INTRODUCTION

Over the past decades, serum uric acid (UA) has emerged as a cardiovascular risk marker. Increased serum UA level is known to predict the risk of hypertension, diabetes mellitus, and renal function. Alcohol is a risk factor for hyperuricemia and gout. Whether changes in alcohol consumption are associated with changes in serum UA levels and factors affecting changes in UA levels remain unclear.

METHODS

Subjects were 5,327 Japanese who underwent two annual health examinations (mean interval, 2.7 years). They were stratified according to changes in serum UA levels and alcohol consumption.

RESULTS

The change in body mass index, waist circumference (WC), low-density lipoprotein cholesterol (LDL-C), UA, aspartate transaminase (AST), and alanine transaminase gradually increased as changes in UA increased for both men and women. In men, the proportion of subjects who consumed ≥ 25 g ethanol/day in the ≥ 0.3 mg/dL UA change group was not particularly higher than that of in non-drinker (17.4% versus 19.7%) at baseline. In women, the proportion of subjects who consumed ≥ 25 g ethanol/day in the ≥ 0.3 mg/dL UA change group was lower than that of in non-drinker (19.3% versus 17.8%) at baseline. Multiple linear regression analysis revealed that changes in WC, LDL-C, triglyceride, AST and γ-glutamyltranspeptidase were associated with changes in UA. When changes in serum UA levels stratified by changes in UA levels and alcohol consumption were investigated, changes in alcohol consumption did not affect UA level changes; however, regardless of alcohol consumption change, anthropometric measures, lipid levels, renal function, and transaminases were worse in the increased UA level group. Subjects who increased alcohol consumption and had increased UA levels showed the worst anthropometry, BP, lipid levels, UA and transaminases changes.

CONCLUSION

Changes in UA level correlated with changes in anthropometry, lipid levels, renal function, and transaminases. Changes in alcohol consumption did not affect changes in UA level; however, subjects who increased alcohol consumption and had increased UA levels had the worst metabolic profile changes.

KEY WORDS uric acid, alcohol consumption, lifestyle habit

ABSTRACT

Objective Serum uric acid (UA) is associated with obesity, insulin resistance, metabolic syndrome components, hypertension, diabetes mellitus, and renal function. Alcohol is a risk factor for hyperuricemia and gout. Whether changes in alcohol consumption are associated with changes in serum UA levels and factors affecting changes in UA levels remain unclear.

Methods Subjects were 5,327 Japanese who underwent two annual health examinations (mean interval, 2.7 years). They were stratified according to changes in serum UA levels and alcohol consumption.

Results The change in body mass index, waist circumference (WC), low-density lipoprotein cholesterol (LDL-C), UA, aspartate transaminase (AST), and alanine transaminase gradually increased as changes in UA increased for both men and women. In men, the proportion of subjects who consumed ≥ 25 g ethanol/day in the ≥ 0.3 mg/dL UA change group was not particularly higher than that of in non-drinker (17.4% versus 19.7%) at baseline. In women, the proportion of subjects who consumed ≥ 25 g ethanol/day in the ≥ 0.3 mg/dL UA change group was lower than that of in non-drinker (19.3% versus 17.8%) at baseline. Multiple linear regression analysis revealed that changes in WC, LDL-C, triglyceride, AST and γ-glutamyltranspeptidase were associated with changes in UA. When changes in serum UA levels stratified by changes in UA levels and alcohol consumption were investigated, changes in alcohol consumption did not affect UA level changes; however, regardless of alcohol consumption change, anthropometric measures, lipid levels, renal function, and transaminases were worse in the increased UA level group. Subjects who increased alcohol consumption and had increased UA levels showed the worst anthropometry, BP, lipid levels, UA and transaminases changes.

Conclusion Changes in UA level correlated with changes in anthropometry, lipid levels, renal function, and transaminases. Changes in alcohol consumption did not affect changes in UA level; however, subjects who increased alcohol consumption and had increased UA levels had the worst metabolic profile changes.
pometric and biological parameters related to MetS such as blood pressure, blood sugar, waist circumference (WC), lipids (TG and HDL-C), and renal function.

This study aimed to investigate whether the changes in alcohol consumption were related to the changes in serum UA level and to identify the parameters that reflect UA change in Japanese.

SUBJECTS AND METHODS

Subjects

A total of 7,013 subjects underwent the baseline annual health examination at the Health Evaluation and Promotion Center at the Tokai University Hachioji Hospital between April 2011 and March 2015; follow-up health examinations were performed at the same institute between January 2012 and March 2016 at a mean follow-up interval of 2.7 years. Information pertaining to the medical history was obtained through self-administered questionnaires and interviews conducted by nurses. After excluding 1,686 subjects who did not meet criteria at baseline, 5,327 subjects were included in this study. The exclusion criteria and total number of subjects were as follows; subjects who were undergoing treatment for hypertension (n = 1,029), diabetes mellitus (n = 200), dyslipidemia (n = 683), hyperuricemia (n = 273), subjects for history for stroke (n = 161), CVD (n = 232) and renal failure (n = 5).

At the first annual health examination, the results of the examinations were explained to all of the subjects, and well-trained medical doctors and nurses provided instructions to all patients regarding lifestyle improvements.

Notably, no fatal atherosclerotic vascular events were recorded during the 2.7-year study period.

Measurements

WC was measured at the level of the umbilicus during mid-expiratory phase in the standing position. Blood pressure was measured at the upper right arm using an automatic blood pressure monitor (TM-2655P; A&D, Tokyo, Japan) while the subject was seated. Blood samples were collected early in the morning after an overnight fast. UA level was measured with an L-Type uricase-N-(3-sulfopropyl)-3-methoxy-5-methylamine method (Wako Pure Chemicals, Osaka, Japan). Hyperuricemia was defined as a plasma UA level >7.0 mg/dL.

The mean UA level was measured with an L-Type UA M kit based on the uricase-N-(3-sulfopropyl)-3-methoxy-5-methylamine method (Wako Pure Chemicals, Osaka, Japan). Hyperuricemia was defined as a plasma UA level >7.0 mg/dL.

Subjects

Subjects

The mean age at baseline was 48.2 years for both men and women. Among men, blood pressure, AST and number of MetS were significantly higher, and BMI, WC, FPG, FIRI, LDL-C, TG, HDL-C, hsCRP, AST, ALT, GGT, smoking, exercise, and alcohol conditions as dependent variables. Variable selection was performed by stepwise procedure, and a dummy-variable model was designed after changes in smoking conditions, exercise conditions and alcohol consumption were categorized. If there were 4 categories, 3 dummy variables were created. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). All P values were two-tailed, and P-values < 0.05 were considered as statistically significant.

RESULTS

Table 1 lists the baseline and follow-up characteristics of the subjects. The mean age at baseline was 48.2 years for both men and women. Among men, blood pressure, AST and number of MetS were significantly higher, and BMI, WC, FPG, FIRI, HOMA-IR, LDL-C, UA, eGFR, ALT, and GGT were significantly lower at follow-up as compared to those at baseline. Among women, blood pressure and number of MetS were significantly higher and FPG, LDL-C, UA, and eGFR were significantly lower at follow-up as compared to those at baseline.

Upper panel of Table 2 lists the changes in the parameters stratified according to changes in UA and gender. Study subjects were divided into four groups according to changes in UA quartile and gender. The mean (±SD) UA change in the < −0.5 mg/dL, −0.5 to < −0.1 mg/dL, −0.1 to < 0.3 mg/dL, and ≥ 0.3 mg/dL group was −1.1 ± 0.7, −0.3 ± 0.1, 0.1 ± 0.1, and 0.7 ± 0.4
Increased alcohol intake is known to be associated with an increased risk of hyperuricemia in both men and women. Therefore, we investigated the relationship between the changes in alcohol consumption and UA changes.

Determinants of changes in serum UA levels were analyzed by multiple linear regression analysis (Table 3). Among the following variables included in this study (changes in BMI, WC, BPs, FBS, FIRI, LDL-C, TG, LDL-C, hsCRP, AST, ALT, GGT, smoking, exercise, and alcohol conditions), five variables (changes in WC, LDL-C, TG, AST and GGT) were selected by a stepwise procedure. The results of the analysis revealed that changes in alcohol consumption were not associated with changes in UA levels.

Table 4 presents the changes in serum UA stratified by changes in UA and alcohol consumption. Bonferroni’s multiple comparison test revealed that mean changes in UA levels according to changes in alcohol consumption (grouped into three: decreased, unchanged and increased) in the same UA change group (i.e. < −0.5 mg/dL, −0.5 to < −0.1 mg/dL, −0.1 to < 0.3 mg/dL, and ≥ 0.3 mg/dL) were not significantly different. In the same UA change group, it is appeared that changes in alcohol consumption did not affect mean UA changes.

Table 5 presents the changes in various parameters stratified by changes in alcohol consumption (decreased, unchanged, or increased) and UA (decreased or increased). In all alcohol consumption change groups, anthropometric measures, lipid level, and renal function in the increased UA group were worse than those in the decreased UA group. Among subjects in the increased alcohol consumption group, in addition to the anthropometric measures, BP, lipid levels, renal function, and transaminases were
Table 2 Characteristics of changes in various parameters in study subjects stratified by changes in UA and gender

(a) Men

| Characteristic | Changes in UA (mg/dL) | (n = 2,900) |
|---------------|----------------------|-------------|
| Age           | < −0.5 (n = 822)     | 2.7 ± 1.2   |
|               | −0.5 to < −0.1 (n = 583) | 2.6 ± 1.2   |
|               | −0.1 to < 0.3 (n = 845) | 2.6 ± 1.2   |
|               | ≥ 0.3 (n = 850)       | 2.7 ± 1.3   |
|               | Total (n = 2,900)     | 2.7 ± 1.2   |
| BMI (kg/m²)   | −0.3 ± 1.2           | 0.0 ± 1.1** |
| Waist circumsference (cm) | −1.4 ± 4.4 | 0.0 ± 4.9** |
| Systolic BP (mmHg) | −0.2 ± 12.6   | 1.0 ± 12.5 |
| Diastolic BP (mmHg) | 0.6 ± 10.2  | 1.7 ± 9.7   |
| FPG (mg/dL)   | −1.8 ± 9.1           | −1.3 ± 7.1  |
| FRI (μU/mL)   | −0.28 ± 3.67         | 0.04 ± 2.67*|
| HOMA-IR       | −0.09 ± 1.08         | 0.00 ± 0.73*|
| TG (mg/dL)    | −6.5 ± 62.8          | −1.9 ± 60.9 |
| LDL-C (mg/dL) | −6.6 ± 23.8          | 0.2 ± 19.6**|
| HDL-C (mg/dL) | −0.1 ± 8.4           | 0.2 ± 8.0   |
| UA (mg/dL)    | −1.1 ± 0.7           | 0.1 ± 0.1** |
| eGFR (mL/min/1.73 m²) | −0.6 ± 7.5    | −1.1 ± 7.6**|
| AST (IU/L)    | −0.9 ± 8.3           | 0.8 ± 11.5  |
| ALT (IU/L)    | −3.4 ± 13.9          | 0.1 ± 12.3  |
| GGTT (IU/L)   | −10.6 ± 34.6         | 2.7 ± 28.6** |
| hsCRP (mg/dL) | 0.01 ± 0.47          | 0.03 ± 0.57 |

Alcohol consumption

| Level | (n = 404) | (n = 598) | (n = 674) | (n = 751) | (n = 2,427) |
|-------|-----------|-----------|-----------|-----------|-------------|
| 0     | 299       | 210       | 225       | 320       | 1,054       |
| 1     | 317       | 218       | 244       | 301       | 1,080       |
| 2     | 63        | 77.7%     | 55        | 85.5%     | 233         |
| 3     | 82        | 10.0%     | 64        | 11.0%     | 312         |
| 4     | 47        | 82%       | 28        | 48.6%     | 172         |
| 5     | 14        | 17.7%     | 10        | 17.7%     | 49          |

(b) Women

| Characteristic | Changes in UA (mg/dL) | (n = 674) |
|---------------|----------------------|-----------|
| Age           | < −0.5 (n = 598)     | 2.6 ± 1.2 |
|               | −0.5 to < −0.1 (n = 598) | 2.6 ± 1.2 |
|               | −0.1 to < 0.3 (n = 674) | 2.6 ± 1.2 |
|               | ≥ 0.3 (n = 751)       | 2.6 ± 1.2 |
|               | Total (n = 2,427)     | 2.6 ± 1.2 |
| BMI (kg/m²)   | −0.2 ± 1.2           | 0.0 ± 1.1* |
| Waist circumsference (cm) | −0.5 ± 4.6    | −0.2 ± 3.9**|
| Systolic BP (mmHg) | 1.8 ± 12.4   | 1.1 ± 12.2 |
| Diastolic BP (mmHg) | 1.4 ± 9.9   | 1.3 ± 9.2   |
| FPG (mg/dL)   | −1.8 ± 9.1           | −1.5 ± 9.6 |
| FRI (μU/mL)   | −0.38 ± 2.90         | 0.11 ± 5.22*|
| HOMA-IR       | −0.13 ± 0.78         | 0.03 ± 1.54*|
| TG (mg/dL)    | −1.0 ± 41.2          | −0.8 ± 31.1 |
| LDL-C (mg/dL) | −6.5 ± 22.6          | −0.5 ± 22.0**|
| HDL-C (mg/dL) | −1.0 ± 10.1          | 0.0 ± 9.2   |
| UA (mg/dL)    | −0.9 ± 0.3           | 0.0 ± 0.1** |
| eGFR (mL/min/1.73 m²) | −1.4 ± 8.2    | −1.0 ± 7.3**|
| AST (IU/L)    | −3.4 ± 35.0          | 0.9 ± 5.0** |
| ALT (IU/L)    | −5.6 ± 38.7          | 0.6 ± 7.3** |
| GGTT (IU/L)   | −3.7 ± 28.1          | 0.9 ± 11.2* |
| hsCRP (mg/dL) | 0.01 ± 0.21          | 0.01 ± 0.38 |

Alcohol consumption

| Level | (n = 598) | (n = 850) |
|-------|-----------|-----------|
| 0     | 145       | 215       |
| 1     | 143       | 216       |
| 2     | 38        | 45        |
| 3     | 44        | 74        |
| 4     | 29        | 33        |
| 5     | 5         | 13        |

Upper panel: variables are given as means ± standard deviations. BMI: body mass index; BP: blood pressure; FPG: fasting plasma glucose; FRI: fasting immunoreactive insulin; HOMA-IR: homeostasis model assessment-Insulin resistance; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; UA: uric acid; eGFR: estimated glomerular filtration rate; AST: aspartate transaminase; ALT: alanine transaminase; GGTT: γ-glutamyltranspeptidase; hsCRP: high-sensitivity C-reactive protein.

* p < 0.01, ** p < 0.05 (-0.5 to < −0.1 vs ≥ 0.3), *** p < 0.01 (-0.5 to < −0.1 vs ≥ 0.3), **** p < 0.01 (-0.5 to < −0.1 vs ≥ 0.3) by Bonferroni’s multiple comparison test.

Lower panel: variables are given as number of subjects (percentage of total). Self-reported alcohol consumption was classified as follows: 0: non-drinker; 1: occasional drinker that defined as no more than two times a week and < 50 g ethanol/day; 2: < 25 g ethanol/day; 3: 25 to < 50 g ethanol/day; 4: 50 to < 75 g ethanol/day; 5: ≥ 75 g ethanol/day.
worse in the subjects with increased UA.

**DISCUSSION**

In this study, changes in UA level correlated with changes in anthropometry, lipid levels, renal function, and transaminases. Changes in the alcohol consumption did not affect the absolute change in UA level; however, subjects with increased alcohol consumption together with increased UA changes revealed the
worst changes in the metabolic profile.

Alcohol is a potential risk factor for increased serum UA and gout. The association of increased alcohol intake with hyperuricemia and risk of gout has been reported in several studies; however, changes in UA were not associated with the changes in alcohol consumption in the present study. Following possibilities might be considered for the result. First, less than 20% subjects consumed ≥ 25 g ethanol/day at baseline. In addition, 75% subjects did not change alcohol consumption during follow-up. Surprisingly, a majority of the subjects who increased the alcohol consumption, revealed reduced UA level. This is partly explained by the fact that among all the subjects who increased alcohol consumption, only 2.8% increased their alcohol consumption to ≥ 25 g ethanol/day.

The kidney is responsible for elimination of 70% of the daily UA production, which explains the negative association between UA and eGFR observed in this study. Besides, UA itself may affect the renal function, since increased UA level over a span of 10 years was reported to be an independent risk factor for decline in eGFR than that of the baseline levels of UA, the presence of hypertension, or diabetes using the in a large cohort of general population.

Although serum UA is known to be positively associated with hypertension, changes in both systolic and diastolic blood pressure were erratic when subjects were divided according to the changes in UA, in this study. The reason for this is not clear, although it may be attributable to the relatively short study span (2.7 years). In contrast, changes in BMI and WC were positively associated with the changes in UA, as expected. In a recent epidemiological study, UA was known to be associated with nonalcoholic fatty liver disease (NAFLD), independent of MetS. Additional studies have revealed that elevated serum UA is an independent predictor of NAFLD. Recently, UA was reported to have directly increased the hepatic fat accumulation via a mechanism that involved induction of mitochondrial oxidative stress. UA induces TG accumulation by SREBP-1c activation via induction of endoplasmic reticulum stress in hepatocytes. In accordance with these reports, we revealed that the changes in the transaminases were significantly higher as UA change increased. Unfortunately, existence of NAFLD was not examined in the present study. It is known that SREBP-1c regulates genes of fatty acid biosynthetic pathways. SREBP-1c activation induces fatty acid synthesis, and thereby induces fatty acid incorporation into TG. This may partly explain the increased TG levels in this study. The reason for association of changes in UA and LDL-C with LDL-C in this study, remains unclear. In a recent cross-sectional study, we reported that serum UA was not associated with LDL-C. Instead, a positive association of UA with oxidized LDL (MDA-LDL) and small-dense LDL was observed.

The present study had certain limitations. All subjects in this study were middle-aged Japanese subjects; therefore, the relationship between UA level and clinical markers may have been affected by ethnicity. Detailed information on diet and beverage intake including alcohol, all of which may affect the UA level, was not obtained. It is probable that serum transaminase levels came from not only NAFLD but also alcoholic liver damage. Eventually, our results were calculated from the data of only a fraction of the subjects who underwent the annual health examination; therefore, our findings may not be entirely generalizable to all Japanese subjects.

In conclusion, changes in UA level correlated with changes in anthropometry, lipid levels, renal function, and transaminases. Changes in alcohol consumption did not affect the UA changes in this study; however, subjects with higher alcohol consumption revealed increased UA changes and worst metabolic profile changes. Therefore, other investigations including anthropometry, blood pressure, lipid levels and transaminases may be considered for subjects who increased both alcohol consumption and UA levels. Cutting down on alcohol and appropriate health guidance by physicians and nurses might be recommended accordingly.

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The author states that he has no Conflict of Interest (COI).

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