

음주연관 안면홍조에 따른 혈중 요산과 호모시스테인 농도 관계의 변화

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The Relationship between Uric Acid and Homocysteine Levels based on Alcohol-related Facial Flushing

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Background: This study aimed to determine the correlation between blood uric acid and homocysteine levels, based on alcohol-related facial flushing.

Methods: Among male adults who visited a health examination center of a university hospital located in Daejeon, Korea, for a personal health examination from March 2013 to February 2014, 702 subjects were analyzed including 401 subjects without alcohol-related facial flushing and 301 with facial flushing. Pearson's correlation and stepwise multivariate linear regression analyses were performed between the log homocysteine levels and other variables including uric acid.

Results: Uric acid showed a significant positive correlation with log homocysteine ($\gamma=0.166$, $P=0.001$) ($\beta=0.176$; $P=0.001$) in the non-flushing group. In contrast, none of the variables showed any significant correlations with log homocysteine in the flushing group.

Conclusions: Alcohol users not exhibiting alcohol-related facial flushing showed a positive correlation between uric acid and homocysteine levels, whereas those without facial flushing showed no such correlation.

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INTRODUCTION

Previously, a high plasma uric acid level was considered

a cause of gout induced by an inflammatory reaction, since uric acid crystals are deposited in the joint capsule. However, following reports that various forms of kidney diseases are also seen in patients with gout, the role of uric acid in organs other than the joints is being studied extensively. Multiple studies have suggested that uric acid is a significant factor involved in cardiovascular mortality, chronic kidney disease, metabolic syndrome, and hypertension; this has led to an expansion in the clinical definition

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of hyperuricemia.¹⁻⁴⁾ Factors related to blood uric acid level include race, dietary habit, body mass index (BMI), alcohol intake, renal function, and intake of medications containing diuretics.^{5,6)}

Homocysteine, a sulfur-containing amino acid, is a product of methionine (essential amino acid) metabolism.⁷⁾ Hyperhomocystinemia is related to an elevated risk in cardiovascular disease, and is an independent risk factor of atherosclerosis.^{8,9)} The factors that affect the level of homocysteine include age, deficiencies in folic acid, vitamin B12 and vitamin B6 levels, nutritional variations, smoking, chronic renal failure, drugs, and presence/absence of menopause.^{10,11)}

Hyperuricemia and hyperhomocystinemia are both believed to be risk factors for cardiovascular disease (CVD). However, a relationship between these two substances has not been accurately reported to date. Prior studies investigating the relationship between blood uric acid and homocysteine levels have reported a direct correlation between uric acid and homocysteine.^{12,13)} In contrast, other studies have claimed that no significant correlations were observed in the levels of homocysteine between patients with gout and the control group patients.^{14,15)}

Alcohol-related facial flushing is a common symptom observed in Asians indicating the expression of an inactive aldehyde dehydrogenase, which reduces the metabolism of acetaldehyde, elevating the levels of acetaldehyde during alcohol metabolism.¹⁶⁾ It is known that this symptom is not only related to alcohol metabolism but also to metabolic reactions and diseases;^{17,18)} therefore, this symptom should be considered in studies targeting the Asian population.

However, previous studies have not investigated the effect of facial flushing on the correlation between blood uric acid and homocysteine levels. This study aimed to determine the correlation between blood uric acid and homocysteine levels, based on alcohol-related facial flushing (associated with metabolism reactions in the body).

METHODS

1. Study subjects

The subjects of this study included Korean male adults who visited a health examination center of a university hospital located in Daejeon, Korea, for a personal health ex-

amination from March 2013 to February 2014. Among the subjects, individuals with diseases potentially influencing the homocysteine and uric acid levels, such as chronic renal disease, impaired kidney function (<60 glomerular filtration rate [GFR]), hypothyroidism, or malignant disease, were excluded. In addition, individuals on medications that would potentially affect the levels of homocysteine and uric acid, such as a uric acid lowering agents, diuretics, methotrexate, phenytoin, carbamazepine, theophylline, multivitamin, and other dietary supplements, were also excluded. To investigate the effects of alcohol-related facial flushing, the subjects displaying accurate symptoms of the presence or absence of alcohol-related facial flushing, and who drank more than 0.5 glass of alcohol per week were targeted. Seven-hundred and two subjects were analyzed, 401 subjects without alcohol-related facial flushing and 301 with facial flushing. The Catholic University of Daejeon St. Mary's Hospital institutional review board approved this study (Institutional Review Board number: DIRB-00129_3-001).

2. Study methods

This is a retrospective study, which reviewed data obtained from a health examination center. Data related to age, disease history, current diseases, smoking status, medications, and alcohol use, were obtained from the participants through a self-administered questionnaire. In addition, BMI was calculated using the Quetelet Index, which used the height and weight data from body measurements.¹⁹⁾

Alcohol use was assessed by investigating the mean daily alcohol consumption and the number of drinks ingested per week in the past year. The amount of alcohol consumed per week was calculated by multiplying the mean daily alcohol consumption and number of drinks taken per week. A standard drink is equal to 14 g of alcohol according to the guidelines recommended by the National Institute on Alcohol Abuse and Alcoholism.²⁰⁾ The presence or absence of alcohol-related facial flushing was indicated by "always", "sometimes", or "never", using a self-administered questionnaire. Participants who answered "always" and "sometimes" were classified into the alcohol-related facial flushing group, and participants who answered "never" were classified into the non-flushing group. This classification method, based on the study conducted by Yokoyama et al.,²¹⁾ aimed to

determine the inactive ALDH2 level and has a sensitivity and specificity of 96.1% and 79.0%, respectively.

Blood taken during the health examination was used to determine the triglyceride, total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (r-GTP), uric acid, and homocysteine levels. The blood samples were collected after 12 hrs of fasting. The biochemical (enzymatic) triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, AST, ALT, r-GTP, and uric acid assays were performed using an automated clinical chemistry analyzer (TBA-200FR NEO, Toshiba, Tokyo, Japan). GFR was calculated using the IDMS-MDRD equation.²²⁾ Blood homocysteine level was examined by fluorescence polarization immunoassay using an IMx homocysteine assay (Axyon 4011, Abbott Laboratories, Chicago, IL, USA).

3. Statistical analysis

The general characteristics, BMI, and blood test results were compared between the facial flushing and non-flushing groups. Categorical variables, including history of smoking, presence or absence of hypertension, and presence or absence of diabetes, were compared and analyzed between the two groups using the chi-square test. Continuous variables, including age; BMI; the amount of alcohol consumed per week; and triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, uric acid, and homocysteine levels, were compared and analyzed by the independent sample Mann-Whitney U-test. The distribution of the continuous variables was examined by the Kolmogorov-Smirnov test. Variables showing normal distribution were presented as mean±standard deviation, whereas variables without normal distribution were presented as median values (quartiles). The values without normal distribution, including those for HDL-C, triglyceride, AST, ALT, r-GTP, and homocysteine, were log transformed for analyses. Pearson's correlation and the stepwise multivariate linear regression analyses were performed between the log homocysteine levels and other variables. The relationship between weekly alcohol consumption and homocysteine levels was examined by dividing the samples into <4, ≥4, <8, and ≥8 groups (according to weekly alcohol consumption), as done in previous stud-

ies investigating the relations between quantity, facial flushing, and metabolism change.^{17,23)} Each drinks-consumed-per-week group and log homocysteine was compared among the facial flushing and non-flushing groups by analysis of variance. The *T*-test was performed to compare the log homocysteine value with facial flushing in each drinks-consumed-per-week group. These analyses were performed using the SPSS ver. 21 software platform (SPSS Inc., Chicago, IL, USA), and *P*-value less than 0.05 was considered statistically significant.

RESULTS

1. General characteristics of the study subjects

The mean±standard deviation age of the patients was 51.2±9.5 and 51.7±9.4 years for the non-flushing and flushing groups, respectively; this difference was not statistically significant. In addition, there were no significant differences in BMI and the presence or absence of hypertension and diabetes between the two groups. Although there was a difference in current smoking patterns between the non-flushing (236 smokers; 58.9%) and flushing (165; 54.8%) groups, which was also not statistically significant. There was a statistically significant difference in the drinks consumed per week between the non-flushing (12.5; 4.0-20.0 glasses) and flushing (7.5; 2.3-19.8 glasses) groups.

The results of the blood tests revealed no significant difference in uric acid and homocysteine levels; the uric acid levels in the non-flushing and flushing groups were 6.4±1.3 mg/dL and 6.3±1.3 mg/dL, respectively, while the homocysteine levels were 11.5 (9.8-13.4) and 11.7 (10.3-13.3), respectively. The HDL-cholesterol levels between the non-flushing (48.0; 42.0-54.0) and flushing (46.0; 40.0-52.0) groups were significantly different. There was no differences in total cholesterol, triglyceride, LDL-cholesterol, AST, ALT, r-GTP, and GFR levels between the two groups (Table 1).

2. Correlations between serum log homocysteine and other parameters

Correlations between log homocysteine and other continuous variables were analyzed using Pearson's correlation

Table 1. Characteristics of study subjects^a

	Non-flushing group (n=401)	Flushing group (n=301)
Age, y	51.2±9.5	51.7±9.4
Body mass index, kg/m ²	25.2±3.2	25.3±2.8
Hypertension	92 (22.9)	69 (22.9)
Diabetes	25 (6.2)	25 (8.3)
Current-smoking	236 (58.9)	165 (54.8)
Drinking amount, drinks/wk	12.5 (4.0-20.0) ^b	7.5 (2.3-19.8) ^b
Uric acid, mg/dL	6.4±1.3	6.3±1.3
Homocysteine, μmol/L	11.5 (9.8-13.4)	11.7 (10.3-13.3)
Total-cholesterol, mg/dL	195.8±35.6	191.8±35.8
LDL-C, mg/dL	111.5±30.5	110.0±30.1
HDL-C, mg/dL	48.0 (42.0-54.0) ^c	46.0 (40.0-52.0) ^c
Triglyceride, mg/dL	144.0 (95.5-206.0)	138.0 (98.5-202.5)
AST, mg/dL	23.0 (19.0-28.0)	23.0 (20.0-30.0)
ALT, mg/dL	26.0 (20.0-35.0)	27.0 (20.0-39.0)
γ-GTP, mg/dL	31.0 (19.5-60.5)	33.0 (20.0-58.0)
eGFR, mL/min/1.73 m ²	92.1 (82.9-104.1)	92.1 (82.6-103.8)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

^aValues are presented as N (%) or mean±SD or median expression (interquartile range).

^b<0.001, analysis with Mann-Whitney test or chi-square test (1 drink=alcohol 14 g).

^c<0.05, analysis with Mann-Whitney test or chi-square test.

in the non-flushing and flushing groups. Uric acid showed a significant positive correlation with the log homocysteine ($\gamma=0.166$, $P=0.001$) in the non-flushing group. A significant correlation was also observed between total cholesterol and log homocysteine ($\gamma=0.111$, $P=0.027$). However, the other variables showed no significant correlations (Table 2).

None of the variables in the flushing group, including blood uric acid levels, showed any correlation with log homocysteine.

The relationship between log homocysteine and the variables were analyzed using a stepwise multivariate linear regression test. Uric acid ($\beta=0.176$; $P=0.001$), BMI ($\beta=-0.125$; $P=0.015$) and total cholesterol ($\beta=0.100$; $P=0.047$) exhibited significant correlations with log homocysteine in the non-flushing group. In contrast, none of the variables showed any significant correlations with log homocysteine in the flushing group.

3. Association between serum total homocysteine concentration and weekly alcohol consumption

We observed a difference in the amount of alcohol con-

Table 2. Correlations between log homocysteine and other variables (non adjusted)

	Non-flushing group (n=401)	Flushing group (n=301)
	r	r
Age	0.070	0.043
BMI	-0.064	-0.093
Total cholesterol	0.111 ^a	0.019
LDL-C	0.088	-0.004
Log HDL-C	0.068	-0.013
Log TG	-0.024	0.045
Uric acid	0.166 ^b	0.087
Log AST	0.038	0.052
Log ALT	-0.055	-0.085
Log γ-GTP	0.091	-0.014

Abbreviations: r, correlation coefficient; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride.

^a<0.05 analysis of variance with Pearson's correlation test.

^b<0.01 analysis of variance with Pearson's correlation test.

Table 3. Log homocysteine by amount of alcohol

Drinks/wk	Non-flushing group (n)	Flushing group (n)
≥0.5, <4	2.5±0.3 (84)	2.5±0.2 (102)
≥4, <8	2.5±0.2 (70)	2.5±0.3 (62)
≥8	2.5±0.3 (247)	2.5±0.2 (137)

Values are presented as mean±SD.

sumed per week between the non-flushing and flushing groups. Therefore, the changes in homocysteine levels related to drinks consumed per week were examined in the non-flushing and flushing groups. Both non-flushing and flushing groups showed no differences in log homocysteine based on the number of drinks consumed per week. In addition, we observed no differences in the groups with similar drinking quantities between the non-flushing and flushing groups (Table 3).

DISCUSSION

This study aimed to reveal the relationship between uric acid and homocysteine based on the presence or absence of alcohol-related facial flushing. The results of this study revealed that alcohol uses not exhibiting alcohol-related facial flushing showed a positive correlation between uric acid and homocysteine levels, whereas those without facial flushing showed no such correlation. This suggests the possibility that alcohol-related facial flushing affects uric acid and homocysteine metabolism.

There have been several studies targeting normal people, which showed a positive correlation between blood homocysteine and uric acid levels.^{12,13)} This study also found a correlation between uric acid and homocysteine levels in individuals not displaying alcohol-related facial flushing, which is consistent with the findings of previous studies. Since Caucasians rarely display alcohol-related facial flushing, the non-facial flushing group in this study could show similar results. These correlations might be attributed to the metabolic syndrome. The results of previous studies- the metabolic syndrome was observed to be common among people with gout,²⁴⁾ while other studies demonstrated a relationship between high homocysteine levels and metabolic syndrome.²⁵⁾

However, it is unclear if the blood uric acid and homocysteine levels were simultaneously increased by metabolic syndrome. In this study, homocysteine levels were not correlated with neutral fat and HDL-C; homocysteine in the non-flushing group exhibited a weak correlation with BMI and total cholesterol when analyzed by stepwise multivariate linear regression. In this study, the facial flushing group exhibited no correlation between homocysteine and uric acid levels. This result are consistent with those of the previous studies.^{14,15)} It is possible that the relationship between homocysteine and uric acid levels is affected by alcohol-related facial flushing. This was because a majority of the previous studies was conducted in Asian countries, where the ratio of alcohol-related facial flushing is high.

In our subjects who did not express facial flushing, uric acid and homocysteine showed a positive correlation. The effect of simultaneous elevation of the homocysteine and uric acid levels on the body remains unclear. Hyperhomocysteinemia and hyperuricemia are believed to be risk factors for atherosclerosis and CVD. These two factors may cause redox stress or epithelial dysfunction in each track (or by a synergistic effect), resulting in the formation of atherosclerosis.^{26,27)} On the other hand, although the role of uric acid in humans remains unclear, it is known to function as an antioxidant during the initial step of atherosclerosis.²⁸⁾ In fact, a number of studies have shown a J-shape pattern relating uric acid and CVD.²⁹⁾ It can be expected that the effect of uric acid on atherosclerosis development decreases owing to this antioxidant effect.

Acetaldehyde is not effectively processed in people with alcohol-related facial flushing, compared to those not show-

ing facial flushing, because of the low activity of ALDH2.¹⁶⁾ When acetaldehyde is retained for a longer time in the body, it has a toxic effect on body metabolism.^{17,18)} Homocysteine and uric acid metabolism is also affected by acetaldehyde, which increases the densities of these two compounds in the body.^{30,31)} Therefore, it has been suggested that the correlation between homocysteine and uric acid levels was inhibited by acetaldehyde in the facial flushing group.

This study has some limitations. Firstly, despite previous study showing high specificity and sensitivity of the classification (based on the questionnaire) and some other studies often utilized this method,^{16,17)} the non-flushing and flushing groups were classified according to the self-administered questionnaire. Secondly, this study is a cross-sectional study, and not a prospective study. In addition, we did not check additional factors such as vit. B group or lipid lowering drugs, which might have influenced on the homocysteine levels between the non-flushing and flushing group. Future studies should be conducted on a large scale and include females and additional data.

In conclusion, the relationship between blood uric acid and homocysteine levels could be altered based on alcohol-related facial flushing. Therefore, the results of this study suggest that alcohol-related facial flushing must be considered when interpreting the relationship between homocysteine and uric acid levels, both risk factors of CVD in the normal population.

요 약

연구배경: 본 연구는 음주연관 안면 홍조 여부에 따라 혈중 요산과 호모시스테인 농도의 연관 관계가 다른지를 분석하였다.

방법: 2013년 3월부터 2014년 2월까지 대전의 한 대학병원에 건강검진을 목적으로 내원한 성인 남성 중 702명(비안면홍조자 401명, 홍조자 301명)을 대상으로 하였다. 비안면홍조자 그룹과 안면 홍조자 그룹에서 로그 호모시스테인과 요산을 포함한 다른 변수들과의 관계를 Pearson's correlation과 stepwise multivariate linear regression analyses로 분석하였다.

결과: 비안면홍조군에서 혈중 요산 농도와 로그 호모시스테인은 유의한 양의 연관관계를 보였다($r=0.166$, $P=0.001$) ($\beta=0.176$; $P=0.001$). 하지만 홍조군에서는 어느 변수도 로그 호모시스테인과 유의한 연관관계를 보이지 않았다.

결론: 음주관련 안면홍조가 없는 음주자의 경우 혈중 요

산과 호모시스테인 농도의 연관관계는 양의 연관관계를 보이지만, 음주관련 안면홍조가 있는 경우에는 연관관계를 보이지 않는다고 판단된다.

중심 단어: 호모시스테인, 요산, 안면홍조, 음주

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