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LETTERS

Early manifestation of hyperuricemia and its pathophysiological interface with adiposopathy and metabolic syndrome among young adult: Cross-sectional study

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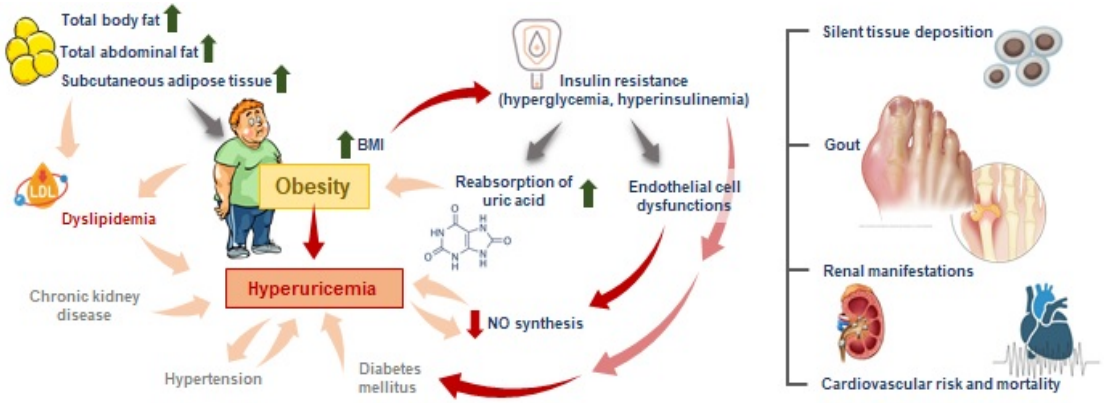
Article

ABSTRACT



The association between serum uric acid (SUA) levels and visceral adipose tissue, subcutaneous adipose tissue, and metabolic syndrome (MetS) in young, healthy subjects warrants scientific investigation. In this cross-sectional research involving 114 subjects, various anthropometric parameters, such as body mass index (BMI), waist circumference (WC), and skinfold measurements were measured. Additionally, fasting blood glucose (FBG), SUA concentrations, lipid profiles, and blood pressure were assessed. Mathematical models estimated body fat percentage (BF), total abdominal fat (TAF), intra-abdominal adipose tissue (IAAT), and subcutaneous adipose tissue (SCAT). SUA concentrations were categorized into quartiles: Q1 ≥3.04 mg/dl, Q2 3.05-3.86 mg/dl, Q3 3.89-4.67 mg/dl, and Q4 4.68-7.87 mg/dl. MetS was delineated using the criteria from the National Cholesterol Education Program Adult Treatment Panel III. Statistical methodologies comprised t-tests, one-way ANOVA, and Pearson's correlation. The incidence rates for MetS, hyperuricemia, and hypertriglyceridemia were 11.4%, 5.26%, and 27.19%, respectively. Abdominal obesity, based on WC, was 19.3%. Males showed a more pronounced increase in IAAT (26.23%) than females (13.20%), leading to a total prevalence of 20.18%. The total SCAT incidence was 21.93%, with females (21.53%) outnumbering males (19.67%). The incidence of elevated FBG was 21.93%, suggesting a pre-diabetic condition. Hypertension rates, represented by systolic and diastolic blood pressures, were 3.51% and 15.79% respectively. Metabolic irregularities escalated with increasing SUA levels. The data indicate that young adults manifesting MetS components often exhibit elevated SUA concentrations, proposing that SUA might be an added MetS factor.

Keywords: body mass index; central obesity; hyperuricemia; metabolic syndrome

INTRODUCTION

In both humans and great apes, serum uric acid concentration (SUAC) is characteristically elevated, a phenomenon attributable to mutations that rendered the uricase or urate oxidase gene inactive approximately 15 million years ago.[1] Consequently, these alterations resulted in uric acid remaining as the terminal metabolite in purine metabolism due to the inability to convert it into the soluble form, allantoin.[1] Adiposopathy, otherwise termed 'sick fat', is characterized by a perturbation in the structural and functional integrity of adipose tissue, thereby disrupting the overall metabolic homeostasis of the organism. The relationship between hyperuricemia and adiposity is multifaceted, with hyperuricemia potentially instigating adiposity through enhancement of hepatic and other fat production.[2] The progression of SUAC is incremental, beginning from an early age and peaking between the ages of 15 and 17. Notably, individuals

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with obesity typically exhibit elevated SUAC in comparison to their normal-weight counterparts.[3] High uric acid levels have been implicated in the risk factors associated with cardio-metabolic syndrome, a cluster of cardiometabolic risk components that include abdominal obesity, hypertension, hyperglycemia, decreased HDL-C levels, and elevated triglyceride levels.[4] Despite recent findings that independently link hyperuricemia with an increased risk of metabolic syndrome (MetS), diabetes, hypertension, and dyslipidemia, the definitive role of uric acid as a causative agent in these disorders remains an area of active investigation.[5–8]

The deposition of adipose tissue in diverse body regions appears instrumental in the onset of cardio-metabolic abnormalities. In particular, the agglomeration of fat within the abdominal sector, chiefly within intra-abdominal adipose tissue (IAAT) and subcutaneous adipose tissue (SCAT), has been associated with the advancement of insulin resistance and additional cardio-metabolic maladies.[9,10] Asian Indians exhibit a distinctive obesity pattern characterized by an abundance of fat, especially in the abdominal area, augmented IAAT and SCAT quantities, and a susceptibility to fat accumulation in non-conventional locations such as the liver and muscles. These factors may potentially enhance their susceptibility to insulin resistance and other metabolic disorders.[11] Current research indicates that the ability of diverse fat depots to contribute to the development of cardio-metabolic abnormalities may differ.[12–14]

The etiology of metabolic syndrome is intricate, involving a multitude of events and interplays between the various facets of metabolic disorders.[15,16] Current investigations reveal a potential correlation between elevated uric acid levels and conditions such as hypertension, increased body mass index, elevated blood glucose, and irregular lipid profiles.[17–21] However, the evidence connecting uric acid to the progression of metabolic syndrome, insulin resistance, and cardiovascular disease is currently insufficient to conclusively affirm it as a contributory element.[22–25] A more comprehensive comprehension of the interrelationships between different components is required to better interpret this intricate syndrome and devise effective prevention and management strategies. This study sought to explore the correlation between elevated uric acid levels and components of metabolic syndrome in young adults residing in central India, in addition to the relationship between hyperuricemia, regional body fat, and cardio-metabolic risk factors.

MATERIALS AND METHODS

Study design and population

This study aimed to assess the effect of SUAC on regional fat distribution and cardiovascular and metabolic risk factors (both anthropological and biochemical) in young adults from a semi-urban area in Rajnandgaon, Chhattisgarh, India. The study was carried out in accordance with the guidelines of the Helsinki Declaration and was approved by the institutional ethics committee. The sample size was determined and 114 individuals, both male and female were selected through random sampling. The participants were all between the ages of 18 and 25 and met the inclusion criteria of being free from recent illnesses and having no history of juvenile diabetes, anemia, hypothyroidism, or any other type of metabolic or endocrine disorder. Participants taking lipid-lowering medication or supplements were excluded.

Anthropometric and Biochemical Measurements

Prior to their participation, all subjects were duly informed about the study and provided written consent.[26] Demographic information and anthropometric measurements, such as height, weight, waist circumference, and hip circumference, were recorded.[26] Anthropometric parameters were measured using standardized protocols. Height (in centimeters) was measured using a stadiometer (SECA Model 217, Seca Gmbh Co., Hamburg, Germany). The individual was asked to stand upright without shoes with his/her back against the vertical backboard, heels together, and eyes directed forward. Weight (in kilograms) was measured with an manual weighing scale that was kept on a firm horizontal flat surface. Subjects were asked to wear light clothing, and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated using the formula weight (kg)/height (m)^2. Predictive equations specifically designed for Asian Indians, which took into account variables such as age, gender, height, weight, BMI, waist circumference, hip circumference, and skinfold thickness, were utilized to estimate body fat percentage, total abdominal fat, and subcutaneous abdominal fat.[11,27] Waist circumference (WC) (in centimeters) was measured using a non-stretchable measuring tape. WC was measured at the smallest horizontal girth between the costal margins and the iliac crest at the end of expiration. The triceps skinfold was measured using skinfold calipers. We estimated percentage BF, TAF, and areas of abdominal adipose tissue subcompartments; IAAT and SCAT using the predictive equations developed for Asian Indians which included simple variables such as age, gender, height, weight, BMI, WC, hip circumference, and skinfold. Cut-off values for TAF, IAAT, and SCAT developed for Asians were used to determine the abnormal values.[10] Overweight and obesity were defined as BMI ≥23–24.9 kg/m2 and BMI ≥25 kg/m2, respectively. WC >90 cm for males and >80 cm for females was considered an indicator of abdominal obesity. Cut-off for % BF was taken as 25.5 for males and 38 for females, respectively. Cutoffs for TAF (≥245.6 cm2 [males] and ≥203.46 cm2 [females]), IAAT (≥135.3 cm2 [males] and ≥75.73 cm2 [females]), and SCAT (≥110.74 cm2 [males] and ≥134.02 cm2 [females]) developed for Asians were used to determine the adiposity.[1]

Systolic blood pressures (SBP) and diastolic blood pressures (DBP) were measured using an arm-type fully automatic blood pressure monitoring system (Easy Care, Ravechi GmbH, Germany). Blood pressure was recorded in the sitting position in the right arm. Two readings were taken 5 min apart and their mean was taken as the blood pressure. The modified criteria (three out of five) of National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) were used to define the MetS. Following an overnight fast, a 5 ml blood sample was collected from the antecubital vein and processed to obtain serum, which was subsequently stored at -20°C until laboratory analysis. In biochemical investigation, enzymatic methods were

applied to measure fasting plasma glucose levels, serum uric acid, total cholesterol, triglycerides, and high-density lipoprotein cholesterol using an automated analyzer (Backmam Coulter AU480).[19] The total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured by an enzymatic method using a commercial kit from Randox Laboratories Ltd. (Antrim, United Kingdom) according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using Origin Pro 8, a software commonly utilized for data analysis in scientific research. Continuous variables were reported as mean±standard deviation (SD), while categorical variables were expressed as numbers and percentages. The study population was divided into quartiles based on SUAC. A one-way analysis of variance (ANOVA) was conducted with a significance level set at 0.05 to compare the average values of cardio-metabolic components among the different quartiles of SUAC.

Table 1. Physiological and cardio-metabolic characteristics.

Variables	Males (61)	Females (53)	P value
Age (Yrs)	19.71±0.28	20.33±0.16	0.94
Height (cm)	173.15±1.38	157.8±1.44	0.088
Weight (Kg)	66.90±2.70	48.5±1.20	<0.00001
BMI (kg/m2)	22.24±0.77	19.48±0.42	0.9974
WC (cm)	82.53±1.98	77.46±0.96	0.9974
Triceps skin fold thickness (cm)	15.15±1.32	11.26±0.604	0.995
Body Fat percentage (%)	21.81±1.51	28.15±0.80	0.0042
Total Abdominal Fat (cm^2)	139.77±6.09	124.79±3.48	0.331
Intra-abdominal Adipose Tissue (cm^2)	87.78±3.42	87.59±2.08	0.606
Subcutaneous Abdominal Adipose Tissue (cm^2)	108.95±5.27	92.06±3.65	0.324
SBP (mm of Hg)	120.64±1.79	109.66±1.88	<0.00001
DBP (mm of Hg)	80.96±1.93	76±1.63	0.95
FBG (mg/dl)	96.15±1.78	87.43±1.43	0.321
TG (mg/dl)	155.56±3.62	144.06±3.46	0.327
HDL (mg/dl)	41.05±0.62	43.51±0.78	0.993
Uric Acid (mg/dl)	4.68±0.27	3.01±0.12	0.321

Values are presented as mean ± SEM; BMI, Body Mass Index; WC, Waist Circumference; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FBG, Fasting blood glucose; TG, Triglycerides; HDL, high Density lipoprotein

RESULTS

Demographical characteristics of study participants

This study included 114 young adults (ranging in age from 18-25) from various communities, with 78% being Hindu, 7% Muslim, 6% Christian, 5% Jain, and 4% Buddhist. The average family income was 7.53 lakhs per year and they lived in a semi-urban area in Chhattisgarh. Out of the 114 individuals, 61 were male (53.5%) and 53 were female (46.5%) with a mean age of 20.01±0.17 years (**Tables 1-5**).

DISCUSSION

Uric acid, a purine metabolism byproduct, is primarily excreted via urine in humans and has been identified as contributing to over 50% of the antioxidant capacity of blood.[18] Hyperuricemia has been implicated in both causal and protective roles in a variety of diseases, such as gout, diabetes, hypertension, and chronic kidney diseases, as well as exhibiting protective effects in neurodegenerative diseases like Alzheimer's disease, dementia, Parkinsonism, and multiple sclerosis.[28,29] It has been reported that Serum uric acid levels to be associated with a variety of cardiovascular ailments. However, the direct association between uric acid levels and metabolic syndrome remains controversial.[18]

The present study investigated the association between uric acid concentrations and Metabolic Syndrome components in

Table 2. Prevalence of different adiposity profile and cardio-metabolic risk factors

Variables	Overall (N=114)	Male (n=61)	Female (n=53)
Hyperureamia	6 (5.26%)	4 (6.56%)	2 (3.77%)
MetS	13 (11.40%)	9 (14.75%)	4 (7.55%)
Overweight (according to BMI)	20 (17.45%)	13 (21.31%)	7 (13.20%)
GO (according to BMI)	16 (14.04%)	10 (16.39%)	6 (11.32%)
(AO) (according to WC)	22 (19.30%)	15 (24.59%)	7 (13.20%)
Obesity (according to BF%)	17 (14.91%)	17 (27.86%)	0
TAF (cm^2)	0	0	0
IAAT (cm^2)	23 (20.18%)	16 (26.23%)	7 (13.20%)
SCAT (cm^2)	25 (21.93%)	12 (19.67%)	13 (24.53%)
Impaired fasting glucose (prediabetic)	25 (21.93%)	16 (26.23%)	9 (16.98%)
Hypertension according to SBP	4 (3.51%)	4 (6.55%)	0
Hypertension according to DBP	18 (15.79%)	18 (29.51%)	0
Prehypertension according to SBP	48 (42.11%)	28 (45.90%)	20 (37.74%)
Prehypertension according to DBP	39 (34.21%)	21 (34.43%)	18 (33.96%)
Hypertriglyceridemia	31 (27.19%)	23 (37.70%)	8 (15.09%)
Decreased HDL-C	26 (22.81%)	13 (21.31%)	12 (22.64%)

MetS= Metabolic Syndrome, BMI= Body Mass Index, GO= General Obesity, AO= Abdominal Obesity, WC= Waist Circumference, BF%= Body fat percentage, TAF=Total Body Fat, IAAF= Intra-abdominal Adipose tissue, SCAT= Subcutaneous abdominal adipose tissue, SBP= Systolic Blood Pressure. DBP= Diastolic Blood Pressure

Table 3. Pearson's rank correlation between uric acid and other variables of the participants with or without metabolic syndrome

Pair	Non-Mets (r value)	Mets (r value)
Uric acid level Vs SBP	0.48	0.52
Uric acid level Vs DBP	0.25	0.37
Uric acid level Vs FBG	0.48	0.69
Uric acid level Vs TG	0.25	0.65
Uric acid level Vs HDL	-0.16	-0.17
Uric acid level Vs WC	0.41	0.57
Uric acid level Vs BMI	0.59	0.58
Uric acid level Vs BF%	0.18	0.23
Uric acid level Vs TAF	0.50	0.58
Uric acid level Vs IAAT	0.24	0.67
Uric acid level Vs SCAT	0.49	0.48

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, TG: Triglycerides, HDL: high Density lipoprotein, WC= Waist Circumference, BMI= Body Mass Index, BF%= Body fat percentage, TAF=Total Body Fat, IAAF= Intra-abdominal Adipose tissue, SCAT= Subcutaneous abdominal adipose tissue.

Table 4. Serum uric acid level among normal or clinical manifestation of different adiposity profile and Mets components in both genders

Variables	Male	Female
Over weight (according to BMI)	4.69 ± 0.02	5.1±0.32
Obese (GO) (according to BMI)	6.67±0.21	5.37±0.27
Non-obese (according to BMI)	4.30±0.34	3.06±0.45
Obese (AO) (according to WC)	7.01±0.29	3.58±0.37
Non-obese (according to WC)	4.42±0.41	3.19±0.31
Normal SCAT	4.26 ± 0.51	3.84±0.42
Increased SCAT	5.50 ± 0.91	5.23±0.16
Normal IAAT	4.58 ± 0.35	3.57 ± 0.45
Increased IAAT	7.10 ± 0.11	6.03± 0.02
Non diabetic	4.40±0.25	3.05±0.48
Pre diabetic	5.74±0.28	4.74±0.22
Hypertensive	7.26±0.56	NA
Pre-hypertensive	6.28±0.58	5.02±0.48
Non hypertensive	4.27±0.38	3.16±0.26
Elevated TG	6.61±0.39	4.32±0.35
Normal TG	4.42±0.44	3.27±0.19
Decreased HDL	6.51±0.48	3.77± 0.41
Normal HDL	4.48±0.29	3.15±0.38
Mets	6.36±0.61	5.28±0.24
Non-Mets	4.43±0.32	3.27±0.21

Values are presented as mean ± SEM; BMI: Body Mass Index, GO: General Obesity, AO: Abdominal Obesity, WC: Waist Circumference, SCAT= Subcutaneous abdominal adipose tissue, IAAF= Intra-abdominal Adipose tissue, TG: Triglycerides, HDL: high Density lipoprotein, MetS= Metabolic Syndrome.

individuals with or without the syndrome.[18] Results demonstrated that uric acid levels were significantly elevated in the Metabolic Syndrome group, and the prevalence of the syndrome increased with rising uric acid levels. The study corroborated that high body fat levels, particularly in the abdominal region, are a crucial factor in the early onset of hyperuricemia in young Indian adults, which is consistent with prior research.[30] Enhanced body fat may contribute to increased uric acid production and impaired excretion, resulting in disrupted uric acid metabolism and hyperuricemia.[31] Studies have also revealed a strong connection between excess body fat and elevated uric acid levels, particularly in postmenopausal women.[32]

The current research revealed that individuals with both general and abdominal obesity exhibited higher SUA levels. Other studies have proposed that adipose tissue possesses significant xanthine oxidoreductase activity, akin to that found in the liver, leading to increased uric acid production and excretion in obesity.[31,33] In this investigation, data demonstrated a robust association between elevated SUA levels and hypertriglyceridemia, as well as low HDL-C (high-density lipoprotein cholesterol). These findings are in accordance with numerous previous studies that have established a correlation between high plasma triglyceride levels and hyperuricemia.[4,18,19,34] Similarly, to the existing investigation, observed that serum uric acid levels were associated positively with triglyceride and negatively with HDL-cholesterol. A potential explanation for this relationship is that triglyceride synthesis accelerates the conversion of ribose-5-phosphate to phosphoribosyl pyrophosphate (PPRP) via the shared NADP-NADPH metabolic pathway, resulting in increased uric acid production.[30] The study determined that SUA levels were statistically significant and positively correlated with both systolic and diastolic blood pressure in subjects. Moreover, SUA was found to be independently associated with hypertension.[35,36] According to Krishnan et al., men with hyperuricemia were at a heightened risk for hypertension, with each increase in SUA corresponding to a 9% elevated risk of developing hypertension.[37] In an animal study, rats with raised SUA levels developed hypertension, exhibiting a direct link between SUA levels and blood pressure.[38] Research has also indicated that hyperuricemia can induce hypertension through pathways involving decreased nitric oxide synthase levels in the kidney's macula densa cells, which activates the renin angiotensin aldosterone system (RAAS) and diminishes renal perfusion.[38] Additional studies have reported hyperglycemia as a significant risk factor for hyperuricemia.[35] Nakanishi et al. discovered that an increased SUAC in males heightened the risk of type 2 diabetes and concluded that hyperuricemia was positively correlated with hyperglycemia.[39] This study also revealed that SUA was significantly associated with fasting blood glucose levels.

Currently, hyperuricemia is not considered part of the MetS criteria according to NCEP ATP III. Our research shows that there is a significant connection between high SUA levels and body fatness and MetS components in young people. Further, long-term studies are necessary to determine whether hyperuricemia should be considered an additional component of the MetS.

Strength and Limitation of the Study

For this investigation, we specifically selected youthful and healthy individuals while excluding those with characteristics that could potentially impact their levels of SUA and the metabolic markers under examination. In a pioneering approach, we employed established and precise equations to estimate

Table 5. Baseline characteristics of the participants according to SUA quartiles.

Baseline Parameters SUAC quartiles	Q1 ≥3.04 mg/dl	Q2 3.05-3.86 mg/dl	Q3 3.89-4.67 mg/dl	Q4 4.68-7.87 mg/dl	*f*-ratio value	P value
Weight (Kg)	48.7±2.56	54.88±2.98	61.41±3.59	70±3.25	20.79	< 0.00001
SBP (mmHg)	109±4.76	115.26±3.38	116.18±4.88	124.44±5.22	18.05	< .00001
DBP (mmHg)	74.66±1.77	79.18±2.45	77.71±2.77	83.37±2.01	4.82	0.003
FBG (mg/dl)	86.97±3.55	89.64±5.12	92.68±4.23	99.42±5.21	12.84	< .00001
TG (mg/dl)	125.63±7.23	122.51±6.21	129.69±7.81	130.56±11.1	1.56	0.202
HDL (mg/dl)	54.33±4.2	55.12±4.09	48.86±3.89	49.14±3.22	5.17	0.002
BMI (kg/m^2)	19.21±1.29	19.35±1.78	22.14±2.01	23.92±2.43	19.96	< .00001
WC (cm)	75.9±2.45	78.51±3.77	81.82±3.67	85.5±3.99	10.03	< .00001
BF (%)	26.62±2.77	23.34±1.89	24.84±2.67	23.65±2.38	1.14	0.334
TAF (cm2)	120.18±7.88	121.94±6.34	142.98±6.87	154.37±7.90	16.03	< .00001
IAAT (cm2)	85.42±2.89	85.04±6.98	94.36±5.44	101.00±36.11	7.40	0.0001
SCAT (cm2)	87.45±3.11	89.07±4.89	107.88±4.88	115.77±4.03	12.36	< .00001

Values are presented as mean ± SEM; SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, TG: Triglycerides, HDL: high Density lipoprotein, BMI= Body Mass Index, WC= Waist Circumference, BF%= Body fat percentage, TAF=Total Body Fat, IAAF= Intra Abdominal Adipose tissue, SCAT= Subcutaneous abdominal adipose tissue.

regional adiposity in young adults from India. This method offers a cost-effective alternative to more expensive techniques like dual-energy X-ray absorptiometry, computerized tomography, and magnetic resonance imaging with specialized software. These methods hold potential for employment in both epidemiological research and clinical settings. It is important to note, however, that since this study adopted a cross-sectional design, it does not allow for establishing causal relationships between uric acid and MetS. Moreover, the limited number of participants in this study may restrict the extent to which the findings can be applied to the broader population.

CONCLUSION

This study postulates that augmented concentrations of uric acid in the context of healthy young individuals can be associated with excessive adiposity, dysregulated lipid profiles, and heightened glycemic levels. Subsequent investigations encompassing molecular assessments are imperative to enhance our comprehension of the intricate interplay between uric acid and metabolic syndrome. Additionally, such inquiries are essential to ascertain the clinical significance of these observations.

Ethical statement

Ethical approval for this study was obtained from the Institutional Ethics Committee (IEC) of Government Medical College, Rajnandgaon, Chattisgarh, India (Ref. No. 11-2018/GMC RJN/I.E.C./2018 dated 06.07.2018).

Conflicts of interest

The authors declare no conflicts of interest.

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