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Research paper

Serum uric acid levels predict high hs-CRP levels in non-diabetic adult

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Abstract

Introduction: High-sensitivity C-reactive protein (hsCRP) is a microinflammation biomarker that has been widely accepted as an assessment tool for cardiovascular risk. Excess of serum uric acid levels is also linked to metabolic disorders and cardiovascular disease risk factors.

Aim: The study aimed to investigate the association between serum uric acid and cardiovascular risk defined based on hsCRP levels in non-diabetic adults.

Material and methods: This cross-sectional study included 90 non-diabetic adult subjects which comprised 45 males and 45 females. The uric acid test was performed by enzymatic colorimetric method while hsCRP was performed by immunoturbidimetric assay. High cardiovascular risk was defined as hsCRP of more than 3 mg/L.

Results and discussion: Serum uric acid had significant correlation with hsCRP levels in male and female subjects ($r = 0.376$, $P = 0.011$ and $r = 0.378$, $P = 0.011$, respectively). In male subjects, the uric acid cut-off of 7.415 mg/dL had 62.5% sensitivity and 83.8% specificity in predicting high cardiovascular risk (AUC = 0.671), while in females, the cut-off of 4.215 mg/dL had 73.3% sensitivity and 63.3% specificity (AUC = 0.704) in predicting the high risk. Males with uric acid of more than 7.415 mg/dL had 8.61 times having high cardiovascular risk compared those below the cut-off ($P = 0.014$, 95%CI = 1.609–46.07). Females with uric acid of more than 4.215 mg/dL had 4.75 times having high cardiovascular risk compared those below the cut-off ($P = 0.02$, 95%CI = 1.214–18.584).

Conclusions: Uric acid and hsCRP levels have a significant association. Serum uric acid levels may predict high cardiovascular risk defined based on hsCRP in males and females.

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1. INTRODUCTION

The final product of purine metabolism is uric acid, which is formed when purines are metabolized to hypoxanthine, xanthine, and uric acid under the activity of xanthine oxidase (XO).[1] Uric acid has an important role in the development of chronic disorders including hypertension, cardiovascular disease (CVD), metabolic syndrome, and kidney disease.[2] The elevation of serum uric acid has been associated with an independent predictor of CVD. High uric acid was reported to have an association with adverse cardiovascular outcomes including sudden cardiac death.[3] Serum uric acid had a significant relationship with the defective vascular structure and function assessed by the thickness of carotid intima-media and the velocity of pulse-wave.[4] In acute coronary syndrome patients, those with hyperuricemia suffered more coronary vessel number involvement than those with normal uric acid levels.[5] Patients with atherosclerotic plaque in the thoracic aorta had higher uric acid levels compared to normal ones.[6]

A plasma protein known as C-reactive protein (CRP), which is primarily synthesized by the liver, has been associated with atherosclerosis due to several characteristics, including complement system activation, apoptosis, monocyte recruitment, accumulation of lipids, activation of the vascular cell, and thrombus formation.[7] High-sensitivity CRP (hsCRP) test has a better quantification value for detecting CRP values less than 1 mg/L. Those with hsCRP levels more than 3 mg/L are considered as having a high risk of developing CVD.[8,9] hsCRP levels showed the ability to predict CVD across countries and ethnicities including Asians, Africans, Caucasians, and Hispanics.[10] The hsCRP levels were also reported to have significant positive associations with age, obesity, glucose and lipid levels, thus explaining its role in metabolic disorders and CVD pathogenesis.[11]

Serum uric acid and hsCRP levels have been linked to CVD, such as ischemic heart disease, coronary artery ectasia, stable coronary heart disease, and subclinical thoracic aortic atherosclerosis, however, their association particularly in non-diabetes adults with no cardiovascular symptoms are rarely investigated.[6,12–14]

2. AIM

This study aimed to investigate the association between serum uric acid and cardiovascular risk in non-diabetic adults as characterized by hsCRP levels.

3. MATERIAL AND METHODS

This was a cross-sectional study, conducted from August to September 2020. The research subjects were voluntary non-diabetic adults, with ages ranging from 20 to 40 years old. The inclusion criteria were healthy adults without a history of cardiovascular symptoms such as typical chest pain and dyspnea, who were willing to take part in the study with signed informed consent in line with the Declaration of Helsinki. Subjects with a history of diabetes mellitus, fasting glucose plasma of more than 126 mg/dL, using medicine to reduce uric acid levels, recently experiencing an infectious condition, or having a history of CVD were excluded from the study. A total of 90 adults participated in this research, consisting of 45 males and 45 females.

Anthropometric (height, weight) assessment, blood sampling, and laboratory tests were conducted at the Laboratory of Clinical Pathology, Hasanuddin University Hospital, Makassar, Indonesia.

Study subjects had an overnight fasting period of 8–12 hours. The subjects' height (in m) and weight (in kg) were recorded, and the body mass index (BMI) was derived using the formula body weight / height^2. Blood sampling was performed after the anthropometric assessment. Using a vacutainer, a 3 cm^3 venous blood sample was obtained from each subject, followed by separation of serum for fasting blood glucose (hexokinase) and uric acid (Trinder method) tests (Abx Pentra 400, Horiba, USA). Type 2 diabetes mellitus subjects were excluded based on fasting blood glucose levels according to the American Diabetes Association (ADA) criteria. The aliquot of serum (200 μL) of each participant was stored at –20°C until the testing of hsCRP by immunoturbidimetric assay (Cobas c 311, Roche, Mannheim). A high risk of developing CVD was defined on subjects with hsCRP levels of more than 3 mg/L, while those with hsCRP levels of less than 3 mg/L was considered as having a low risk of developing CVD.

The Kolmogorov–Smirnov test was performed to assess the parameters' normality distribution. The Mann–Whitney test was employed on parameters with non-normal distribution, whereas the *t*-test was used in normally distributed parameters. The subjects were then divided into male and female groups, and statistical analysis of each group was performed separately. The Pearson test was used to examine the correlation between normally distributed parameters while the Spearman test was used on non-normally distributed parameters. The effectiveness of uric acid levels in predicting a high risk of developing CVD based on hsCRP levels in males and females was evaluated using receiver operating characteristic (ROC) curves.

The ideal cut-off point for uric acid levels in both male and female groups in predicting a high risk of developing CVD was then established by the highest sum of sensitivity and specificity by analyzing the area under the ROC curve (AUC). Based on the best cut-off point of uric acid levels revealed by AUC, the odds ratio (OR) of having high CVD risk between those with uric acid levels above the cut-off and those below the cut-off was determined by χ^2 or Fisher's exact test. The Statistical Package for the Social Sciences, v. 21.0 (SPSS Inc, Chicago, IL, USA) software was used to conduct all statistical analyses.

4. RESULTS

Table 1 shows the characteristics of both the male and female groups of research participants. Age, BMI, and diastole do not differ significantly between male and female groups. Uric acid levels and systole are significantly higher in males while hsCRP is higher in the female group.

In males, a significant correlation is shown between uric acid and hsCRP levels, while BM and BMI significantly correlate with uric acid and hsCRP levels (Table 2).

The same correlations are found in females as in males. Also, systole and diastole have a significant correlation with hsCRP levels (Table 3).

ROC curve analysis (figure not shown) reveals that the AUC of uric acid levels in males and females has a significant value in predicting high CVD risk based on hsCRP levels (defined as hsCRP of more than 3 mg/L). In males, the uric acid cut-off of 7.415 mg/dL has the highest sum of sensitivity and specificity in predicting high CVD risk, while in females, the best cut-off is 4.215 mg/dL (Table 4).

Table 1. Characteristics of all, male and female subjects[a].

Variable	All , $n = 90$	Male , $n = 45$	Female , $n = 45$	P
Age, year	30.04 ± 4.99	29.76 ± 4.41	30.33 ± 5.46	0.582[b]
Body mass, kg	69.68 ± 16.58	75.57 ± 17.85	63.79 ± 12.90	<0.001[c]
Height, m	1.62 ± 0.08	1.68 ± 0.06	1.56 ± 0.04	<0.001[c]
BMI, kg/m^2	26.41 ± 5.38	26.54 ± 5.61	26.29 ± 5.20	0.885[c]
Systole, mmHg	115.72 ± 8.46	118.33 ± 7.69	113.11 ± 8.48	0.006[c]
Diastole, mmHg	75.33 ± 6.22	76.22 ± 5.76	74.44 ± 6.59	0.179[c]
Uric acid, mg/dL	5.16 ± 1.65	6.13 ± 1.67	4.18 ± 0.89	<0.001[c]
hsCRP, mg/L	2.24 ± 2.30	1.83 ± 2.24	2.64 ± 2.31	0.041[c]

Comments: [a] mean ± standard deviation; [b] *t*-Test; [c] Mann–Whitney test. *P* value is used to measure the difference between male and female groups.

Table 2. Correlation between uric acid and hsCRP with other parameters in the male group.

Variable	Uric Acid		hsCRP	
	r	P[a]	r	P[a]
Age	0.108	0.481	0.023	0.883
Body mass	0.733	<0.001	0.374	0.011
Height	–0.038	0.802	–0.239	0.483
BMI	0.812	<0.001	0.483	0.001
Systole	0.139	0.362	0.164	0.282
Diastole	0.060	0.693	0.018	0.908
Uric acid	–	–	0.376	0.011

Comments: [a] Spearman correlation test.

Table 3. Correlation between uric acid and hsCRP with other parameters in the female group.

Variable	Uric Acid		hsCRP	
	r	P[a]	r	P[a]
Age	0.206	0.174	0.813	0.23
Body mass	0.437	0.003	0.738	<0.001
Height	0.303	0.043	0.111	0.469
BMI	0.345	0.020	0.730	<0.001
Systole	0.222	0.143	0.341	0.022
Diastole	0.105	0.491	0.298	0.047
Uric acid	–	–	0.378	0.011

Comments: [a] Spearman correlation test.

Table 4. The AUC, sensitivity, and specificity of uric acid levels by the most optimal cut-off point in predicting high CVD risk based on hsCRP levels.

Gender	AUC (95% CI)	Sensitivity	Specificity	Cut-off point
Male	0.671 (0.436-0.905)	0.625	0.838	7.415
Female	0.704 (0.539-0.870)	0.733	0.633	4.215

Table 5. The odds ratio of having high CVD risk based on the most optimal uric acid levels in the male group.

Uric acid level	hsCRP		P^a	OR(95%CI)
	High risk, *n*(%)	Low risk, *n*(%)		
More than 7.415 mg/dL	5(45.5)	6(54.5)	0.014	8.61(1.609–46.07)
Less than 7.415 mg/dL	3(8.8)	31(91.2)		Reference
Total	8(17.78)	37(82.22)		

Comments: [a] Fisher's exact test.

Table 6. The odds ratio of having high CVD risk based on the most optimal uric acid levels in the female group.

Uric acid level	hsCRP		P^a	OR(95% CI)
	High risk, *n*(%)	Low risk, *n*(%)		
More than 4.215 mg/dL	11(50.0)	11(50.0)	0.02	4.750(1.214–18.584)
Less than 4.215 mg/dL	4(17.4)	19(82.6)		Reference
Total	15(33.33)	30(66.67)		

Comments: [a] Fisher's exact test.

In the male group, those with uric acid levels of more than 7.415 mg/dL have 8.61 times having high CVD risk compared to those with uric acid below the cut-off levels (Table 5). Females with uric acid levels of more than 4.215 mg/dL have a 4.75 times probability of having high CVD risk compared to those below the cut-off (Table 6).

5. DISCUSSION

In this research, it was shown that uric acid levels had a significant correlation with hsCRP levels, both in healthy non-diabetic adult male and female groups. This finding was also supported by several other reported studies among type 2 diabetes mellitus subjects, postmenopausal women, and healthy octogenarians.[15–17] On the contrary, a non-significant correlation was reported in young and middle-aged healthy subjects, although CRP levels were reported to increase in hyperuricemia subjects.[18]

Uric acid is produced predominantly in the liver as the result of exogenous purine pool metabolism derived mainly from protein intake and endogen degradation of the nucleic acid of dead cells. Uric acid can get through the fibers of vascular smooth muscle, activating several signal transduction pathways, triggering the increased inflammatory mediator expression, thus increasing the arterial pressure and causing the hypertrophy of vascular smooth muscle cells.[19] XO creates reactive oxygen species (ROS) along the process of converting hypoxanthine to xanthine, and finally to uric acid. The ROS produced may cause endothelial dysfunction, contributing to atherosclerosis development. On the other hand, the XO act on macrophages may increase the formation of foam cells, and the production of ROS, therefore triggering the CVD.[20]

CRP is an inflammatory protein produced mainly by the liver with 2 isoforms, a pentameric isoform, and a monomeric isoform. CRP is produced in pentameric isoform and may be dissociated irreversibly to 5 monomeric isoforms. Monomeric CRP selectively binds very low-density-lipoprotein (VLDL) and low-density lipoprotein (LDL) while pentameric CRP interacts with oxidized LDL (oxLDL) and minimally modified LDL. CRP increases the uptake of ox-LDL, forming foam cells and stimulates cholesterol esters accumulation in macrophages. Interaction between both CRP isoforms induces the atherosclerosis process.[7]

As hsCRP is widely accepted as an inflammation biomarker in predicting cardiovascular risk, its significant correlation with uric acid levels may reflect the ability of uric acid in predicting high hsCRP levels as a CVD risk biomarker.[8] The significant correlation between uric acid and hsCRP levels of our findings can be described by several explanations. Uric acid in serum might have a role in inflammation by directly stimulating mitogen-activated protein (MAP) kinases in vascular cells, and activating of nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-kB), thus enhancing the production of CRP and monocyte chemoattractant protein-1 (MCP-1).[21] One study reported that human hepatoma HepG2 cells that were incubated with uric acid increased messenger ribonucleic acid (mRNA) expression of pro-inflammatory markers including CRP through the activation of the NF-kB signaling pathway, proving that uric acid may act independently in triggering cells to produce CRP.[22]

There is a significant correlation between BMI and both uric acid and hsCRP. This shows that the correlation between uric acid and hsCRP may also be mediated by the excess body weight and adiposity reflected by BMI. Higher BMI had been linked with worse cardiovascular parameter evaluations.[23] The increased consumption of food and drinks which is rich in fructose and high amount of protein intake may lead to an increase in body weight, and accumulation of abdominal fat, and therefore cause the increased production of uric acid through exogenous metabolism.[19] Excess of fat especially in the abdominal region which may induce the microinflammation state is the main determinant factor of CRP synthesis in the liver due to the response to pro-inflammatory cytokines production, particularly interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[24]

The AUC analysis of our report showed that the best uric acid cut-off with the highest sum of sensitivity and specificity in predicting high CVD risk based on hsCRP levels were 7.415 mg/dL (sensitivity 62.5%, specificity 83.8%) in males and 4.215 mg/dL (sensitivity 73.3%, specificity 63.3%) in females. Male subjects with uric acid levels of more than 7.415 mg/dL had an 8.61 times odd ratio of having high CVD risk compared to those below the cut-off, whereas female subjects with uric acid levels of more than 4.215 mg/dL had 4.75 times risk compared to those below the cut-off. The interesting thing was that the cut-off value in males was only a bit higher than the upper limit reference range of male uric acid levels (7 mg/dL), while the cut-off in females was situated within the normal reference range of female uric acid levels (2.7–6.1 mg/dL). This seemed that a minor increase in uric acid levels might have a significant impact on microinflammation leading to higher CVD risk. Those with high uric acid levels tended to have high hsCRP levels and therefore had a higher risk of CVD in the future. The interaction between uric acid and hsCRP seemed to be mediated through the adiposity state, though uric acid alone could trigger the increase in hsCRP production as reported before.[19,22,24]

This was one of few studies concerned about the association between uric acid and hsCRP in healthy non-diabetic adults which reported the uric acid cut-off in predicting high CVD risk among the male and female populations.

This research has several limitations. First, the study's cross-sectional design cannot account for the causal relationship between hsCRP and uric acid. Second, the population of this study only consisted of adults aged from 20 to 40 years old, thus the cut-off may not be generated for the older population. Third, we only evaluate the direct relationship between uric acid and hsCRP without accounting for the contribution of other factors that may be related to hsCRP levels.

6. CONCLUSIONS

(1) Uric acid has a significant association with hsCRP levels.
(2) Serum uric acid levels may predict high cardiovascular risk defined based on hsCRP in males and females.

Conflict of interest
None declared.

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Ethics
The Hasanuddin University-Faculty of Medicine's Ethical Committee authorized the ethical recommendation and assigned it the approval recommendation number 395/UN4.6.4.5.31/PP36/2020.

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