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ASSOCIATION BETWEEN SERUM URIC ACID AND C-REACTIVE PROTEIN WITH METABOLIC SYNDROME RISK FACTORS -A CROSS SECTIONAL STUDY

Sundus Aslam[1], Amber Shahzadi[2]

[1]Center for Applied Molecular Biology, Punjab University, Lahore-Pakistan

[2]Kinnaird College for women, Lahore-Pakistan

Address for Correspondence:

Sundus Aslam

Center for Applied Molecular Biology, Punjab University, Lahore-Pakistan

Email: sundusaslam18@outlook.com

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Contribution

SA conceived, designed and did statistical analysis & manuscript writing. AS did data collection and manuscript writing. SA and AS did review and final approval of manuscript

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ABSTRACT

Objective: To examine the relationship of Serum uric acid (SUA) and C-reactive protein (CRP) with the components of metabolic syndrome and association with cardiometabolic risk factor.

Methodology: This cross-sectional study was conducted in Kinnaird College for Women, Lahore, Pakistan from 1st October 2016 to 31st March 2017, included subjects, individuals with metabolic syndrome (MetS), individuals with elevated uric acid level (pre-MetS) and non-metabolic syndrome control samples (Non-MetS) between the age group of 30-70 years. MetS was defined with the help of International diabetes Federation (IDF) criteria. All the required information of the participants was collected through structured questionnaire. Data of anthropometric measurements and blood pressure was gathered from the hospital and tests for fasting glucose and serum lipid profile, serum uric acid and C-reactive protein were conducted in the laboratory.

Results: Total of 90 individuals and 30 control samples (Non-MetS) included in the study , 40 of metabolic syndrome and 20 with raised uric acid levels. Serum uric acid was significantly associated with cholesterol, LDL-C, triglyceride and VLDL in MetS patients ($p<0.005$). C-reactive protein in metabolic syndrome patients shared significant relationship with obesity ($p<0.001$), fasting glucose ($p<0.046$) and hypertension ($p<0.001$). Uric acid shared a significant correlation with the BMI ($p=0.001$) in pre-MetS group. group uric acid shared a significant correlation with the BMI ($p=0.001$). The elevated C-reactive protein had a significant association with obesity and uric acid ($p<0.001$, $p=0.041$ respectively). Presence of both uric acid and CRP increased the risk of developing MetS after making adjustments (OR: 3.06 95 %CI: 1.043-8.98).

Conclusion: Elevated levels of serum uric acid (SUA) and C-reactive protein (CRP) have a strong association with metabolic syndrome components.

Key Words: Uric Acid, C-reactive protein, Metabolic Syndrome, Visceral obesity.

INTRODUCTION

Metabolic syndrome (MetS) is characterized as a group of analogous metabolic deformities, including central obesity, insulin resistance, atherogenic dyslipidemia and high blood pressure.[1] These metabolic abnormalities more often occur together than by chance alone and increase the risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[2,4] People belonging from South Asian ethnicity background has maximum risk of developing heart diseases and coronary heart disease (CHD) proven to be prime element of death in this region. [5,6] The prevalence of metabolic syndrome with respect to different definition's has been reported to be ranging from 18%-46% in Pakistan. [7]

Numerous factors such as inflammatory markers and serum uric acid have been related to CVD events. The association of serum uric acid and C-reactive protein with MetS debated for a long time to be added in the definition criteria of MetS. [8-10] Serum uric acid is synthesized by liver as the end product of purine metabolism, elevation in its level is proposed to be associated with metabolic syndrome.[11] Several epidemiological studies reported uric acid as a mediator of systemic inflammation and C-reactive protein (CRP), best considered and consistent biomarker of systemic inflammation. [12] CRP an acute phase protein is released by liver following the elevation of Interleukin-6 (IL-6) and reported to be correlated with each individual factor of metabolic syndrome.[10,13,14] Gigantic knowledge gap exists whether elevation of uric acid and CRP either linked with pathophysiology of the syndrome or act as prognostic markers of developing cardiometabolic abnormalities. In this study we assess the relationship of serum uric acid and CRP with metabolic risk factors as predictive markers in the population. High prevalence of metabolic syndrome observed in Pakistan directed towards the need of this research.

METHODOLOGY

This cross-sectional study was conducted from 1st October 2016 to 31st March 2017. Subjects between the age group of 30-70 years took part in the research that visited Akhtar Saeed Trust Hospital, Lahore Pakistan. Subjects with past reported history of cardiovascular disease, cancer, stoke, liver disease, kidney disease or any infectious disorder were excluded from the study. The protocol used for the study was approved by institutional Human Research Ethic Committee in agreement with the principles of Declaration of Helsinki. All the research objectives were clearly explained to the participants and their written consent was taken.

In the present study International Diabetes Federation (IDF) criteria was used to define metabolic syndrome. IDF criteria defined central obesity with respect to the specific ethnicity. A person to be categorized as MetS patient must have central obesity and any two other metabolic risk factors. Central obesity defined according to South Asian ethnic background have waist circumference for male ≥ 90cm and female ≥80cm or BMI > 30 kg/m2 and having any two of the following components: raised triglycerides (TG) level (≥ 150mg/dl or specific treatment for lipid abnormality); reduced level of HDL-C (< 40 mg/dl in males < 50 mg/dl in females or any treatment); elevated blood pressure(BP) (systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension); raised fasting glucose (≥ 100 mg/dl or previously diagnosed type 2 diabetes).

Anthropometric measurements were performed using standardized protocol by the trained paramedical staff. Calibrated Digitone weight balance were used to measure the weights of subjects in kilograms (Kg) without shoes. Height and waist circumference were measured with measuring tape (to the nearest 0.1cm). Height measured barefooted with their shoulders at normal position. Waist circumference measured midway between lowermost rib margin and iliac crest.

Participants were seated for 15 minutes before taking Blood pressure measurements. Systolic and diastolic BP had been measured by using Certeza Aneroid sphygmomanometer. Information about physical activity, smoking habits (yes/no), drinking habits (yes/no) and special diet consumption were taken by structured self-reported questionnaire.

Subjects were fasted overnight approximately for 10 hours before the blood sample had been drawn and refrigerated at -10 C after centrifugation. Human Liquicolor kits were used for the quantification of cholesterol, high-density Lipoprotein (HDL-C),triglyceride, fasting glucose and uric acid for all the subjects with the help of ROBERT RIELE GmbH & Co. KG semi-automated photometer 5010 v5+. HumaTex CRP kit was used for C-reactive protein assay.

Continuous variables were presented as mean ± standard deviation (SD), non-normally distributed variables as median and interquartile range (IQR) and categorical variables were reported in numbers and percentages. Independent sample t-test was applied for normally distributed data, Mann-Whitney test was applied for non-normally distributed data and chi square test was applied for categorical variables to analyze the difference between test and control sample population.

The normality of all the variables were tested with Shapiro-Wilk test. Non-normally distributed variables were transferred by Templeton's two step method before applying statistical analysis. Pearson correlation was applied to estimate the partial correlation between uric acid and metabolic syndrome risk factors.

Chi-square test was applied to observe the relationship of C-reactive protein with MetS components. A logistic regression was performed to analyze the relationship of the incidence of MetS with elevated serum uric acid, C-reactive protein and its combined effect.

All the hypothesis were tested at significance level 95% (0.05). The statistical analysis was carried out on Statistical package for the Social Sciences (SPSS) version 18. Data for continuous variable presented as mean ± Standard deviation, categorical variables as frequency (percentages) and non-normal distributed data as median and interquartile range (25th and 27th interquartile range)."

Table 1: Characteristics of Subjects with and Without Metabolic Syndrome

Variables		Non-MetS (n=30)	Set 1		Set 2	
			MetS group (n=40)	p -value	Pre-MetS (n=20)	p-value
Age		48.77 ±7.44	49.35±9.19	0.777	49.50±5.88	0.713
Gender (%Females)		23(76.7%)	29(72.5%)	<0.001	17(85.0%)	<0.001
Waist circumference		79.03 ±8.51	112.90±7.39	<0.001	79.0±5.09	0.988
BMI		21.31±1.87	31.44±1.95	<0.001	25.355±3.94	<0.001
Blood pressure	Systolic Blood pressure	120(117.5-120)	145(140-160)	<0.001	120(120-130)	0.212
	Diastolic Blood pressure	80(70-80)	100(90-110)	<0.001	80(70-83.75)	0.857
Fasting Glucose		94 ±7.51	156.35±25.11	<0.001	95.20±6.92	0.778
Cholesterol		119.37 ±19.81	139.50±38.93	0.006	125.30±25.51	0.360
LDL-C		53.98 ±20.07	63.20±33.47	0.157	60.80±24.38	0.286
HDL-C		42(42 -43)	42(42-43)	0.535	42(41.2-42.7)	0.889
Triglyceride		116.10±18.65	169.5±100.89	0.002	111.50±22.70	0.437
VLDL		23.22±3.73	33.90±20.17	0.002	22.30±4.47	0.437
Uric Acid		4.57±0.70	4.68±1.07	0.609	8.31±1.30	<0.001
CRP (%Negative)		30(100%)	20(50%)	<0.001	9(45%)	<0.001

RESULTS

Total of 90 subjects were included. About 40 subjects were identified as metabolic syndrome patients according to IDF criteria, 20 have elevated uric acid level (hyperuricemia) with no reported MetS condition characterized as pre-MetS and 30 control samples without any past history of metabolic syndrome risk factors.

The average age of the studied population was 49.19 ± 7.91 years and 76.7% participants were females. All the participants were from the same age group. The characteristics of the subjects are summarized in Table 1. Subjects characterized in MetS group had significantly higher values of Waist circumference (WC), BMI, Blood pressure, fasting glucose, cholesterol, TG, VLDL and CRP in comparison with the participants in Non-MetS group (control). Participants of pre-MetS with hyperuricemia had significance difference only in the means of BMI, uric acid and CRP.

Table 2 displays correlation between serum uric acid and metabolic syndrome risk variables in both the studied population. Serum uric acid showed a significant correlation with cholesterol (r=0.437, p<0.001), LDL-C (r=0.405, p=0.001), triglyceride (r=0.306, p=0.010) and VLDL (r=0.306, p=0.010) in the subjects of MetS group. The subjects from pre-MetS group only shared a positive correlation with BMI (r=0.468, p=0.001). Figure 1 graphically represents the difference in the means of BMI in the studied population.

Figure 1: BMI in study Population

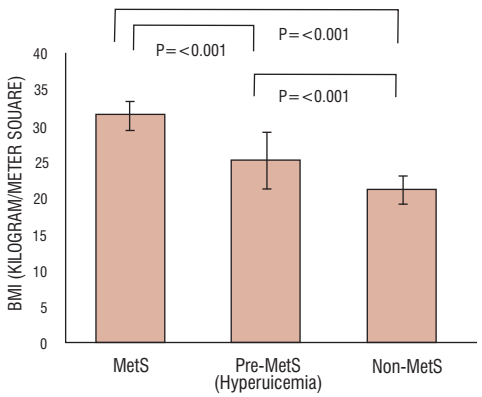

Table 2: Partial Correlation between Metabolic Risk Factors and Uric Acid.

Variables		MetS group Hs-CRP (mg/L)			Pre-MetS Hs-CRP (mg/L)		
		<6 Negative	>6 Positive	p-value	<6 Negative	>6 Positive	p-value
Age		49.26±7.91	48.70±9.841	0.096	48.64 ±7.01	50.55±6.10	0.751
Gender %(Females)		38(76%)	14(70%)	0.604	31(79.5%)	9(81.8$)	0.863
Waist circumference		92.17±18.09	113.91±7.62	<0.001	78.86 ±7.89	79.69±4.68	0.167
BMI		25.14 ±5.11	31.98±1.81	<0.001	21.67±2.31	27.39 ±3.31	<0.001
Blood pressure	Systolic Blood pressure	120(117.5-120)	160(140-168.75)	<0.001	125(120-130)	120(112.5-120)	0.009
	Diastolic Blood pressure	80(70-80)	110(95-110)	<0.001	80(70 -85)	80(70 -80)	0.464
Fasting Glucose		118.60±34.8	158.10±22.73	0.046	94.34±7.26	96.64±7.10	0.428
Cholesterol		129.58±33.4	134.10±34.40	0.083	121.03±21.54	124.27±25.4	0.283
LDL-C		57.87±27.48	62.68±32.01	0.101	56.11±21.69	58.82±23.63	0.492
HDL-C		42(42-43)	42(42-43)	0.695	42(41-44)	42(42-42.7)	0.188
Triglyceride		147.12±89.7	145.35±56.94	0.070	113.82±20.87	115.82 ±18.8	0.458
VLDL		29.42±17.94	29.07±11.38	0.070	22.76±4.16	23.18±3.68	0.371
Uric Acid		4.77 ±0.97	4.29±0.73	0.131	5.44±1.81	8.28±1.42	0.041

Table 3: Correlation of C-reactive protein with the Study Samples

Variables		Set 1 (MetS group)		Set 2 (Pre -MetS group)	
		Pearson's Coefficient	p -value	Pearson's Coefficient	p -value
Age		0.062	0.608	0.138	0.338
Waist circumference		0.081	0.508	0.039	0.786
BMI		0.088	0.470	0.468	0.001
Blood pressure	Systolic Blood pressure	-0.091	0.456	0.086	0.555
	Diastolic Blood pressure	0.002	0.984	-0.037	0.800
Fasting Glucose		-0.029	0.812	0.092	0.524
Cholesterol		0.437	<0.001	0.169	0.240
LDL -C		0.405	0.001	0.194	0.176
HDL -C		-0.10	0.936	0.029	0.840
Triglyceride		0.306	0.010	-0.132	0.359
VLDL		0.306	0.010	-0.132	0.359

In Table 3 correlation of C-reactive protein with the study samples has been presented. C-reactive protein in MetS group had a positive relationship with waist circumference (p=<0.001), BMI (p=<0.001), blood pressure (p<0.001) and fating glucose (p=0.046). Participants with reported hyperuricemia shared a significant relationship between CRP and BMI (p=<0.001) and uric acid (p=0.041).

The association of elevated uric acid, CRP and both markers (SUA+CRP) in incidence of metabolic syndrome was evaluated by using logistic regression analysis shown in table 4. Model I was crude model without any adjustment, Model II was adjusted for age and gender and Model III was further adjusted for BMI. Increase in OR's was observed after making adjustment for age gender and BMI in SUA and SUA+CRP groups. The regression analysis showed that elevation of 1 mg/dl in the level of serum uric acid (adjusted for age, gender, BMI) increased the odds ratio of the incidence of metabolic syndrome about 2.9-fold (OR:2.95, 95 %CI: 1.144-7.62). Elevation of 1 mg/dl in both uric acid and C-reactive protein increase the odds ratio of the incidence of metabolic syndrome approximately 3-fold (OR: 3.06 95 %CI: 1.043-8.98). In case of only CRP a significant results was observed in model I and II with about 1 mg/dl elevation in CRP increased the e risk 3.5-fold of the incidence of metabolic syndrome.

Table 4: Association between Incidence of Metabolic Syndrome with Serum Uric Acid SUA, C-Reactive Protein (CRP) and Combined Effect of Both Markers (SUA+CRP) in Logistic Regression Models

	Model I (crude)		Model II		Model III	
	OR(95 %CI)	p-Value	OR(95 %CI)	p-Value	OR(95 % CI)	p-Value
SUA	1.71(1.24-2.36)	<0.0001	1.72(1.24-2.39)	0.001	2.952(1.144-7.62)	0.025
SUA+CRP	1.11(0.75-1.63)	0.604	1.09(0.74-1.61)	0.651	3.06(1.043-8.98)	0.042
CRP	3.54(1.42-8.83)	0.007	3.52(1.41-8.79)	0.007	0.124(0.01-1.76)	0.123

Model I: Crude model, Model II: Adjusted for age and gender, Model III: Adjusted for age, gender and BMI

DISCUSSION

In the present study, we observed the relationship of serum uric acid level and C-reactive protein in the participants characterized in metabolic syndrome, pre-metabolic syndrome and non-metabolic syndrome groups. The level of serum uric acid shared a significant correlation with metabolic syndrome components. A positive association was found between serum uric acid and serum lipids including cholesterol, triglycerides, VLDL and LDL-C in MetS patients. Same results were observed in previous studies, synthesis of triglycerides speed up the production of uric acid, through the NADP-NADPH pathway of ribose-5-pathway to phosphoribosyl pyrophosphate.[15,16] Hyperuricemia is linked as a potential risk factor of atherosclerotic diseases but its independent association with metabolic syndrome remained controversial. [17] The relationship of uric acid with individual component of MetS has also been debated for a long time. Uric acid was found to be an independent predictor of MetS in various studies conducted on different populations with different ethnic backgrounds.[18,19] Zhang et al. in a longitudinal cohort based study verified that uric acid level was an independent predictor of metabolic syndrome after adjusting potential cofounding variables in men population.[20]

It can be inferred from the present study that C-reactive protein, systemic inflammatory marker had significant relation with metabolic syndrome components as previously reported. Ridkeret al. [21] conducted a cohort follow up study of eight years with 14719 healthy American women. The study reported that level of serum C-reactive protein gives prognostic evidence with respect to the incident of metabolic syndrome. Furthermore a positive relation was observed between high blood pressure (p<0.001) and fasting glucose (p=0.046) with C-reactive protein.

Studies on animal models has independently related CRP with metabolic syndrome risk factors. It has been observed that induction of transgenic CRP expression in spontaneously hypertensive rats results in increased expression of IL-6 resulting in oxidative damage. This leads to further elevation in blood pressure and initiation of insulin resistance in hepatic tissue.[22]

Furthermore a significant relationship between obesity both in terms of waist circumference and BMI with CRP (p<0.001) had been evaluated in MetS patient group.

Subjects from pre-MetS group have all the values of metabolic syndrome risk factors in the normal range except for the concerned markers uric acid and CRP. It was confirmed from the results of one-way ANOVA that the BMI of all three groups, MetS, pre-MetS and non-Mets shared a significance difference in means (p<0.001). The mean BMI value (25.35 Kg/m2) of pre-MetS group falls in over-weight or pre-obese group according to WHO criteria and different from non-MetS studied population (21.30 Kg/m^2).

In this study, participants with reported hyperuricemia had a direct correlation between uric acid and BMI (p=0.001). Obesity interferes in urate synthesis, uric acid excretion and

cause renal and glomerulus damage which in result increases the level of uric acid in blood.[21,24]

Uric acid found to be related with CRP in hyperuricemia patients (P=0.041). In past study, uric acid was observed to be responsible for inducing the expression of IL-6, TNF-β, IL-1β and CRP protein in human vascular cells in-vitro.[25] The level of CRP increased as the serum uric acid quartile, specified the association of uric acid with low-grade systemic inflammation which is not only a risk factor of metabolic syndrome but also leads towards diabetes, cardiovascular diseases and stroke.[26] No such association was observed in MetS patients because the medical history showed that the patients were prescribed with Metformin, Sitagliptin and Sibutramine, which effect the level of serum uric acid.[27,28]

A linear independent relation was reported by Corine et al. between CRP and obesity in the subjects without any other reported metabolic syndrome risk factor.[29] However we have found a significant relationship with BMI in overweight range (p<0.001) with C-reactive protein from the pre-MetS group

It was found that elevated uric acid even in its normal range was significantly associated with increased ratio of metabolic syndrome incidence even after making adjustment for other cofounding variables (age, gender and BMI). Increase of 1 mg/dl of uric acid in serum elevates the odds of the incidence of metabolic syndrome about 2.9 fold. Previous studies also showed that participants with higher uric acid level are at 2-fold risk of developing MetS.[30]

One of the interesting finding of the present study is that the elevation of one unit in the level of uric acid and CRP increased the incidence of metabolic syndrome approximately 3 fold (OD: 3.06, 95 %CI: 1.114-7.62) after making adjustment for age, gender and BMI. Presence of both the markers increased the risk of developing of metabolic syndrome in the subject. Participants with reported hyperuricemia (pre-MetS) had no metabolic syndrome component. Their BMI was in pre-obese range (≥25.00) and the level of both biomarkers uric acid and CRP were elevated from normal range. In the light of these findings we can anticipate that individuals of pre-MetS are at 3 fold higher risk of developing metabolic syndrome and Serum uric acid coupled with CRP act as predictive marker of cardiometabolic risk.

LIMITATIONS

This study had some limitations. First, due to cross-sectional nature of the study causal relationship between concerned biomarkers and MetS could not be determined. Second, the number of participants in the study was very small which limits the generalization of the results. Third, most potential confounding variables were cautiously controlled, since there was multiple risk factors in the study, possibility was there that immeasurable cofounders may exist in the research.

CONCLUSION

It was concluded from this study that elevated level of serum uric acid (SUA) and C-reactive protein (CRP) have a strong association with metabolic syndrome components. Serum uric acid coupled with C-reactive protein increased the risk of developing MetS three fold. Our findings suggest that uric acid and C-reactive protein may be considered as predictive marker for the incidence of MetS and prognosis of CVD and diabetes. Participants from pre-MetS group may be at higher risk of developing cardiometabolic abnormalities in future. Due to increasing prevalence of MetS, obesity and cardiovascular disease in the population additional studies should be conducted to find out the role of serum uric acid and CRP in the pathogenesis of metabolic abnormalities.

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