalance (high DBP) or through both mechanisms.

Interestingly, despite no statistical difference in RHR and SBP, the myocardial work stress marker RPP was highest in patients with DM with high BMI [Table 2]. This was also positively associated with increased UA level. The findings of the present study indicate the presence of increased myocardial work stress in DM in the high BMI range which is associated with a steady rise in UA level which is known antioxidant within physiological range. Despite the absence of significance in SBP and RHR, RPP was significantly higher in Group 3 [Table 2]. Higher resting RPP has been reported earlier in patients with Type 2 diabetes.[22] Our finding corroborates with previous reports. However, higher RPP in patients with DM in relation to their difference in BMI was not reported earlier. Therefore, it indicates that the resting myocardial oxygen load is higher in patients with DM with higher BMI.

In our study, RPP correlated with higher UA level in all patients with DM [Table 3] and in DM with high BMI as well [Table 4]. To the best of our knowledge, effect of BMI on RPP and correlation of RPP with a metabolic parameter UA in DM has not been reported before. This is the first report of its kind, from our present study.

RPP is a measure of myocardial blood flow. UA being an antioxidant within its range correlates with increased resting RPP. The positive association of UA and RPP in high BMI DM patients may suggest that the metabolic antioxidant demand is correlating with myocardial stress in terms of oxygen demand.

If resting RPP is higher than normal, then when body has more oxygen demand, the capacity to compensate would decrease. This is the reason why heightened resting RPP in patients with DM of high BMI DM patients is of concern. This indicates that myocardial oxygen demand will be met unsatisfactorily in this group compared to healthy nondiabetics or DM with normal BMI making them more vulnerable for CV risk. Therefore, patients with DM with higher BMI should monitor their CV profile more closely.

Limitations of the study

As this was a short-term study for ICMR STS project, the sample size was modest. Also, inclusion of other cardiovascular parameters such as autonomic or vascular function tests could have made the study outcome robust.

Conclusion

Findings of the present study indicate that the association of UA with fasting glucose in patients with diabetes does not follow a linear relationship with their BMI. Patients with DM with BMI more than the normal range are at greater risks of developing CVD, which is reflected in terms of their high FSG and UA and increased resting RPP denoting myocardial oxygen load. Therefore, in diabetes, simple routine parameters such as FSG, UA, BMI, and RPP may be employed to routinely monitor the CVD risk in patients with DM, especially in rural settings where other CV markers may not be analyzed on a routine basis.

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Conflicts of interest

There are no conflicts of interest.

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