Alcohol Quantity and Type on Risk of Gouty tophi

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Abstract

Objective: The aim of this study was to explore the impact of drinking alcohol on tophi and its surrounding inflammation in the joints by ultrasound.

Methods: We conducted a cross-sectional study on 356 gout patients and collected their information of drinking history, clinical biochemical parameters and ultrasound results. Multiple regression analyses including several variables and potential confounders were then performed.

Results: Relative to no drinking, more alcohol intake (>200 g/week), longer drinking time (>20 years) and higher frequency of drinking (>2 times/week) had significant positive effects on the size of tophus after controlling for potential confounders (P=0.024; P=0.002; P=0.040). Further subgroup analysis of different ages illustrated that more alcohol consumption had positive effects on the size of tophi only in the younger gout patients (≤50 years old), rather than in older ones (>50 years old). However, alcohol consumption had no significant association with the formation and number of tophus, and the associations between type of drinking and tophi was not observed in the current study. Moreover, except for tophi, there was no relationship between alcohol consumption and other ultrasound signs including double-contour sign (DCS), bone erosion, effusion and synovial hypertrophy.

Conclusion: Alcohol consumption is closely associated with ultrasound-detected tophi in gout patients. More alcohol intake, longer drinking time and higher frequency of drinking are crucial factors that positively affect the size of tophus, especially in younger gout patients. However, significant association between type of alcohol and tophi was not observed in the current study.

Introduction

Gout is inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals in various joints and soft tissues [1-4]. Epidemiological data indicate that the global prevalence of gout has risen from 0.08% in 2010 to the range of <1% to 6.8% in 2020 [2-5]. The persistent deposition of MSU is a dynamic process with a low-level continuous recruitment, which can result in tophi, bone erosion, loss of cartilage, tendon damage and inflammation of the joints, followed by an increase in social and economic burdens [6-13].

Alcohol consumption has long been considered a potential trigger for hyperuricemia and gout attacks. Most previous studies focused on the relevance between alcohol consumption and the risk of occurrence of gout, which have illustrated that ethanol intake can increase serum urate by reducing urate excretion and increasing urate production, leading to the fluctuation of blood uric acid levels, thereby increasing the risk of first and recurrent attacks of gout [14-20]. Besides, alcohol consumption has been shown to have a significant dose-response relationship with the risk of recurrent gout [20, 15]. However, whether this is associated with the occurrence and development of tophi and its surrounding joint inflammation has not been clearly revealed. Clarification of the joint damage for gout imparted by alcohol consumption would have practical clinical implications for management of patients with established gout.

With the development of medical imaging technology, ultrasound has been increasingly used in the clinical diagnosis of gout in recent years, as a painless, non-invasive, reliable, reproducible and low-cost method without radiation exposure [3, 21-24]. The use of ultrasound provides convenience for the early detection of the smaller tophus, which solves the problem that visual identification of subcutaneous tophus is not accurate and sensitive enough [21, 25]. Moreover, compared with other imaging methods, ultrasound can more sensitively identify not only tophi but also erosion in and around the joints as well as inflammation of the surrounding soft tissues [3, 24, 26, 27]. Consequently, in the current research, we analyzed the information on history of alcohol, ultrasound results and clinical biochemical indicators of 356 gout patients in detail, aimed at exploring the relationship between alcohol consumption and joint damage such as tophi and bone erosion, help to avoid the adverse consequences caused by tophi and other complications, and provide rational recommendations for the scientific management of patients with gout.

Methods

Patients enrollment and study design

The cross-sectional study was conducted on 505 gout patients who visited the Shandong Province Gout Clinic, the Affiliated Hospital of Qingdao University from August 2015 to October 2019 and performed joint ultrasound examination, which mainly analyzed via electronic medical records, and called back the unclear parts of the medical records. All patients satisfied the 2015 ACR/ EULAR classification criteria for gout [28]. Exclusive criteria were: (1) Patients with a history of arthritis other than gout; (2) Patients with a history of trauma or surgery at the ultrasound site; (3) Patients who experienced acute gout attacks during the examination; (4) Patients unable to cooperate with examination and medical history collection. This study finally included 356 patients.

We retrieve the electronic medical records of all subjects and record their age, gender, disease duration, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), transaminase ratio(AST/ALT), blood urea nitrogen (BUN), serum creatinine (Cr), the estimated glomerular filtration rate (eGFR) , Body Mass Index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum uric acid (UA), fasting blood glucose(GLU), serum triglyceride (TG), serum cholesterol (CH), urate-lowering therapy (ULT), family history of gout, history of alcohol and ultrasound examination results of all patients . The estimated glomerular ltration rate (eGFR) was calculated from the CKD-EPI equation: $GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. All subjects received standard clinical and laboratory examinations and evaluations. The study was approved by the ethics committee of Affiliated Hospital of Qingdao University, and obtained the informed consents of all participants.

Assessment of alcohol history

At the Clinical Medical Center of Gout of the Affiliated Hospital of Qingdao University, the trained doctors conducted systematic interviews or telephone return calls to all participants to determine their history of alcohol. Data on history of alcohol include: frequency of drinking (times/ week), alcohol intake (g/week), drinking time (years), type of drinking (beer/ liquor/ wine). The type of drinking was recorded as the most frequently consumed alcoholic beverage. Alcohol intake (g/ week): According to the ratio recommended in the "Dietary Guidelines for Chinese Residents" (2007): 25g alcohol (ethanol) is equivalent to 750mL beer, 250mLwine, and 50g liquor, we determined the alcohol intake each time via multiplying the consumption of each alcoholic beverage by its ethanol content, and then multiplied by the frequency of drinking (times/ week) to calculate the average weekly alcohol intake. Participants were divided into three categories according to their alcohol intake status: non-drinkers, former drinkers, and drinkers. People who used to drink alcohol frequently in the past, but have not drunk in the past year before the ultrasound examination were defined as former drinkers [29].

Assessment of potential confounders

Alcohol consumption and tophi may be affected by various other conditions. Therefore, we systematically assessed the potential confounding factors of all participants. Previous studies have shown that in addition to drinking, age, disease course, blood pressure, eGFR, UA and ULT are also risk factors of tophi[30, 31]. We analyzed whether there were differences in the above indicators between patients in different groups, and conducted independent risk factor analyses of tophi. As shown in Supplementary Table 1, age, duration of gout, SBP, DBP, TG, BUN, Cr, eGFR, family history of gout and alcohol consumption are independent risk factors for tophi. Hence, we included the above indicators except alcohol consumption as confounding factors into the subsequent regression analyses.

Ultrasonographic assessments

The ultrasound examination was performed by two experienced sonographers who were blind to each other's diagnosis and the subjects' clinical information. Sonographic examinations were performed using the ALOKA 70 ultrasound system (HITACHI) with a 9-13 MHz linear transducer. Ultrasound examination was performed on the affected joint/joints of each subject, which was/were the most frequent or most painful areas of gout attack. A total of 427 joints were examined on 356 subjects, and the examination sites include the first to fifth metatarsophalangeal (MTP) joints, ankle, knee, calcaneus, as well as metacarpal (MCP) joints, wrist and elbow joints. All the above joints were explored on both transverse and longitudinal planes from the dorsal, palmar, medial and lateral aspects. Besides, all joint areas were examined by ultrasound in a standardized manner.

A total of five ultrasound signs were observed and recorded during the inspection (Fig. 1), as shown below:(1) Tophi was an inhomogeneous substance with poorly defined margins, low to high echo, single or clustered, sometimes accompanied by calcification or surrounding low echo halo (Fig. 1a and Fig. 1b) [32, 26]. (2) Effusion was defined as an abnormal echo-free space existing in or around the joint cavity, without color Doppler signals (Fig. 1c). (3) Synovial hypertrophy appeared as abnormally low echo tissue in the joint space, and were concentric thickening of the synovium (Fig. 1d). (4) According to the OMERACT standard, bone erosion was defined as the discontinuity of the hyperechoic bone surface profile in two perpendicular planes (Fig. 1e) [26]. (5)Double contour sign (DCS) was defined as an irregular hyperechoic band on the edge of articular cartilage surface, which could be continuous or intermittent, regardless of the angle of ultrasound (Fig. 1f) [26, 28]. All ultrasound features were defined as the present or absent. During the ultrasound examination, we recorded the presence or absence of the above five signs in the affected joints, the number (recorded as "none", "single ", "multiple") and size [recorded as the maximum diameter (cm)] of tophus.

Statistical analysis

The characteristics of the subjects were described by simple descriptive statistics: mean ± standard deviation [SD] or median (25th 75th percentiles) for the continuous variable and the frequency of the categorical variable (%). Quantitative data to the normal distribution were compared using the 1-way analysis of variance, while for variables not following the normal distribution and ordered categorical variable, the non-parametric test (Kruskal-Wallis test) were used to compare the differences between the groups. Unordered categorical variables were analyzed using the chi-squared test (χ^2test) and Fisher's exact test. In order to explore the relationship between alcohol consumption and ultrasound signs such as tophi in gout patients, we performed regression analyses as follows. To begin with, we performed multiple regression analyses with the history of alcohol as independent variables and the five ultrasound signs as dependent variables. In our analyses, no drinker was used as the reference in each model to compare the effect of alcohol consumption relative to no drinking. Moreover, we tested two models to control for potential confounders that might affect the association between alcohol consumption and ultrasound signs. The first model (model 1) did not contain any covariates and the second model (model 2) included age, sex, duration of gout, SBP, DBP, BUN, Cr, eGFR, UA, ULT, Family history of gout as covariates. Subsequently, a multiple linear and logistic regression were conducted to explore the specific effects of alcohol consumption on the size and number of tophus, meanwhile controlling for the same covariates.

What's more, to investigate the effects of age, duration of gout and ULT on the association between alcohol consumption and the size of tophus in above analyses, a similar regression analysis was repeated including a 2-way interaction term between history of alcohol and age, duration of gout and ULT as additional independent variables, the size of tophus as dependent variable. Subsequently, further subgroup analyses were conducted based on the results of above analyses.

Tests were two-tailed and P <0.05 was considered statistically significant. All data were analyzed using SPSS Statistics version 25.0.

Results

Clinical demographics of Participants

A total of 356 patients were selected for this study, including 350 men and 6 women. The median age and median disease duration of gout patients were 42 years old and 4 years respectively. The demographic and clinical characteristics of the participants are shown in Table 1. Among these participants, frequency of drinking, alcohol intake and drinking time of men were all significantly higher than which of women. Gout patients who had more alcohol intake, longer drinking time and higher frequency of drinking were relatively older, had a longer duration of gout, and had a higher SDP. However, no significant difference was observed in UA between these groups, which might because most of the subjects (92.4%) were undergoing ULT.

Association of alcohol consumption with ultrasound-detected tophus

As illustrated in Table 2, the multiple linear regression analysis revealed that more alcohol intake (>200 g/week), longer drinking time (>20 years) and higher frequency of drinking (>2 times/week) all had significant positive effects on the size of tophus relative to no drinking (P =0.004; P<0.001; P =0.006), even after controlling for potential confounders (P =0.024; P =0.002; P =0.040). However, two multiple logistic regression analyses showed that the existences of tophi and multiple tophus were not significantly related to alcohol consumption. Without considering the potential confounders, longer drinking time (>20 years) and drinking liquor had a positive effect on the formation of multiple tophus (Modle1), while after including confounding factors, there was no significant association between alcohol history and multiple tophus (Modle2). Furthermore, beer, liquor and wine were all not significantly associated with tophi after adjusting for confounding factors, although drinking liquor showed a positive effect on the number and size of tophi in model1.

Association of alcohol consumption with other ultrasound signs

There was no significant association between alcohol consumption and the ultrasound signs including DCS, bone erosion, effusion and synovial hypertrophy, even after additional controlling for all the covariates (Table 3), which suggesting that alcohol might have little effect on soft tissue and bone around tophi in gout patients.

Sensitivity analyses

As sensitivity analyses, we performed the same analyses after excluding former drinkers from current drinkers in order to reduce the potential influence of forced abstainers who stopped drinking due to other diseases. Sensitivity analyses after excluding former drinkers showed similar results (Supplementary Table 2 and Supplementary Table 3).

Influence of age, duration of gout and ULT on the association between alcohol consumption and the size of tophus

As shown in Supplementary Table 4, the interaction between more alcohol intake (>200 g/week), higher frequency of drinking (>2 times/week) and age was significant (P =0.032; P =0.029), indicating that age moderates the association between heavy alcohol intake, frequent drinking and the size of tophi. However, no significant interaction between more alcohol intake (>200 g/week), higher frequency of drinking (>2 times/week) and each of ULT, duration of gout was observed.

Further subgroup analysis of different ages illustrated that more alcohol intake (>200 g/week), higher frequency of drinking (>2 times/week) and longer drinking time (>20 years) had significant positive effects on the size of tophi only in the younger subgroup (≤50 years old) (P =0.004; P =0.033; P =0.015), not in the older subgroup (>50 years old) (P =0.358; P =0.188; P =0.089) (Table 4), which suggested that drinking alcohol may have a greater impact on younger gout patients with tophi than on elder ones.

Discussion

To the best of our knowledge, this is the first study to report the relationship between the alcohol consumption and tophi detected by ultrasound in gout patients. Our results manifested that patients with more alcohol intake, longer drinking time and higher frequency of drinking were more likely to have tophus with larger sizes. Nevertheless, the history of alcohol was not significantly associated with the formation and number of tophus. Additionally, no significant association was observed for alcohol and the other four signs of ultrasound in the present study.

In recent decades, alcohol has been considered as a potential risk factor for increased uric acid and gout attacks [14-16, 19, 17, 18, 33]. A large population cohort study suggested that alcohol dependence was a key determinant of gout risk [14]. Similarly, a prospective Internet-based case-crossover study indicated that excessive alcohol consumption was strongly related to an increased risk of recurrent gout attacks [15]. Moreover, extensive evidences have demonstrated that drinking alcohol can independently change various pathways and molecules related to the recruitment of neutrophil, and affect its key functions such as phagocytosis, NETs formation, and ROS production [34-39]. Significantly, alcohol can impair the exocytosis of macrophages and induce the polarization of phagocytic cells towards the pro-inflammatory phenotype, thereby the removal of NETs is hindered [35]. Hence, we can reasonably deduce that alcohol consumption is prone to the continued existence of NETs in the gout-infected joints, which will directly promote the continued deposition of MSU and the continuous growth of tophi. What's more, the effect of alcohol on the innate immune system is dose-dependent. Under the long-term effect of alcohol, neutrophils stay in the inflammation site and continue to be recruited to the inflammation site for a longer time, which tends to cause long-term inflammation and tissue damage of the body [34, 40]. Take together, the above mechanisms explain the positive effects of more alcohol intake, longer drinking time and

higher frequency of drinking on size of tophus in the results of our regression analysis (Table 2), which are consistent with the conclusion that there is a significant dose-response relationship between alcohol consumption and the risk of gout attacks reported in previous studies [15, 18].

We did not find any significant relationship between alcohol consumption and the formation or number of tophus in this study (Table 2). The development of tophi is a dynamic process of continuous low-level recruitment and infiltration of inflammatory cells. If macrophages do not entirely terminate the down-regulation of inflammatory signals, local neutrophil infiltration and inflammatory response will continue [12, 13]. Moreover, the matrix metalloproteinases (MMPs) expressed by macrophages in formed tophi had been proved to digest the extracellular matrix in the lesion and hinder the development of tophi [13], while alcohol has been reported to down-regulate the MMP pathway [41]. Nevertheless, the relationship between MMPs and the initial formation of tophi has not been revealed. Hence, we speculate that alcohol consumption has little effect on the initial formation of tophi, but focuses on its development stage [34, 6].

Nakamura et al. [42] and Neogi et al. [15] reported that regardless of the type of alcoholic beverages, habitual or regular alcohol intake increased the risk of hyperuricemia and gout attacks, which is consistent with the result that different drinking types had the same influence on tophus in our study (Table 2), indicating the total volume of ethanol intake rather than the specific ingredients of an alcoholic beverage may be responsible for the gout attacks and the formation or development of tophus. On the contrary, previous studies have also shown that beer and spirits have a higher risk of gout attacks than wine [33, 18]. But it is worth noting that compared to people who drink beer or spirits, those who drink wine tend to have a healthier lifestyle, so the lack of connection between wine and gout attack in the above studies may have association with residual confounding induced by other healthy lifestyle factors. Therefore, the influence of drinking type on tophi needs to be further investigated by studies on large samples.

Except for tophi, there was no significant relationship between the other four ultrasound signs and alcohol consumption (Table 3). Previous research reported that DCS was often strongly affected by UA and ULT [30]. While in our study, most patients (92.4%) had been received ULT, so the effect of drinking on DCS may be diluted by uric acid-lowering drugs and not be found in the current study. Similarly, the study by Dalbeth et al. [43] manifested that ULT could improve the structural damage of gout patients with tophi, especially bone erosion, hence, the effect of alcohol consumption on bone erosion, synovial hypertrophy and effusion in this study may be offset by ULT like DCS. There are few studies on the relationship between alcohol consumption and ultrasound signs in patients with gout, so more studies are needed to verify the association between them.

Compared with the elderly (>50 years), the enhancing effect of more alcohol consumption on size of tophi was more prominent in younger individuals (≤50 years) (Table 4), which may be because the immune cells and immune responses are more active and the influence of alcohol on immune signals is amplified to a much greater extent in younger gout patients than those of elder ones [44, 45]. This finding is different from our expectations, suggesting that younger patients with tophaceous gout are more sensitive to alcohol than elderly ones, so it is necessary to avoid alcohol intake in daily life, especially for younger gout patients.

The limitations of our study are as follows. First, the sample size is not large enough, and it is necessary to increase the sample size to further explore the relationship between drinking history and other ultrasound signs. Second, the size of tophi was replaced by the largest diameter, which may cause a certain error in the final result. Nevertheless, the advantages of this study are also obvious. First, the use of ultrasonography provides convenience for the early detection of the smaller tophus, which solves the problem that visual identification of subcutaneous tophus is not accurate and sensitive enough [21, 25], and compared with other imaging methods, ultrasound can more sensitively identify not only tophi but also erosion in and around the joints as well as inflammation of the surrounding soft tissues [26, 27, 3, 24]. Second, in our study, the information on history of alcohol is detailed, including alcohol intake, frequency of drinking, drinking time and type of drinking, instead of a single descriptive indicator, so it can more comprehensively analyze and evaluate the relationship between alcohol consumption and ultrasound signs. Third, the sensitivity analysis after excluding former drinkers also confirmed the consistency of the results. Overall, our study still shows high reliability.

In conclusion, alcohol consumption is closely associated with the size of tophi in gout patients. More alcohol intake, longer drinking time and higher frequency of drinking are crucial factors that positively affect the size of tophi, especially in younger patients with gout. Therefore, in addition to the general medical management for gout, patients with diagnosed gout, especially younger ones with tophaceous gout ought to consider restricting all types of alcohol intake to prevent further growth of tophi, avoid the physical or psychological damage caused by overlarge tophus, and eventually improve the quality of life.

Declarations

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Conflicts of interest:

The authors have no conflicts of interest to disclose.

Availability of data and material:

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

Code availability:

Not applicable.

Authors' contributions:

All authors conceived the study concept and design. LH, RZL, JYP, JS and YW did the statistical analyses and interpreted the data. RZL, ZL, CW and JW wrote the first draft. LH, WR, SJC, YC and CGL critically revised the paper for important intellectual content. All authors approved the final draft.

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Tables

Table 1
Demographic and clinical characteristics of participants by category of alcohol consumption

Characteristic	alcohol intake (g/week)			Drinking time(years)			Frequency of drinking(times/week)			Type of drinking		
	No drinking	≤ 200	> 200	No drinking	≤ 20	> 20	No drinking	≤2	> 2	No drinking	Beer	Liquor
Number	111	110	124	111	179	66	111	112	121	111	120	109
Sex, male (n (%))	105* (94.6)	110 (100)	124 (100)	105* (94.6)	179 (100)	66 (100)	105** (94.6)	148 (100)	87 (100.0)	105* (94.6)	120 (100)	109 (100)
Age (year)	35.0** (24.0–51.0)	40.0 (33.8–50.3)	47.0 (39.0–56.0)	34.0** (24.0–51.0)	39.0 (31.0–48.0)	57.0 (51.0–64.3)	35.0** (24.0–51.8)	39.0 (32.3–48.8)	48.0 (39.5–57.0)	35.0** (24.0–51.8)	38.5 (30.0–47.0)	51 (44.0–60.0)
Duration of gout (years)	3.0* (1.0–7.0)	3.0 (1.0–9.3)	6.0 (2.0–10.0)	3.0** (1.0–7.0)	1.0 (1.0–7.0)	7.0 (4.0–13.0)	3.0* (1.0–7.0)	3.0 (1.0–7.0)	5.0 (1.5–10.0)	3.0** (1.0–7.0)	3.0 (1.0–7.0)	6.0 (2.0–11.0)
BMI (kg/m^2)	27.7 (24.2–30.3)	28.0 (25.3–30.1)	27.1 (24.8–30.0)	28.1* (24.3–30.7)	27.9 (25.5–30.3)	25.5 (24.1–28.7)	27.7 (24.3–30.6)	28.1 (25.4–30.1)	27.0 (25.9–29.9)	27.7 (24.3–30.6)	27.7 (25.4–30.4)	26.4 (24.9–29.1)
SBP (mmHg)	136.5 (123.5–146.0)	133.0 (122.0–146.0)	133.5 (123.0–145.0)	136.0 (123.3–145.8)	134.0 (122.0–145.0)	133.0 (120.0–149.0)	136.5 (124.3–146.0)	131.0 (121.0–143.0)	134.0 (123.0–145.0)	136.5 (124.3–146.0)	135.0 (126.0–145.5)	132.0 (121.0–146.0)
DBP (mmHg)	82.0* (72.0–89.5.0)	84.0 (77.0–92.5)	86.0 (78.0–95.0)	81.5* (72.0–89.8)	85.0 (77.0–93.0)	86.0 (78.0–94.0)	82.0* (72.0–89.8)	83.0 (77.0–92.0)	86.0 (79.0–96.0)	82.0* (72.0–89.8)	87.5 (78.0–95.5)	83.0 (77.0–92.0)
ALT (U/L)	31.5 (20.9–58.5)	30.0 (21.0–54.0)	28.0 (18.0–40.5)	31.0* (19.3–50.5)	30.0 (21.0–51.0)	22.0 (16.0–33.0)	31.5 (20.0–57.8)	30.0 (21.0–57.8)	28.0 (18.0–38.5)	31.5 (20.0–57.8)	31.5 (23.0–48.5)	27.0 (18.0–38.0)
AST(U/L)	22.0 (18.0–31.0)	22.5 (17.0–29.0)	20.0 (16.0–26.0)	22.0 (18.0–29.8)	22.0 (17.0–28.5)	19.0 (15.0–25.0)	22.0 (18.0–31.0)	23.0 (17.0–29.8)	19.0 (16.0–25.0)	22.0* (18.0–31.0)	20.5 (17.0–32.5)	21.0 (16.0–26.0)
AST/ALT	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.8 (0.6–1.0)	0.7* (0.6–0.9)	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.7 (0.6–1.0)	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.8 (0.6–1.0)
GLU (mmol/l)	5.4 (5.0–5.7)	5.4 (5.1–5.8)	5.5 (5.1–6.0)	5.4 (5.0–5.8)	5.4 (5.1–5.8)	5.6 (5.2–5.9)	5.4 (5.0–5.8)	5.4 (5.0–5.8)	5.5 (5.1–5.9)	5.4 (5.0–5.8)	5.5 (5.1–5.8)	5.5 (5.2–5.9)
TG (mmol/l)	1.9 (1.3–2.5)	2.0 (1.3–2.8)	1.8 (1.3–2.6)	1.9 (1.3–2.5)	2.0 (1.4–2.7)	1.4 (1.2–2.4)	1.9 (1.3–2.5)	2.1 (1.5–2.9)	1.8 (1.3–2.5)	1.9 (1.3–2.5)	2.0 (1.4–2.7)	1.8 (1.3–2.5)
CH (mmol/l)	4.7 (4.1–5.4)	5.0 (4.2–5.6)	4.7 (4.0–5.3)	4.7 (4.1–5.4)	4.7 (4.1–5.4)	4.6 (4.1–5.4)	4.7 (4.1–5.4)	5.0 (4.2–5.5)	4.7 (4.0–5.4)	4.7 (4.1–5.4)	4.7 (4.1–5.3)	5.0 (4.1–5.6)
BUN (mmol/L)	4.6 (4.0–5.5)	4.7 (4.0–5.8)	4.9 (4.3–6.3)	4.6* (4.0–5.5)	4.7 (4.0–5.9)	5.2 (4.3–6.6)	4.6 (3.9–5.5)	4.7 (3.9–5.7)	4.8 (4.3–6.3)	4.6* (3.9–5.5)	4.6 (3.9–5.4)	5.4 (4.3–6.6)
Cr (μmol/l)	85.5 (76.5–97.0)	84.0 (76.0–94.0)	83.0 (74.5–92.5)	85.5 (76.3–97.0)	84.0 (76.0–94.0)	83.0 (76.0–92.0)	85.5 (76.3–93.0)	83.5 (76.0–94.0)	83.0 (74.5–92.0)	85.5 (76.3–97.0)	84.0 (76.0–92.5)	84.0 (76.0–96.0)
eGFR (ml/min/1.73m^2)	97.5 (81.7–113.2)	96.2 (84.3–109.3)	92.5 (81.8–103.3)	99.0** (80.7–114.0)	99.7 (85.4–109.7)	88.0 (79.3–97.1)	97.5 (81.7–113.2)	98.5 (85.4–109.2)	94.9 (82.7–103.1)	97.5* (81.7–113.2)	98.8 (87.3–109.3)	91.8 (76.9–102.1)
UA (μmol/L)	512.9± 147.0	512.4± 127.7	484.0± 130.7	514.4± 145.1*	515.9± 131.8	458.9± 112.1	512.9± 147.0	512.4± 127.7	487.0± 130.7	512.9± 147.0	511.6± 137.9	495.7± 118.7
ULT treatment												
Febuxostat (n (%))	77 (69.4)	75 (68.2)	92 (74.2)	77 (69.4)	120 (67.0)	49 (74.2)	77 (69.4)	72 (64.3)	94 (77.7)	77 (69.4)	79 (65.8)	85 (80.0)
Benzbromarone (n (%))	23 (20.7)	21 (19.1)	22 (17.7)	23 (20.7)	34 (19.0)	10 (15.2)	23 (20.7)	26 (23.2)	18 (14.9)	23 (10.4)	26 (21.7)	17 (15.6)

Characteristic	alcohol intake (g/week)			Drinking time(years)			Frequency of drinking(times/week)			Type of drinking		
	No drinking	≤ 200	> 200	No drinking	≤ 20	> 20	No drinking	≤2	> 2	No drinking	Beer	Liquor
Allopurinol (n (%))	2 (1.8)	4 (3.6)	2 (1.6)	2 (1.8)	3 (1.7)	3 (4.5)	2 (1.8)	5 (4.5)	1 (0.8)	2 (1.8)	2 (1.7)	4 (3.7)
Family history of gout (n (%))	23 (20.7)	26 (23.6)	27 (21.8)	23 (20.7)	33 (18.4)	20 (30.3)	23 (20.7)	28 (25.0)	25 (20.7)	23 (20.7)	26 (21.7)	23 (21.1)

* P<0.05

** p<0.001

Continuous variables of normal distribution were expressed as mean ± SD. Continuous variables of non-normal distribution were expressed as median(mix-m
Proportions were expressed as percentages. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure ; ALT: serum alanine aminotransferase; AST: serum aspartate aminotransferase; GLU: fasting blood glucose; TG: serum triglyceride; CH: serum cholesterol; BUN: blood urea nitrog serum creatinine; eGFR: estimated glomerular filtration rate; UA: serum uric acid; ULT: urate lowering therapy.

Table 2
The associations of alcohol consumption with tophus in participants overall

	Tophaceous (yes/no)	Size of tophus (cm)	Number of tophus [Multiple tophus(yes/no)]
Alcohol consumption	OR (95% CI) † P-value	B (95% CI) ‡ P-value	OR (95% CI) † P-value
Alcohol intake (g/week)			
Model 1[a]			
≤200	1.361(0.779–2.376) 0.279	0.189(-0.108–0.487) 0.212	1.568(0.898–2.736) 0.114
> 200	1.679(0.966–2.918) 0.066	0.425(0.138–0.712) 0.004	1.614(0.941–2.769) 0.082
Model 2[b]			
≤200	1.326(0.683–2.574) 0.405	0.099(-0.237–0.435) 0.561	1.697(0.882–3.267) 0.113
> 200	1.431(0.723–2.831) 0.303	0.380(0. 005–0.710) 0.024	1.576(0.817–3.041) 0.175
Drinking time(years)			
Model 1[a]			
≤20	1.349(0.811–2.245) 0.249	0.181(-0.088–0.449) 0.186	1.440(0.869–2.386) 0.156
>20	2.061(1.026–4.137) 0.042	0.713(0.379–1.047) <0.001	2.114(1.076–4.152) 0.030
Model 2[b]			
≤20	1.393(0.757–2.564) 0.287	0.166(-0.139–0.470) 0.286	1.688(0.929–3.068) 0.086
>20	1.340(0.515–3.487) 0.549	0.669(0.248–1.091) 0.002	1.688(0.634–3.831) 0.334
Frequency of drinking (times/week)			
Model 1[a]			
≤2	1.522(0.868–2.668) 0.143	0.225(-0.068–0.519) 0.132	1.611(0.924–2.807) 0.093
> 2	1.496(0.864–2.590) 0.151	0.394(0.113–0.675) 0.006	1.576(0.917–2.706) 0.099
Model 2[b]			
≤2	1.607(0.828–3.145) 0.160	0.215(-0.119–0.548) 0.207	1.958(1.017–3.769) 0.044
> 2	1.253(0.606–2.381) 0.599	0.345(0.016–0.675) 0.040	1.430(0.739–2.768) 0.288
Type of drinking			
Model 1[a]			
Beer	1.478(0.853–2.561) 0.163	0.232(-0.058–0.522) 0.116	1.539(0.892–2.656) 0.121
Liquor	1.679(0.947–2.976) 0.076	0.409(0.115–0.702) 0.007	1.837(1.046–3.228) 0.034
Wine	1.217(0.389–3.806) 0.735	0.369(-0.254–0.993) 0.245	1.095(0.364–3.293) 0.871
Model 2[b]			
Beer	1.635(0.848–3.153) 0.142	0.231(-0.095–0.558) 0.164	1.866(0.980–3.554) 0.058

	Tophaceous (yes/no)	Size of tophus (cm)	Number of tophus [Multiple tophus(yes/no)]
Liquor	1.240(0.590–2.496) 0.600	0.216(-0.130–0.563) 0.220	1.506(0.752–3.016) 0.248
Wine	1.193(0.254–4.191) 0.965	0.491 (-0.207–1.188) 0.167	1.754(0.400–6.037) 0.524

[†]By multiple logistic regression analysis (no drinking served as the reference group).

[‡]By multiple linear regression analysis (no drinking served as the reference group).

[a] Not adjusted.

[b] Adjusted for age, sex, duration of gout, SBP, DBP, BUN, Cr, eGFR, UA, ULT, Family history of gout.

OR, odds ratio; CI, confidence interval; B, beta.

Table 3
The associations of alcohol consumption with other ultrasound signs in participants overall

	DCS	Bone erosion	Effusion	Synovial hypertrophy
Alcohol consumption	OR (95% CI)[†] P-value			
Alcohol intake (g/week)				
Model 1[a]				
≤200	1.312(0.773–2.229) 0.314	0.963(0.519–1.786) 0.905	1.220(0.720–2.069) 0.364	0.775(0.444–1.352) 0.369
> 200	1.191(0.712–1.994) 0.505	1.287(0.719–2.304) 0.395	0.875(0.523–1.465) 0.612	1.083(0.621–1.887) 0.779
Model 2[b]				
≤200	1.281(0.689–2.384) 0.434	0.979(0.465–2.063) 0.956	1.325(0.721–2.435) 0.364	0.752(0.400–1.416) 0.378
> 200	1.127(0.605–2.096) 0.707	1.209(0.587–2.420) 0.628	0.900(0.489–1.657) 0.735	1.114(0.578–2.146) 0.747
Drinking time(years)				
Model 1[a]				
≤20	1.068(0.656–1.741) 0.790	0.947(0.537–1.669) 0.850	0.994(0.612–1.614) 0.288	0.953(0.566–1.606) 0.383
> 20	1.664(0.896–3.092) 0.107	1.436(0.727–2.838) 0.298	0.955(0.516–1.768) 0.884	0.969(0.500–1.877) 0.925
Model 2[b]				
≤20	1.164(0.653–2.073) 0.606	1.077(0.541–2.144) 0.832	1.021(0.584–1.783) 0.943	0.939(0.512–1.720) 0.837
> 20	1.432(0.638–3.213) 0.384	1.045(0.395–2.267) 0.901	1.047(0.450–2.180) 0.981	0.734(0.306–1.763) 0.490
Frequency of drinking (times/week)				
Model 1[a]				
≤2	1.222(0.721–2.071) 0.456	0.988(0.535–1.824) 0.970	1.095(0.647–1.852) 0.736	0.797(0.458–1.389) 0.424
> 2	1.334(0.795–2.239) 0.275	1.131(0.625–2.047) 0.683	0.978(0.583–1.638) 0.931	1.132(0.646–1.983) 0.666
Model 2[b]				
≤2	1.367(0.735–2.543) 0.324	1.179(0.565–2.458) 0.661	1.210(0.662–2.212) 0.536	0.807(0.428–1.521) 0.508
> 2	1.211(0.641–2.286) 0.556	0.987(0.481–2.079) 0.999	0.963(0.520–1.784) 0.904	1.075(0.547–2.092) 0.843
Type of drinking				
Model 1[a]				
Beer	1.228(0.731–2.063) 0.438	1.096(0.604–1.990) 0.763	1.027(0.612–1.722) 0.921	0.994(0.570–1.731) 0.982
Liquor	1.337(0.786–2.273) 0.284	1.236(0.678–2.255) 0.489	0.998(0.587–1.694) 0.993	0.896(0.510–1.574) 0.703
Wine	0.875(0.292–2.626) 0.812	0.222(0.028–1.769) 0.155	1.702(0.568–5.104) 0.343	1.266(0.377–4.257) 0.703
Model 2[b]				
Beer	1.521(0.827–2.798) 0.178	1.295(0.630–2.663) 0.482	1.034(0.569–1.878) 0.912	0.936(0.498–1.759) 0.838

	DCS	Bone erosion	Effusion	Synovial hypertrophy
Liquor	0.972(0.509–1.896) 0.957	0.872(0.413–1.843) 0.720	1.094(0.577–2.077) 0.782	0.783(0.401–1.584) 0.517
Wine	0.817(0.223–2.986) 0.760	0.224(0.025–2.042) 0.185	2.244(0.627–8.028) 0.214	3.338(0.578–14.857) 0.194

[†]By multiple logistic regression analysis (no drinking served as the reference group).

[a] Not adjusted.

[b] Adjusted for age, sex, duration of gout, SBP, DBP, BUN, Cr, eGFR, UA, ULT, Family history of gout.

OR, odds ratio; CI, confidence interval; DCS, double-contour sign.

Table 4
The associations between alcohol consumption and the size of tophus by age subgroup

Variable	B (95% CI) [†]	P-$_{value}$
Younger (≤50 y) (n = 242)		
Alcohol intake(g/week)		
≤200	0.204(-0.189–0.598)	0.307
>200	0.610(0.198–1.023)	0.004
Frequency of drinking (times/week)		
≤2	0.288(-0.112–0.687)	0.157
>2	0.454(0.037–0.870)	0.033
Drinking time(years)		
≤20	0.302(-0.064–0.668)	0.105
>20	0.827(0.164–1.490)	0.015
Older (>50 y) (n = 114)		
Alcohol intake(g/week)		
≤200	0.074(-0.604–0.753)	0.828
>200	0.269(-0.311–0.850)	0.358
Frequency of drinking (times/week)		
≤2	-0.005(-0.681–0.670)	0.988
>2	0.374(-0.186–0.934)	0.188
Drinking time(years)		
≤20	-0.071 (-0.724–0.581)	0.829
>20	0.494(-0.077–1.065)	0.089

[†] By multiple linear regression analysis controlling for duration of gout, sex, SBP, DBP, BUN, Cr, eGFR, UA, ULT, Family history of gout.

CI, confidence interval; B, beta.

Figures

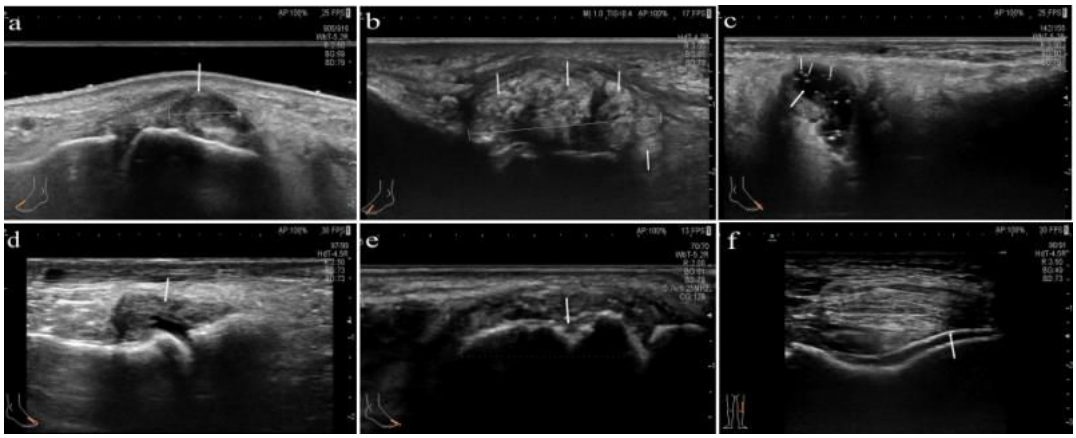

Figure 1

Ultrasound images of gout patients (a) a US image of the left first metatarsophalangeal(MTP1) joint in the longitudinal plane showing single hypoechoic tophi(arrow), which longest diameter represented by the white line segment. (b) a US image of the left second MTP joint in the longitudinal plane showing multiple hyperechoic tophus (arrow), which longest diameter represented by the white line segment. (c) Longitudinal US image of the MTP1 joint cavity on the right. The liquid dark area is effusion (coarse arrow), and hyperechoic spots (fine arrow) are seen in it. (d) Longitudinal US image of the MTP1 joint cavity on the right showing synovial hypertrophy(arrow). (e) Longitudinal US image of the distal metatarsal bone on the right showing bone erosions(arrow). (f) Transverse US image of left knee joint showing double contour sign (DCS). Linear hyperechoic deposit (arrows) is seen at the surface of the intercondylar cartilage at the end of the femur.