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Original Article

Relationship between insulin resistance, metabolic syndrome components and serum uric acid

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ABSTRACT

Background: Metabolic syndrome is cluster of abnormality related with increasing cardiovascular events. Hyperuricemia is level of uric acid more than 7 mg/dL for men. Some research have reported relation between metabolic syndrome mediated by insulin resistance with increasing of serum uric acid level.
Objective: Assess relationship between insulin resistance and metabolic syndrome components with the level of serum uric acid.
Method: Observational study with cross sectional approach conducted on 102 outpatient subjects at Dr. RSUP Wahidin Sudirohusodo (RSWS) hospital and Hasanuddin University Hospital in the period of July –September 2018.
Results: Subjects with IR were found to be significantly higher for having MetS (88.23% vs. 11.77% p = 0,000). In subjects with IR, the average serum uric acid level was higher compared to non-IR subjects, but this difference was not significant (6.63 vs 6.42 mg/dL; P = 0.325). In subjects with MetS, the average serum uric acid level was higher compared to subjects with non-MetS but this difference was not significant (6.62 vs. 6.28 mg/dL; P = 0.556). No significant relationship was found between IR and MetS with serum uric acid level.
Conclusion: Insulin resistance is related to the incidence of MetS and in both of these circumstances an independent tendency is found to increase uric acid levels. The role of insulin resistance in the relationship between metabolic syndrome and uric acid levels was not proven in this study.

1. Introduction

Metabolic Syndrome (MS) is collection of abnormality of metabolic component associated with increasing risk of cardiovascular disease (CVDs). Several consensuses consisted of World Health Organization (1998), European Group for the Study of Insulin Resistance (1999), American Association of Clinical Endocrinologist (AACE) (2003), International Diabetes Federation (2005) and National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) in Asian (2005) had proposed several different diagnostic criterias for MS [1].

The simple and practical criteria used in daily practice is based on NCEP ATP III consisted of central obesity, hypertension, elevated serum triglycerides, depressed HDL (High Density Lipoprotein) and impaired glucose tolerance [2]. The confirmation of diagnosis of MS is when 3 of 5 factors are confirmed. This syndrome is defined as insulin resistance syndrome (IR) because this underlying mechanism is responsible on the creation of MS [3].

Hyperuricemia is a condition where serum uric acid level exceeds the normal level of 5.7 mg/dL for female and 7 mg/dL for male. Hyperuricemia can lead to gout arthritis and nephropathy. However, recent studies have found that hyperuricemia can link to cardiovascular events.

Several studies reported that there is correlation either MetS or its factors with elevation of serum uric acid. In 2014, one study reported that waist circumference, body mass index and triglycerides level tend to be higher in male with hyperuricemia [4]. Subjects with hyperuricemia have risk of 2.95 for developing MetS compared to male with normouricemia. In a 5 year prospective cohort study [5] found that male subjects with hyperuricemia had risk of 1.5 for developing MetS compared to normouricemia.

Several studies also reported that there is a two-way relationship between insulin resistance and hyperuricemia. Increasing

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serum uric acid can cause insulin resistance through depressed bioavailability of Nitric Oxide (NO) and eventually creates oxidative stress in mitochondria. IR also can cause hyperuricemia through increased sodium reabsorbtion mechanism which caused the increasing absorbtion of uric acid. Elevation of serum uric acid negatively correlated with insulin sensitivity. This data indicated that hyperuricemia is an important component in MetS and can predict IR [6,7].

From all those facts, we hypothesized the possible correlation of MetS and hyperuricemia mediated IR. Therefore, we conducted our research to investigate the relationship between IR and MetS component to serum uric acid level.

2. Methods

2.1. Participants and study design

This was an observational study with cross sectional approach. The sample participants consisted of 102 consecutive participants where they were taken at outpatient care based on inclusion criteria in Wahidin Sudirohusodo Hospital, Makassar and Hasanuddin University Hospital. The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance to the tenet of the Helsinki Declaration and has been approved ethically by the Institutional Review Boards of Faculty of Medicine, Hasanuddin Univeristy (approval number 713/H4.8.4.5.31/PP36- KOMETIK/2018). The patients were informed consent prior to participation.

2.2. Measurements

Samples underwent a standard evaluation which included medical history, physical examination, antropometric measurements, fasting insulin, HOMA-IR levels and laboratory examination consisted of blood routine, urinalysis, ureum, creatinine, SGOT, SGPT, FPG, lipid profile and serum uric acid.

Antropometric measurements included blood pressure, body weight, and body height to determine body mass index and waist circumference. Blood pressure was measured with sphygmomanometer. The tools used have been calibrated well and the measurement was taken in sitting position with the arm put above the desk in line with the level of the heart. First *Korotkoff* sound was defined as systole and fifth *Korotkoff* sound was defined as diastole. Blood pressure was measured for 3 different occasions. The first measurement was excluded then the last 2 measurements were calculated for the mean and defined as the blood pressure of the subjects. If possible, the measurement was conducted by two different assessors. Before the measurement was conducted, the subject had to take a rest for 5 min and were persuaded to not withstand their urination during the measurement. Blood pressure was defined as mmHg. For waist circumference, it was measured using ruler with cm as its unit. The measurement was conducted while the patient did not use any footwear with standing up straight position and the distance between both legs were 25–30 cm. WC was measured by circling horizontally in the top middle point of iliac crest with lower border of costa X in middle axillary line and was defined as cm.

Biochemical assays consisted of fasting blood glucose was examined with hexokinase-glucose-6- phosphate dehydrogenase using *Dimension* tool and was defined as mg/dL. Lipid profile examination was conducted to check total cholesterol, triglycerides, HDL and LDL with enzymatic method (*Roche, Basel, Switzerland*) and was defined with unit of mg/dL. We measured uric acid using URICASE/POD methods implemented at auto-analyzer tool (*Boehringer Mannheim, Mannheim, Germany*) and was defined with the unit of mg/dL. The measurement of fasting insulin was using immunometric chemiluminescent assay method with the tool of Advia Centaur XP Immunoassay using insertion kit Immulite® 2000 with the unit of mikrounit/ml. The measurement of HOMA-IR with fasting insulin formula (mikrounit/ml) times fasting blood glucose (mg/dL) then divided with 22.5.

2.3. Definition of variables and outcomes

Metabolic syndrome was diagnosed using NCEP ATP III criteria which is if there are 3 or more components consisted of central obesity (WC > 90 cm), triglyceride elevation (≥150 mg/dL), depressed HDL cholesterol (<40 mg/dL), hypertension (≥130/85 mmHg) and alteration in fasting blood glucose (≥110 mg/dL). Range of HOMA-IR value were grouped into tertiles. Samples were diagnosed with IR if their HOMA-IR values ranged in 3rd tertile and non-IR if HOMA-IR values ranged between 1st and 2nd tertile. Hyperuricemia was diagnosed using cut-off value of 7 mg/dL. Samples were defined as hyperuricemia if the serum uric acid level exceeded ≥7 mg/dL and nomoruricemia if the value was <7 mg/dL. Central obesity was defined if WC > 90 cm and non central obesity if WC is WC ≤ 90.

2.4. Statistical analysis

To estimate the sample sizes (n) required for this study, we used the equation $n = NZ^2P(1\text{-}P)/d^2(N\text{-}1) + Z^2\ P\ (1\text{-}P)$, where N = 200, Z = 1.96, P = 0.500 and d = 0.07. The miminum sample size required for our study is 100 samples. To estimate the possibility of samples drop out, we used the calculation of n+(n x 10%) = 110. Therefore, samples needed for our study are 110 subjects. Descriptive statistics were used to determine the characteristics of study population. Independent *t*-test, Correlation test and Anova test were used. A $P < 0.05$ was considered to indicate the statistical significance. All analyses were performed using SPSS version 20.0 (IBM Co., Armonk, NY, USA).

3. Results

3.1. Participants characteristics

From 102 samples, we subdivided the patient population into the absence 38 (37%) or presence 64 (63%) of metabolic syndrome. The participants demographic, clinical and laboratory characteristics are shown in Table 1 and the distribution variables are shown in Table 2. The mean age of the patients were 51 ± 6.6 years, mean WC was 93.23 ± 9.76 and the mean serum uric acid was 6.49 ± 1.48.

Table 1
Participants demographic, clinical and laboratory characteristics (n = 102).

Variables	Range	Mean	SD
Age (years)	40 - 65	51,05	6,60
FBG (mg/dl)	73 - 313	111,77	48,40
Fasting Insulin	2,00 - 108,00	9,15	12,03
HOMAIR	0,36 - 7,48	2,18	1,84
HDL (mg/dl)	25 - 66	42,18	8,44
TG (mg/dl)	63 - 510	175,93	92,77
Uric Acid	2,6 - 11,0	6,49	1,48
Systolic Blood Pressure	110 - 189	136,26	16,45
(mmHg) Diastolic Blood Pressure	60 - 125	85,55	10,86
(mmHg) WC (cm)	70 - 116	93,23	9,76

Table 2
Serum uric acid, HOMA-IR, and MetS components variables distribution.

Variables	Categories	n	%
Waist Circumferences	Central obesity	68	66,7
	Non-central obesity	34	33,3
FPG	Impaired fasting plasma glucose	39	38,2
	Normoglycemia	63	61,8
Blood Pressure	Hypertenson	75	73,5
	Normotension	27	26,5
HDL	Normo-HDL	57	55,9
	Hypo-HDL-emia	45	44,1
TG	Hypertriglyceride	56	54,9
	Normotriglyceride	46	45,1
Uric Acid	Hyperuricemia	68	66,7
	Normouricemia	34	33,3
HOMA-IR	Non-IR	68	66,7
	IR	34	33,3

3.2. Accuracy of insulin resistance in the diagnosis of metabolic syndrome

The range of HOMA-IR 0.36–7.48 was classified into tertiles where 3rd tertile was considered as IR, and 1st to 2nd tertiles were considered as non-IR. The relationship of IR and MS are shown in Table 3. Subjects with IR were found higher in numbers and statistically significant in MetS compared to non-MetS, meanwhile subjects with non-IR, non-MetS and MetS were not found any statistical significance (88.23% vs 11.77%; 50% vs 50%; p = 0.000). In other words, IR has relationship in diagnosis of MetS.

3.3. Association between serum uric acid and insulin resistance

Bivariate analyses was perfomed to evaluate the association between insulin resistance and serum uric acid. The detailed results are shown in Table 4. The mean value of serum uric acid was 2.6–11 mg/dL. In subjects with IR, it was found that the mean uric acid was higher compared to subjects with non-IR. However, statistical significance was not found. (6.63 vs 6.42 mg/dL; P = 0.325).

3.4. Association between serum uric acid and metabolic syndrome

Bivariate analyses was perfomed to evaluate the association between MetS and serum uric acid. The detailed results are shown in Table 5 and Fig. 1. In subjects with MetS, the mean serum uric acid level was higher than subjects with non-MetS. However, statistical significance was not found. (6.62 vs 6.28 mg/dL, P = 0.556).

3.5. The association of MetS component and serum uric acid

If the subjects were classified according to the amount of MetS component, it showed that there was the tendency which the more MetS components then the higher the serum uric acid level. However, there was no statistical signifance found (Table 6 and Fig. 2).

Table 3
Relationship of insulin resistance and metabolic syndrome.

HOMA-IR	n	Non-MetS	MetS	P
Non-IR	68	34(50%)	34 (50%)	0,000
IR	34	4 (11,77%)	30 (88,23%)	

Table 4
Association between insulin resistance and serum uric acid.

HOMA-IR	Serum Uric Acid			
	n	Range	Mean	P
Non-IR	68	3,4–10,6	6,42	0,325
IR	34	2,6-11	6,63	

Table 5
Association of serum uric acid and metabolic syndrome.

Variable	Categories	n	%	Mean Uric Acid (mg/dL)	SD	P
MetS	Yes	64	62,7	6.62	1,4965	0,556
	No	38	37,3	6.28	1,4683	

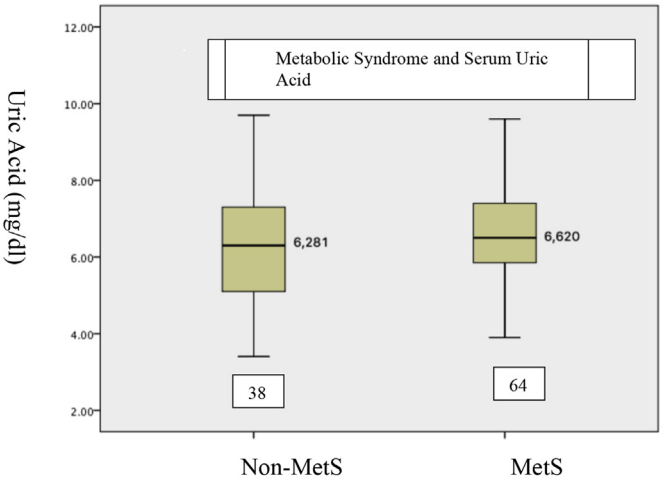

Fig. 1. Association of serum uric acid and metabolic syndrome (n = 102).

Table 6
The Association of the amount of MetS components and serum uric acid.

Variable	Categories	n	%	Mean SUA (mg/dL)	SD	P
The amount of components	0	5	4.9	5.92	1.00846	0,221
	1	12	11.8	6.2	1.58305	
	2	21	20.6	6.39	1.60046	
	3	33	32.4	6.5	1.59778	
	4 & 5	31	30.3	6.67	1.34405	

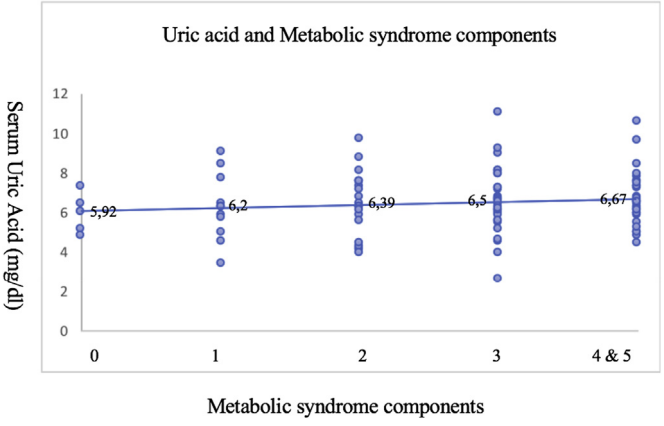

Fig. 2. The Association of serum uric acid and MetS components (n = 102).

3.6. The association of insulin resistance and metabolic syndrome with serum uric acid

The association of IR and MetS with serum uric acid showed that there was no significant relationship found between IR and non-IR from MetS with serum uric acid (Table 7).

4. Discussion

In our research, as shown in Table 3, it was found that there was significant difference in IR groups between MetS and non-MetS (30 with 88,23% vs 4 with 11.77%, P = 0.000). One reported study [8] found that IR was a contributive factor in developing MetS. They reported that metabolic syndrome was a result from the alteration in hypertension, lipid profile and blood glucose caused by central obesity which hyperinsulinemia and insulin resistance played important role. Since the examination of plasma insulin in this two decades is easy to do, there are many researches reporting insulin hormone level significantly correlated with plasma triglyceride, HDL cholesterol, uric acid and blood pressure. Subjects with hyperuricemia, dyslipidemia and hypertension were found often having hyperinsulinemia. Viazzi et al. [9] in 2014 stated that this mechanism happened because the role of hyperinsulinemia which acted as a good marker in measuring insulin resistance. Insulin resistance is a condition often found in an abnormal component of MetS subjects. Insulin resistance is thought to correlate with several risk factors of MetS such as dyslipidemia and hypertension. Subjects having essential hypertension are found to have IR even in the normotension condition. Insulin resistance is associated with severe hypertension. In a study from Ferranini et al. [10] in 1997 reported that insulin have peripheral vascular dilatation effects. The average vasodilatation respond from IR estimated between 15 and 30% in subjects with severe IR, diastolic and systolic blood pressure are reported having inverse relationship to insulin sensitivity with r value (0.18 vs 0.34; P < 0.005). Insulin resistance also has a role in lipoprotein metabolism. This case correlated with the elevation of triglyceride level and depressed HDL. High insulin sensitivity has inverse relationship with HDL-triglyceride ratio [11]. A new insulin mechanism theory which is reported by Yamashita et al. [12] in 2010 was that insulin can prevent the outflow of HDL Cholesterol from Acute Monositic Leukimia from its cells from macrophage through the inhibition mechanism of cholesterol ester hydrolase and ATP binding cassette transporter GI expression in study of invitro.

Several studies had already shown that there is a relationship of serum uric acid with IR and the causal relationship between these two were not yet explained with firm. Serum uric acid and hyperinsulinemia are often related with risk of hypertension, obesity and dyslipidemia. Subjects with high serum uric acid are associated to high HOMA-IR level. Our study found that serum uric acid range in IR between 2.6 and 11.0 mg/dL compared to non IR 3.4–10.6. The mean value of serum uric acid in IR tended to be higher than in non IR, but it failed to show significant difference (6.63 vs 6.412; P = 0.325) (Table 4).Our study was consistent with previous studies where they found significant high risk for developing hyperinsulinemia with serum uric acid in follow up study among non diabetic subjects. One study in their mice model reported that the depression of serum uric acid using XO inhibitor could reduce the incidence of IR [13]. Hyperuricemia should be early diagnosed and treated to prevent hyperinsulinemia occurred [14].

Our results showed that the amount of our subjects having metabolic syndrome is higher compared to non metabolic syndrome (62.7% vs 37.3%). The serum uric acid level also were found to be higher in MetS subjects compared to non MetS. However, no statistical significant was found (6.62 vs 6.28 mg/dL; P = 0.556) (Table 5). Our study was consistent with the findings from Nejatinamini et al. [15] which reported that there was a significant relationship between serum uric acid and the incidence of MetS. Individual having MetS had significantly higher in the level of serum uric acid compared to non-MetS (5.70 ± 1,62 vs 4,97 ± 1,30 mg/dL; p = 0,001). Other study conducted [16] found that serum uric acid was an independent risk factor from MetS and high concentration associated with the incidence of MetS. Previous studies [17,18] found that serum uric acid was an independent risk factor for developing hypertension. Hyperuricemia could cause hypertension through reduced nitric oxide synthase in kidney macula densa which stimulates renin angiotensin system (RAAS) and reduces kidney perfusion [24]. The most interesting part from these mechanisms was that uric acid-lowering drugs can repair this pathology. In a 2016 cohort study [19] found that metabolic syndrome was found in 39.1% with OR 1.89 (1.45–2.45 mg/dL) and central obesity was the cause of serum uric acid level variation.

Our results showed that there was positive tendency between serum uric acid and the amount of MetS component. The difference in mean between serum uric acid in MetS compared to non-MetS was found. According to Table 5 and Fig. 1, it shows how the increasing mean serum of uric acid is lineary proportional to the increasing of MetS component eventhough no significant difference was found from amount of component. This signified conclusion that the greater the amount of MetS components then the greater the serum uric acid. This is because serum uric acid contributes to the development of MetS and elevation of serum uric acid is associated with IR eventhough this mechanism is not clear yet. This study suits to the study conducted by Yoo et al. [2] in 2005 which reported that there was a correlation between serum uric acid concentration, IR and the number of MetS component. They divided the serum uric acid concentration into 4 groups and the concentration of serum uric acid was proportional to the number of MetS component according to NCEP ATP III (p < 0.001). They suggested hyperuricemia to be included as MetS component which depict the IR role. They also recommended hyperuricemia to be included as addition to become MetS components despite this still becomes controversy. The result [15] also supported the association of serum uric acid with the risk of MetS but until today, hyperuricemia is not included in NCEP criteria as MetS component. Our data showed that serum uric acid has positive trend associated with the number of MetS component. Further studies are required to evaluate the effect of hyperuricemia to MetS component.

One study [20] found that there is an association between MetS and hyperuricemia because the elevation of serum uric acid is a consequence from the increased absobrtion of uric acid in secondary proximal tubule causing hyperinsulinemia. Hyperuricemia

Table 7
The Association of insulin resistance and MetS with serum uric acid (n = 102).

		N	%	SUA Mean	P
IR -	Non-MetS	33	32.1	6.13	0,234
	MetS	35	34,3	6.69	
IR +	Non-MetS	5	4.9	7.24	0,577
	MetS	29	28,4	6,53	

subjects had RR of 1.6 for developing MetS. Our results do not find any significant relationship between non IR with MetS and non MetS with serum uric acid (6.69 vs 6.13 mg/dL; $p > 0.234$). In IR subjects, there was difference in mean serum uric acid between MetS and non-MetS, but no statistical significance was found. (7.24 vs 6.53 mg/dL; $P = 0.5777$). Our study was different with research conducted by Heshmat et al. [21] in 2016 who found that there was significant elevation serum uric acid in MetS compared to non-MetS. This was possible because number and distribution of samples are limited.

Hyperinsulinemia and IR were found in healthy subjects and both of these metabolic abnormality were often linked to dyslipidemia, hyperuricemia and hypertension [8]. In a study from 3681 samples found that the elevation of serum uric acid concentration increased the risk of type 2 diabetes melitus statistically significant. Insulin resistance is a connector between elevation of fasting blood glucose and elevation of uric acid. Insulin resistance was also said to have an important role in linking MetS, type 2 diabetes and hyperuricemia. The mechanism which is responsible is how it has been found that the effect of serum uric acid in promoting endotel dysfunction and overproduction of ROS especially in adipose tissue. A meta analysis conducted from 11 studies revealed that every 1 mg/dL raised of serum uric acid is associated with 17% risk of diabetes [22]. From study conducted by Yoo et al. [2], grouping subjects into 4 groups based on serum uric acid quartiles found that incidence of hypertension was higher than first quartile group compared to 3rd and 4th group (OR 1.192, $p < 0.001$). Their study also found that HOMA-IR was associated with serum uric acid level (OR 1.193, $p < 0.001$) and serum uric acid positively correlated with risk factor of MetS. The same result was also found [23] that every 1 mg/dL raised of serum uric acid was associated with the elevation of insulin action which is assessed using hyperinsulinemic-euglicemic clamp in 245 subjects. Subjects with MetS had higher serum uric acid compared to subjects without MetS ($5{,}70 \pm 1{,}62$ vs $4{,}97 \pm 1{,}30$ mg/dL; $P = 0{,}001$). After controlling gender, age and BMI, it was found that serum uric acid level was associated with triglyceride and negatively correlated with HDL cholesterol level [15].

5. Conclusion

Our study revealed that insulin resistance is associated with metabolic syndrome and both of these circumstances were independently found that there was tendency of the increasing serum uric acid. The role of insulin resistance in the relationship between metabolic syndrome and serum uric acid level was not proven in this study.

Declarations

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Conflict of interest

None declared.

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