Effect of green tea catechins on uric acid metabolism after alcohol ingestion in Japanese men: a randomized crossover study

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Abstract

Background

Alcohol consumption is associated with hyperuricemia and gout. Previous studies have indicated a role for green tea catechins in uric acid (UA) metabolism. This study aimed to elucidate the effect of green tea catechins in terms of enhancing urinary excretion of UA and xanthine/hypoxanthine (Xa/HX) after alcohol ingestion.

Methods

In a randomized crossover study, 10 healthy subjects consumed test meals, including a Japanese distilled spirit (Shōchū) with water (SW) or Shōchū with catechin-rich green tea (SC), each containing 20 g of alcohol. The SC contained 617 mg of total catechin. Serum and urine UA and Xa/HX concentrations were measured. Blood samples were collected after 2.5 h, and urine samples were collected between 0 and 5 h after consuming the test meal.

Results

Urine UA and Xa/HX excretions were significantly higher in the SC group than in the SW group ($P < 0.05$). UA clearance and fractional UA excretion tended to increase more in the SC group than in the SW group. No significant differences in S-UA and S-Xa/Hx concentrations were observed between the SW and SC groups.

Conclusions

Based on these observations, it was concluded that green tea catechins can enhance the excretion of UA and Xa/HX, even though alcohol is ingested.

Trial registration

The protocol was approved by the Ethics Committee of the University of Shizuoka and registered with UMIN (University Hospital Medical Information Network in Japan). Trial registration number: UMIN000040076. Registered 7 April 2020 – Retrospectively registered, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000045687

Keywords

hyperuricemia, green tea catechins, xanthine, hypoxanthine, alcohol ingestion

Background

Hyperuricemia is the main risk factor for gout and is also closely associated with metabolic syndrome, chronic kidney disease, and cardiovascular disease [1-5]. It was reported that common dysfunctional variants of ATP binding cassette subfamily G member 2 (ABCG2) have a much stronger impact on the progression of hyperuricemia than several environmental risk factors, such as obesity and alcohol consumption [6]. However, changes in lifestyle might have an impact on hyperuricemia, since the prevalence rates of gout and hyperuricemia continue to rise [7]. Thus, lifestyle improvement may be important for preventing hyperuricemia.

A previous study reported that alcohol consumption is associated with the development of gout [8]. Alcohol consumption results in increased serum uric acid (UA) concentrations because of accelerated purine metabolism and decreased renal clearance of UA [9]. It was reported that allopurinol, a xanthine oxidase (XO) inhibitor, seems to be effectively controlling the rapid increase in plasma UA concentrations following beer ingestion [10]. However, few studies have evaluated the potential of food components on UA metabolism after alcohol consumption.

Green tea, which is widely consumed in Asian countries, contains polyphenols, particularly catechins. The major catechin present in green tea is epigallocatechin gallate. Previously, green tea polyphenols were observed to reduce the expression of XO and renal urate transporters and to decrease serum UA concentrations in hyperuricemic mice [11]. In addition, green tea extract lowers serum UA concentrations in healthy individuals to some extent [12]. These studies together indicate a role for green tea catechins in UA metabolism. However, the effect of green tea catechins in terms of enhancing the urinary excretion of UA after alcohol ingestion remains to be understood. Since humans do not have a uricase, which is only found as a non-functional pseudogene in the human genome [13], it is necessary to elucidate the physiological response in human intervention studies.

Therefore, this study aimed to elucidate the effects of green tea catechins on UA metabolism after alcohol ingestion.

Methods

Subjects

Ten healthy men were recruited in this study. Exclusion criteria were liver or renal dysfunction, alcohol dependence, and receiving treatment for hyperuricemia or gout. Subjects who had alcohol intolerance were also excluded. The clinical and biological characteristics of the subjects are shown in Table 1. The mean values ± standard deviation (SD) of age and body mass index were 25.0 ± 4.5 years and 22.1 ± 2.4 kg/m^2, respectively.

The present study was performed after obtaining written informed consent from all subjects and was approved by the Ethics Committee of the University of Shizuoka.

The study was performed in accordance with the Helsinki Declaration.

Study protocol

We used a randomized crossover study design. The experiment was conducted so that the test days were separated by a washout period of at least 7 days. All the subjects were asked to avoid heavy exercise and any intake of alcohol and purine-rich foods (more than 200 mg/100 g) for 3 days prior to each study day. All the subjects were instructed to eat from 20:00 to 21:00 h prior to each test day. After an overnight fast, the subjects were provided with the same prescribed foods (breakfast) at 08:00 h and were required to consume breakfast within 20 min. The subjects were provided with their test meals (lunch) at 13:00 h and required to consume each test meal within 20 min. During the experimental period, all subjects were instructed to drink water, 100 mL/h. All subjects underwent a 5 h urine collection from 13:00 to 18:00 h. Venous blood samples were collected at 15:30 h, which was the mid-point of the 5 h urine collection.

Test meals

Two different test meals were used: a Japanese distilled spirit (Shōchū) with water (SW) and Shōchū with catechin-rich green tea (SC). The SW and the SC each contained 20 g alcohol and were made up to produce a final total volume of 500 mL. We used catechin-rich green tea, which is a commercial beverage, and the SC contained 617 mg of total catechin. All test meals were ingested with 60 g steamed chicken and 10 g sesame dressing (Table 2). Steamed chicken contained about 85 mg/60 g purines and Shōchū did not contain purine according to the guidelines for the management of hyperuricemia and gout in Japan.

Blood and urine analysis methods and anthropometric measurements

Blood samples were centrifuged at 2,400 rpm for 10 min at 4°C and separated into serum and stored at −80°C until analysis of serum creatinine (Cre), UA, and xanthine/hypoxanthine (Xa/Hx) concentrations. Urine samples were used for analysis of pH, Cre, UA, and Xa/Hx concentrations. The analyses of serum and urine samples were performed by a blood test company, SRL, Inc. (Tokyo, Japan), except for the analyses of urine pH and Xa/Hx concentrations. The pH was measured using a portable pH meter (LAQUA act, D-71, Horiba Scientific, Kyoto, Japan). The concentration of Xa/Hx was measured using a Xa/Hx colorimetric assay kit (Bio Vision, USA). Anthropometric measurements were determined using a bioelectrical impedance analysis method (innerscan DUAL RD-909, TANITA Corporation, Tokyo, Japan). Height was measured using a stadiometer.

Calculating formulas

We calculated the creatinine clearance (Ccr), filtered UA load (F_{UA}), UA clearance (C_{UA}), urinary UA excretion per kilogram of body weight per hour (U-UA excretion), and renal fractional UA excretion (FE_{UA}) using the following formulas (U denotes urine, S denotes serum, BSA denotes body surface area, and BW denotes body weight):

$$Ccr = U\text{-volume} \times U\text{-Cre} / (S\text{-Cre} \times min) \times 1.73 / BSA$$

$$F_{UA} = (S\text{-UA} / 100) \times Ccr$$

$$C_{UA} = U\text{-volume} \times U\text{-UA} / (S\text{-UA} \times min) \times 1.73 / BSA$$

$$U\text{-UA excretion} = U\text{-UA} \times (U\text{-volume}/100) / BW / h$$

FE_{UA} = (U-UA × S-Cre) / (U-Cre × S-UA) × 100

We also calculated filtered Xa/Hx load ($F_{Xa/Hx}$), Xa/Hx clearance ($C_{Xa/Hx}$), urinary Xa/Hx excretion per kilogram of body weight per hour (U-Xa/Hx excretion), and renal fractional Xa/Hx excretion ($FE_{Xa/Hx}$) using the following formulas:

$F_{Xa/Hx}$ = S-Xa/Hx × Ccr

$C_{Xa/Hx}$ = U-volume × U-Xa/Hx / (S-Xa/Hx × min) × 1.73 / BSA

U-Xa/Hx excretion = (U-Xa/Hx/1000) × U-volume / BW / h

$FE_{Xa/Hx}$ = (U-Xa/Hx × S-Cre) / (U-Cre × S-Xa/Hx) × 100

Statistical analysis

All data are shown as means ± SD. The Shapiro–Wilk statistic was used for data normality testing. Parametric analysis was used for normal distribution data, and non-parametric analysis was used for data exhibiting a non-normal distribution. Differences between the SW and SC groups were identified using a paired *t*-test or the Wilcoxon signed-rank test. Probability (*P*) values less than 0.05 were considered statistically significant in all analyses. Statistical analyses were performed using SPSS for Windows, release 26.0 (SPSS, Chicago, IL).

Results

Serum UA and Xa/Hx concentrations

The S-UA concentration in the SW group was 6.3 ± 1.0 mg/dL, and in the SC group, it was 6.3 ± 0.9 mg/dL. The S-Xa/Hx concentration in the SW group was 11.7 ± 12.7 μg/mL, whereas 11.4 ± 12.2 μg/mL in the SC group. No significant differences were observed in S-UA and S-Xa/Hx concentrations between the two groups.

Urinary volume and pH

Urinary volume in the SW group was 848 ± 157 mL, whereas 991 ± 252 mL in the SC group. Urinary pH in the SW group was 6.5 ± 0.2, and in the SC group, it was 6.5 ± 0.3. No significant differences in urinary volume and pH were observed between the two groups.

Renal UA metabolic indices

Renal UA metabolic indices are shown in Figure 1. F_{UA} did not differ significantly between the SW and SC groups (Figure 1A). U-UA excretion in the SC was significantly higher than in the SW group (SW, 0.45 ± 0.08; SC, 0.52 ± 0.09 mg/kg/h; $P < 0.05$) (Figure 1C). Although C_{UA} and FE_{UA} did not differ significantly between the SW and SC groups, C_{UA} and FE_{UA} were slightly higher in the SC group than in the SW group (C_{UA}: SW, 7.76 ± 2.14; SC, 8.75 ± 2.23 mL/min/1.73 m^2; $P = 0.054$; FE_{UA}: SW, 6.08 ± 1.36; SC, 6.64 ± 1.42%; $P = 0.060$) (Figure 1B, D).

Renal Xa/Hx metabolic indices

Renal Xa/Hx metabolic indices are shown in Figure 2. No significant differences in $F_{Xa/Hx}$, $C_{Xa/Hx}$, and $FE_{Xa/Hx}$ were observed between the SW and SC groups (Figure 2A, B, D). U-Xa/Hx excretion in the SC group was significantly higher than in the SW group (SW, 0.08 ± 0.04; SC, 0.16 ± 0.05 mg/kg/h; $P < 0.01$) (Figure 2C).

Discussion

In the present study, we investigated the effects of green tea catechins on UA

metabolism after alcohol ingestion. We showed that U-UA and U-Xa/Hx excretions in the test individuals receiving Shōchū with catechin-rich green tea (SC group) were significantly higher than in those who received Shōchū with water (SW group). C_{UA} and FE_{UA} in the SC group were slightly higher than in the SW group but not significantly so.

Hyperuricemia is defined as a S-UA concentration higher than 7.0 mg/dL. The S-UA concentration is tightly regulated by UA reabsorption and excretion in the kidney, and various urate transporters mediate UA reabsorption and excretion [14]. Urate anion transporter 1 (URAT1), which transports UA across the apical membrane of proximal tubule cells, is the major urate reabsorption transporter. The organic anion transporters (OAT) 1 and OAT3 are localized at the basolateral side of the proximal tubular epithelial cells membrane and play an important role in UA excretion. Ethanol ingestion increases the concentration of lactate in the blood [9, 10], and lactate reportedly reduces renal excretion of UA by competing for OAT1 and OAT3 with UA [14]. In addition, lactate accelerates the reabsorption of UA in the renal epithelial cells via URAT1 [15]. In contrast, it was reported that green tea polyphenols reduce URAT1 expression and increase OAT1 and OAT3 expressions in the kidney of hyperuricemic mice [11]. In this study, we observed an increase of U-UA excretion in the SC group. Accordingly, our result suggested that green tea catechins might increase U-UA excretion through increasing UA clearance via urate transporters, even though alcohol was ingested.

XO is the key enzyme that produces UA. Previously, green tea polyphenols dose-dependently decreased XO activity in the liver of the hyperuricemic mice [11, 16]. It was also reported that the consumption of green tea inhibited the increase in plasma XO activity induced by exercise in weight-trained men [17]. In this study, U-Xa/Hx excretions were significantly higher in the SC group than in the SW group, indicating

that the increase in U-Xa/Hx excretion in the SC group might be due to the effect of green tea catechins on XO activity, although we could not measure XO activity directly.

Although we did not directly measure plasma catechin concentrations, several previous studies reported that plasma catechin concentrations are elevated within 1–2 h after intake of green tea [18-20]. This could suggest that the promoting effect on UA and Xa/Hx excretions in the SC group was due to green tea catechins.

There was a trend toward urinary volume being higher in the SC group than in the SW group ($P = 0.073$). During the experimental period, all subjects were instructed to drink water, 100 mL/h, and so the total fluid intake was equal. Previous studies suggested that a diuretic response to caffeine-containing drinks is likely to occur in response to an acute dose of caffeine of about 300 mg or more, being unlikely, however, at doses of about 250 mg or less [21]. In addition, it was reported that a caffeine intake of 6 mg/kg in the form of coffee can induce an acute diuretic effect, whereas 3 mg/kg does not disturb the fluid balance in healthy adults [22]. The catechin-rich green tea used in this study contained 91.4 mg caffeine (equivalent to one cup of coffee), which is a lower dose than used in previous studies [21, 22]. Hence, these results suggested that the increase in U-UA excretion in the SC group was due to the effect of green tea catechins and not the effect of caffeine.

No significant differences were observed between the two groups regarding S-UA and S-Xa/Hx concentrations. In this study, venous blood samples were collected only at 150 min after ingestion of test meal, which is the mid-point of the 5 h urine collection. A previous report showed that plasma concentrations of UA, hypoxanthine, and xanthine peak at 30 or 90 min after beer ingestion (10 mL/kg body weight) [10]. Thus, we were not able to observe the peak values in S-UA and S-Xa/Hx

concentrations.

Several limitations of our study should be considered. We did not examine the effect of water ingestion, which could have been done by adding a control group. To determine the effect of green tea catechins on UA metabolism, it is necessary to examine the effect of water ingestion and monitor the time course of serum and urinary UA, hypoxanthine, xanthine, and catechin concentrations. Finally, we used catechin-rich green tea, which is equivalent to five cups of regular green tea. Therefore, it is necessary to investigate whether the effect of green tea catechins can be dose-dependently observed for regular green tea.

Conclusions

This study showed significantly higher U-UA and U-Xa/Hx excretions in healthy men receiving Shōchū with catechin-rich green tea than in those receiving Shōchū with water. In conclusion, this study illustrates the potential of green tea catechins to enhance the excretion of UA and Xa/Hx, even when alcohol is ingested simultaneously.

Abbreviations

ATP binding cassette subfamily G member 2: ABCG 2; UA: uric acid; XO: xanthine oxidase; SD: standard deviation; SW: Shōchū with water; SC: Shōchū with catechin-rich green tea; Cre: creatinine; Xa/Hx: xanthine/hypoxanthine; Ccr: creatinine clearance; F_{UA}: filtered uric acid load; C_{UA}: uric acid clearance; U-UA excretion: urinary uric acid excretion per kilogram of body weight per hour; FE_{UA}: renal fractional uric acid excretion; $F_{Xa/Hx}$: filtered Xa/Hx load; $C_{Xa/Hx}$: Xa/Hx clearance; U-Xa/Hx excretion: urinary Xa/Hx excretion per kilogram of body weight per hour; $FE_{Xa/Hx}$: renal fractional Xa/Hx excretion; URAT1: urate anion transporter 1; OAT: organic anion transporters.

Declarations

Acknowledgments

We are grateful to the volunteers who participated in the study.

Authors' contributions

The authors' contributions to manuscript were as follows: YK and HA conceived the research idea and designed the study. YK, AY, MH, MA, and TA collected, analyzed, and interpreted the data. TA and TH contributed significant advice. YK and AY drafted the manuscript. HA edited the manuscript. All the authors contributed to revisions of the manuscript and reviewed the final version.

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Availability of data and materials

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of the University of Shizuoka.

Consent for publication

Prior to data collection, the purpose of the study was explained to the participants and their informed consent was recorded.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Uric acid metabolic indices

(A) Filter load of uric acid, F_{UA}; (B) uric acid clearance, C_{UA}; (C) urinary uric acid excretion per kilogram of body weight per hour, U-UA excretion; (D) renal fractional excretion of uric acid, FE_{UA}.

SW, Shōchū with water; SC, Shōchū with catechin-rich green tea.

Values are means ± SD represented by vertical bars. * denotes significant differences between the SW and SC groups ($P < 0.05$).

Figure 2. Xanthine/hypoxanthine metabolic indices

(A) Filter load of xanthine/hypoxanthine, FXa/Hx; (B) xanthine/hypoxanthine clearance, $C_{Xa/Hx}$; (C) urinary xanthine/hypoxanthine excretion per kilogram of body weight per hour, U-Xa/Hx excretion; (D) renal fractional excretion of xanthine/hypoxanthine, $FE_{Xa/Hx}$.

SW, Shōchū with water; SC, Shōchū with catechin-rich green tea.

Values are means ± SD represented by vertical bars. ** denotes significant differences between the SW and SC groups ($P < 0.01$).