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CLINICAL RESEARCH STUDY

Alcohol Consumption as a Trigger of Recurrent Gout Attacks

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ABSTRACT

BACKGROUND: Alcohol consumption has long been considered a trigger for recurrent gout attacks; however, this hypothesis has not been formally tested.

METHODS: We conducted an Internet-based case-crossover study to assess several putative risk factors, including alcohol consumption, thought to trigger recurrent gout attacks. Subjects who had an attack within the past year were recruited online and asked to provide access to medical records pertaining to their gout. Data were obtained on the amount and type of alcoholic beverage consumed on each day over the 2-day period before a gout attack and on each day over a 2-day period during the intercritical period. We examined the amount and type of alcohol consumption and the risk of recurrent gout attacks using a conditional logistic regression adjusting for diuretic use and purine intake.

RESULTS: A total of 197 subjects were recruited online over a 10-month period. Of those, 179 (91%) fulfilled the American College of Rheumatology Criteria for gout. Compared with no alcohol consumption, odds ratios for recurrent gout attacks were 1.1, 0.9, 2.0, and 2.5 for 1 to 2, 3 to 4, 5 to 6, and 7 or more drinks consumed over the 2-day period, respectively ($P<.005$). A dose-response relationship of risk of gout attacks was more evident for alcohol consumed over the last 24 hours. An increased risk of recurrent gout attacks was found for each type of beverage consumed.

CONCLUSION: Alcohol consumption triggers recurrent gout attacks. This effect was likely to occur within 24 hours after its consumption.

KEYWORDS: Alcohol; Recurrent gout attacks; Internet; Case-crossover study

Gout is a common form of inflammatory arthritis, often causing recurrent episodes of pain and swelling of certain joints. Although the pathophysiology of gout is well understood and clinically efficacious therapies are available, recent studies have shown that the prevalence and incidence of gout in the United States are increasing.[1-4] Recurrent gout attacks are often attributed to "triggers," that is, precipitating factors immediately before gout attacks. Avoidance of triggers is a central preventive strategy in the management of gout. To date, few epidemiologic studies have been conducted to identify the potential triggers for recurrent gout and assess their effects owing to methodologic and logistical difficulties.

Previous studies have shown that alcohol consumption increases the level of serum uric acid[5-8] and that excess intake of alcohol is associated with an increased risk of initial occurrence of gout.[9-13] Results from the Health Professionals Follow-up Study showed that the risk of incident gout attack increased as the amount of alcohol consumed increased and that this risk varied according to the type of alcoholic beverage consumed. Beer conferred a larger risk than spirits, whereas moderate wine drinking did not increase risk.[14]

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Although many people believe that alcohol intake triggers recurrent gout attacks, we are unaware of any study that has formally tested this hypothesis. Clarification of such associations has potential implications for gout management. First, many patients with gout have other comorbidities, including obesity, type-2 diabetes mellitus, dyslipidemia, hypertension, and coronary heart disease,[15-20] and studies have shown that light-to-moderate alcohol intake is associated with a reduction of risk for these diseases.[21-25] Quantifying the relation of amount of alcohol consumption to the risk of recurrent gout attacks will allow these patients to make informed decisions about their alcohol consumption. Second, although the results from the Health Professionals Follow-up Study found the effect on the development of gout varied based on the type of alcoholic beverage consumed, such findings need to be verified with regard to recurrent gout attacks.[14]

Assessing whether alcohol intake triggers recurrent gout attacks is challenging. A case-control study poses serious problems for control selection, whereas a cohort design is unwieldy for participants and investigators and extremely expensive. Both designs also pose problems of recruitment. We conducted an Internet-based case-crossover study to assess the relation of amount and type of alcoholic beverages to the risk of recurrent gout attacks. We also estimated the approximate time interval in which a recurrent attack would occur after alcohol consumption.

CLINICAL SIGNIFICANCE

- Although the pathophysiology of gout is well characterized and clinically efficacious therapies are available, many patients with gout continue to experience recurrent attacks.
- Alcohol consumption has long been considered a trigger for recurrent gout attacks; however, this hypothesis has not been formally tested.
- In this study, we demonstrated that alcohol consumption, even a light-to-moderate amount, triggers recurrent gout attacks.
- Thus, subjects with established gout should avoid drinking alcohol to decrease their risk of recurrent gout attacks.

METHODS

We constructed a website for this study (https://dcc2.bumc.bu.edu/GOUT) on an independent secure server within the Boston University Medical Center domain. The study website provided information about the study, invited applicants to participate, administered a screening questionnaire, linked eligible respondents to an online consent form, and administered additional questionnaires to assess risk factors and features of respondents' recurrent gout attacks.

The study was advertised on the Google search engine (www.Google.com) by linking an advertisement to the search term "gout." When a search was conducted containing the keyword "gout," a study advertisement appeared on the screen. Interested individuals who clicked on the box containing our advertisement were immediately directed to the study website. To be eligible for the study, a subject had to: report a diagnosis of gout by a physician, have had a gout attack within the past 12 months, be at least 18 years of age, reside in the United States, and be willing to release medical records pertaining to gout diagnosis and treatment. All subjects were asked to complete an electronic informed consent form before taking part in the study. In addition, a hard-copy consent form was mailed to each subject along with a Research Authorization and Medical Record Release Form.

Eligible subjects were asked to complete baseline questionnaires. These included Sociodemographic Questionnaire (name, age, gender, home address, home and work phone number, e-mail address, date of birth, years of education, and household income) and Medical History Questionnaire (medication use, self-reported comorbidities, and history of gout attacks).

When a recurrent gout attack occurred, subjects completed a Hazard-period Questionnaire, which inquired about the date of the attack, clinical symptoms, medication used to treat the attack, and frequency as well as quantity of potential risk factors, including alcohol consumption, on each of two 24-hour periods before the gout attack. Subjects completed a Control-period Questionnaire during an attack-free interval at four time points: at study entry, and at 3, 6, and 9 months of follow-up. The questions used to assess the risk factors over the control period were the same as those used in the hazard period.

Questions on alcohol consumption included the number of servings of beer, wine, or spirits (either straight or in a mixed drink) consumed on each day over the control or hazard periods. The serving sizes were provided along with color images of standard drink sizes and containers, that is, 12-ounce bottle or can of beer; 5-ounce glass of wine, and 1 to 1.5 ounces of spirits. Other potential risk factors, such as foods rich in purine and diuretic use were also collected over the control and hazard period. The total purine intake from food was estimated using established food purine contents.[26]

We obtained medical records pertaining to the participant's gout history and/or a checklist of gout symptoms completed by the subject's physician. A rheumatologist reviewed all medical records and the checklist information. We used information abstracted from medical records or the checklist, and data collected from the questionnaires submitted by the participant to confirm the diagnosis of gout

according to American College of Rheumatology (ACR) Criteria for gout.[27] A subject was considered as having a confirmed history of gout if his/her medical record showed the presence of characteristic urate crystals either in the joint fluids or in tophus, or presence of at least 6 of the 12 clinical, laboratory, and radiography phenomenon listed in ACR Criteria.[27]

STATISTICAL ANALYSIS

Total alcohol consumption (grams) for each day and over the 2-day period was calculated by multiplying the average alcohol content in beer, wine, and spirits times the number of drinks consumed over the specified period. The total alcohol intake per day (in grams) was estimated as ([0.57 × the number of cocktails per day] + [0.44 × the number of bottle or cans of beers per day] + [0.40 × the number of glasses of wine per day]) × 28.35. This latter term represents 28.35 g of alcohol per fluid ounce.[28] One typical drink is approximately 12 g of alcohol. The total alcohol intake on each day and over the 2-day period was divided into five categories: no alcohol consumption, 1 to 2 drinks, 3 to 4 drinks, 5 to 6 drinks, and more than 6 drinks.

We examined the relation of total alcohol consumption to the risk of recurrent gout attacks using a conditional logistic regression model. In a multivariable regression model, we adjusted for diuretic use and total purine intake in foods. We estimated the approximate effect-period of alcohol intake on the risk of recurrent gout attacks by comparing the odds ratios of alcohol consumed over the last 24 hours with that of over 25 to 48 hours before attack. Either overestimation or underestimation of the effect-period would, in general, result in nondifferential exposure misclassification and would therefore tend to dilute the association. Thus, the better estimate of the effect-period is the one that maximizes the odds ratio.[29]

We also assessed the effect of each specific alcoholic beverage on the risk of recurrent gout attacks. We first examined the independent effect of each type of alcoholic beverage and then evaluated whether this effect, if it exists, is the result of components other than alcohol. To do this we added the total alcohol intake, diuretic use, purine-rich food intake, and number of drinks of specific alcoholic beverages to the multivariable regression model.

RESULTS

Of 197 subjects who completed both Hazard-period and Control-period Questionnaires, 179 subjects (91%) fulfilled the ACR Criteria for gout.[27] Gout diagnosis was confirmed by the presence of the crystal in only 37 subjects (19%). A total of 186 subjects (94.4%) returned a signed Medical Record Release Form. Of those, we obtained 172 subjects' medical records or physician's checklists from their physicians, and 164 (95.3%) met ACR Criteria for gout.[27]

The characteristics of the participants are presented in Table 1. The average age of the subjects was 52 years. Participants were predominantly male (80%) and white (88%), and more than half received a college education. Subjects were recruited from 41 states and the District of Columbia. During the 1-year follow-up period, 321 recurrent gout attacks occurred. The median time between the date of the gout attack and the date of completion of the Hazard-period Questionnaire was 2 days.

Table 1 Characteristics of Participants in the Internet-based Case-crossover Study of Gout, 2003 to 2004

Characteristics	
Sex (n, %)	
Men	158 (80.2)
Women	39 (19.8)
Age (median, range)	52 (29-83)
Education (n, %)	
High school graduate	14 (7.1)
Some college/technical school	70 (35.5)
College graduate	61 (31.0)
Completed professional or graduate school	52 (26.4)
Household income (n, %)	
<$25,000	10 (5.1)
$25,000-$49,999	42 (21.3)
$50,000-$74,999	42 (21.3)
$75,000-$99,999	30 (12.2)
>$100,000	54 (27.4)
Missing	19 (9.6)
Race (n, %)	
Black	2 (1.0)
White	174 (88.3)
Other	16 (8.1)
Missing	5 (2.5)
Number of days between attack date and log-on (median, range)	2 (0-24)
Years of disease duration (median, range)	8.2 (0-36)

During the follow-up period, 53 subjects did not consume any alcoholic beverage, 13 drank only wine, 29 drank only beer, 14 drank only liquor, and the remaining 88 subjects drank more than one type of alcoholic beverage. As shown in Table 2, compared with the group with no alcohol consumption over 48 hours, the odds ratios for recurrent gout attacks were 1.1, 0.9, 2.0, and 2.5 for consumption of 1 to 2, 3 to 4, 5 to 6, and 7 or more alcoholic drinks over 48 hours before gout attack, respectively ($P<.005$). When the effect of amount of alcohol consumed during the different time periods was examined, an apparent dose-response relation was observed for amount of alcohol consumed over the last 24 hours before gout attack ($P<.023$). Such a pattern, however, was not evident for alcohol consumed over the 25- to 48-hour period before recurrent gout attacks.

When the effect of specific alcoholic beverage (ie, beer, wine, or spirits) was assessed separately, the risk of recurrent gout attack increased as the number of drinks of each specific alcoholic beverage increased (Table 3). The results were similar when we limited our analysis to subjects who only drank one type of alcoholic beverage. However, with further adjustment for total alcohol consumption, none of the specific alcoholic beverages were associated with an

Table 2 Alcohol Consumption and Risk of Recurrent Gout aAttack

Alcohol consumption (number of drinks)	Number of hazard periods	Number of control periods	Crude OR (95% CI)	Adjusted OR* (95% CI)
Within last 48 h				
0 (reference)	147	213	1.0	1.0
1-2	29	56	1.3 (0.8-2.3)	1.1 (0.7-2.0)
3-4	25	69	1.0 (0.5-2.0)	0.9 (0.4-1.8)
5-6	33	34	2.4 (1.1-5.1)	2.0 (0.9-4.5)
≥7	77	68	3.6 (1.6-8.2)	2.5 (1.1-5.9)
Within last 24 h				
0 (reference)	199	296	1.0	1.0
1-2	58	79	1.5 (0.9-2.5)	1.4 (0.6-2.4)
3-4	41	44	2.0 (0.9-4.4)	1.6 (0.7-3.5)
5-6	13	13	2.8 (1.0-8.0)	2.7 (0.9-8.0)
≥7	10	8	3.4 (1.1-10.7)	3.1 (1.0-11.0)
Within last 25-48 h				
0 (reference)	292	203	1.0	1.0
1-2	71	45	1.3 (0.7-2.2)	1.1 (0.6-2.0)
3-4	53	30	1.8 (0.9-3.6)	1.6 (0.8-3.2)
5-6	16	14	1.4 (0.5-4.2)	1.1 (0.3-3.4)
≥7	8	20	12.2 (3.2-46.6)	7.3 (1.8-29.2)

OR = odds ratio; CI = confidence interval.
*Adjusted for purine intake and diuretic use.

increased risk of recurrent gout attacks, suggesting that the total amount of ethanol intake, rather than a particular component of a specific alcoholic beverage, may be responsible for the increased risk.

When we limited the analyses to the subjects whose gout diagnoses fulfilled ACR Criteria (n = 179), the results were similar. Compared with the nondrinking category, the odds ratios for each increased category of alcohol intake consumed within the last 48 hours were 1.2 (95% confidence interval [CI]: 0.6-2.1), 1.0 (95% CI: 0.4-2.2), 2.0 (95% CI: 0.9-4.7), and 3.0 (95% CI: 1.2-7.7), respectively ($P<.003$).

DISCUSSION

Although alcohol has long been considered a risk factor triggering recurrent gout attacks, to our knowledge, this is the first study that has formally tested this hypothesis. Our results suggest that alcohol intake, irrespective of the type of beverage consumed, was associated with an increased risk of recurrent gout attacks. The effect-period of alcohol was short, likely to occur within the first 24 hours after alcohol consumption.

Although many studies have found that alcohol consumption increases the levels of uric acid,[5-7] its relation to

Table 3 Specific Alcoholic Beverage Intake Over the Last 48 Hours and Risk of Recurrent Gout Attack

Specific alcoholic beverage intake (number of drinks)	Number of hazard periods	Number of control periods	Adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Beer				
0 (reference)	215	304	1.0	1.0
1-2	34	56	1.1 (0.6-1.9)	0.9 (0.5-1.6)
3-4	21	22	1.7 (0.7-4.0)	0.8 (0.3-2.2)
≥5	51	58	1.6 (0.8-3.4)	0.2 (0.1-0.9)
Wine				
0 (reference)	246	345	1.0	1.0
1-2	38	50	1.2 (0.7-2.2)	0.9 (0.5-1.6)
3-4	16	32	0.9 (0.4-2.2)	0.4 (0.1-1.1)
≥5	21	13	4.7 (1.5-15.0)	1.2 (0.3-4.9)
Spirits				
0 (reference)	240	339	1.0	1.0
1-2	21	48	0.8 (0.4-1.4)	0.5 (0.2-1.0)
3-4	27	17	2.0 (0.8-5.1)	0.7 (0.2-2.2)
≥5	33	36	1.8 (0.7-4.4)	0.2 (0.1-0.7)

OR = odds ratio; CI = confidence interval.
*Adjusted for purine intake, and diuretic use.
†Adjusting for purine intake, diuretic use, and total ethanol consumption.

the risk of incident gout attack has not been consistent. Hochberg et al.[30] found no association between alcohol use and risk of development of gout among participants in two cohort studies. However, the number of incident gout cases in that study was small, and more than 90% of the participants drank alcohol at the baseline examination. Results from the Normative Aging Study reported that alcohol consumption increased the risk for the initial gout attack, but such an association disappeared when additional adjustment was made for the baseline serum levels of uric acid.[16] It is debatable whether one should adjust for serum levels of uric acid when effect of alcohol consumption on the risk of gout attacks is evaluated. If alcohol affects the risk of gout attacks through its effect on uric acid, then uric acid level should not be adjusted for. Recently, Choi et al.[14] showed a strong dose-response relationship between the amount of alcohol consumed and the initial gout attack. In the current study, we confirmed that alcohol intake, even a light-to-moderate amount, will trigger recurrent gout attacks.

Several biologic mechanisms have been proposed to explain the relation of alcohol consumption to the risk of incident gout. Studies have demonstrated that alcohol consumption causes accelerated hepatic breakdown of adenosine triphosphate and urate production.[31] Others also found that consumption of lead-tainted moonshine results in chronic renal tubular damage, eventually leading to secondary hyperuricemia and "saturnine" gout secondary to chronic lead poisoning.[15] The high purine content in some alcoholic beverages, such as beer, is another potential explanatory factor associated with an increased risk of gout attacks.[32] Our results suggest that the effect of alcohol on these biologic mechanisms and its subsequent predisposition to gout attacks occurs within a short period of time, perhaps less than 24 hours.

Numerous studies have shown that light-to-moderate alcohol consumption is inversely associated with coronary heart disease and metabolic syndrome.[15-20] Both conditions are common among subjects with gout. Thus, elucidation of the relation of light-to-moderate alcohol consumption to the risk of recurrent gout attacks has important clinical implications. For example, in the current study we found that a light-to-moderate amount of alcohol intake increases the risk of recurrent gout attacks within the first 24 hours and that the effect is not trivial. Thus, subjects with gout should avoid drinking alcoholic beverages entirely, despite the salutary effects of light-to-moderate alcohol intake on other diseases.

We did not find that the effect of alcohol consumption on the risk of recurrent gout attacks varied according to beverage type. Our data suggest that risk of recurrent gout attacks increases regardless of which type of alcoholic beverage is consumed. We believe that the total amount of ethanol, rather than other components in different types of alcoholic beverages, is responsible for triggering recurrent gout attacks.

Studying the triggering effect of alcohol intake on the risk of recurrent gout attacks is challenging. In a case-control study, selection of control group poses a serious problem because neither healthy subjects from the community nor patients with other diseases from a hospital are optimal comparison groups for cases with recurrent gout attacks. Ideally, the control group should be selected from subjects who have a history of gout and are currently in remission. However, few, if any, subjects would seek health care in the absence of a recurrent gout attack, and thus identification and recruitment of such subjects are difficult. Another approach would be to assemble a group of subjects with a history of gout, and then follow them up for the recurrence of gout attacks. However, because we are interested in risk factors triggering unpredictable recurrent acute events within a short latency period, we would have to assess exposures repeatedly on all cohort members. The cost would be high and the respondent burden considerable.

In this study we applied 2 approaches, the case-crossover study design and the Internet, to conduct an innovative epidemiologic study that addressed this challenging and clinically important question. This methodology enables us to recruit subjects with intercritical gout from large geographic areas, such as the whole United States. Furthermore, this method allowed us to assess both exposure and disease occurrence in real-time, which minimizes the potential recall bias.

Our study has some limitations. First, although we used validated questionnaires to assess the risk factors for gout, including alcohol consumption, and subjects were asked to recall these putative risk factors occurring within the last 48 hours, it is still possible that misclassification of risk factors may have occurred. Such misclassification, if it occurred, is likely to be nondifferential and would bias the results toward the null. Second, the current study design allowed us to assess the effects of changing level of alcohol consumption on the risk of recurrent gout attacks; however, it is not ideal for examining the effects of a chronic, constant level of alcohol consumption. Nevertheless, we foresee no major problem in that our study may not include subjects who are chronically addicted to alcohol because it is hard to argue that the biologic relations of alcohol consumption to the risk of recurrent gout attacks would differ for those who drink alcohol intermittently from those who drink alcohol chronically. Finally, the number of subjects who only drank a specific type of alcoholic beverage was relatively small; thus, we do not have adequate power to assess the dose-response relationship between intake of specific alcoholic beverage and the risk of recurrent gout attacks.

CONCLUSION

The present study found that alcohol intake, even a light-to-moderate amount, triggers recurrent gout attacks. We suggest that subjects with established gout avoid drinking alcohol to lower their risk of recurrent gout attacks.

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