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# Purine-Rich Foods Intake and Recurrent Gout Attacks

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**Abstract**

BACKGROUND: Purine intake is a known risk factor for incident gout; however, no study has examined whether its intake triggers recurrent gout attacks over a short period of time.

METHODS: We conducted a case-crossover study to assess purine intake from various sources and the risk of recurrent gout attacks. Patients with a history of gout were recruited online and were followed for one year. Frequency of food intake with serving size specified on each day over the 2-day period prior to an acute gout attack and over the 2-day period during an intercritical period was assessed using an online questionnaire. Total amount of purine intake over these 2-day periods was estimated and divided into quintiles. We performed conditional logistic regressions to examine the relation of total purine intake as well as purine from animal (i.e., meat, seafood) and non-animal (i.e., fruits, vegetables) sources to the risk of recurrent gout attacks while adjusting for use of alcohol, allopurinol, and diuretics.

RESULTS: We analyzed data from 633 participants with gout. Compared with the lowest quintile of total purine intake over a 2-day period, odds ratios (OR) of recurrent gout attacks were 1.18, 1.39, 2.22, and 4.76, respectively, with each increasing quintile (p for trend < 0.001). The corresponding ORs were 1.45, 1.43, 2.00, and 2.97 for increasing quintiles of purine intake from animal sources (p for trend <0.001), and 1.11, 1.04, 1.38, and 1.69 for those of purine intake from non-animal sources (p<0.003), respectively. The effect of purine intake persisted across subgroups by sex, use of alcohol, diuretics, and allopurinol (all p-values for trend <0.001).

CONCLUSION: These large-scale study findings indicate that acute purine intake increases the risk of recurrent gout flares up to five times. Avoiding or reducing purine purine-rich foods, especially those with ananimal origin (e.g……), would help reduce the risk of recurrent gout attacks.

Gout is a common and excruciatingly painful inflammatory arthritis caused by hyperuricemia. While the pathophysiology of gout is well understood and efficacious pharamacological regimens are available, the disease burden of gout remains substantial and is growing (1). In addition, many patients with gout continue to experience recurrent gout attacks (2, 3). Such attacks are frequently ascribed to triggering events such as dietary intake, and avoidance of these triggers is widely promulgated as a central strategy in the management of gout. Despite this advice on dietary strategies being widespread the risk purine intake confers on gout recurrence is unknown.

Purine intake is associated with hyperuricemia (4) and an increased risk of incident gout (5). To date, however, no study has examined whether purine-rich foods intake triggers recurrent gout attacks over a short period of time. Clarifying this link and quantifying its magnitude would help gout patients make informed decisions on food items that should be avoided to help lower their risk of recurrent gout attacks.

To address these issues, we conducted an online case-crossover study and examined the relation of total amount of purine intake as well as purine from animal and non-animal sources to the risk of recurrent gout attacks. We also assessed whether the impact of purine intake varied by other known major risk factors of gout.

**Methods**

The details of the Online Case-crossover Study of Triggers for Recurrent Gout Attacks have been described previously (6). Briefly, we constructed a study website on an independent secure server in the Boston University School of Medicine domain (https//dcc2.bumc.bu.edu/GOUT). The study was advertised on the Google search engine (www.Google.com) by linking an

advertisement to the search term ‘gout.’ Interested individuals who clicked on the study advertisement were directed to the study website. To be eligible for the study, a subject had to report gout diagnosed by a physician, have had a gout attack within the past 12 months, be at least 18 years of age, reside in the U.S., and agree to release medical records pertaining to gout diagnosis and treatment. To confirm a subject’s diagnosis of gout, we obtained medical records pertaining to the participant’s gout history and/or a checklist of gout symptoms completed by the subject’s physician. Two rheumatologists (DJH, TN) reviewed all medical records and the checklists and determined whether the participants had a diagnosis of gout according to the American College of Rheumatology Criteria for gout (7).

Participants were asked to complete a gout Hazard-period Questionnaire when experiencing a recurrent gout attack. Data were collected regarding the onset date of the recurrent gout attack, clinical symptoms and signs, medications used to treat the attack, and presence of a set of purported risk factors during the 2-day period prior to the gout attack. Participants also completed a Control-period Questionnaire at four time points: at study entry (for the subjects who entered the study because of experiencing gout flare), and at 3, 6, 9, and 12 (for the subjects who entered the study at intercritical period) months of follow-up. The questions used to assess the risk factors during the control period were the same as those used in the hazard period.

Questions on food intake included the number of servings and serving size of each food consumed on each day of the past 2 days over the control and the hazard periods. We estimated the total amount of purine intake from all foods consumed during these periods according to the purine content table of different food items (8, 9).

**Statistical Analysis**

The total amount of purine intake over two days was divided into quintile groups. We examined the relation of total purine intake to the risk of recurrent gout attacks using a conditional logistic regression model. In a multivariable regression model we adjusted for use of alcohol, allopurinol, and diuretics. To graphically display the relation between the amount of purine intake and the risk of recurrent gout attacks, we used restricted quadratic splines conditional logistic model to smooth the dose-response curve (10). Using the same approach, we evaluated the effect of purine intake from animal sources (i.e., meat, seafoods) separately from non-animal sources (i.e., fruits, vegetables) on the risk of recurrent gout attacks. Finally, we assessed potential subgroup effects of purine consumption according to gender, alcohol use (abstainer vs. drinker), allopurinol use (yes vs. no) and diuretic use (yes vs. no) and tested for a modification of effect by adding an interaction term to our final multivariable regression models.

**Results**

We analyzed 633 gout patients who completed both Hazard-Period and Control-Period Questionnaires. Among *** subjects (**.*%) who returned a signed Medical Record Release Form, we obtained *** subjects' medical records or physician's checklists from their physicians, ***(**.*%) met American College of Rheumatology Criteria for gout.

The characteristics of the participants are presented in **Table 1**. The average age of the participants was ** years. Participants were predominantly male (**%), White (**%), and over a half received a college education. Subjects were recruited from ** states and the District of Columbia. During the one-year follow-up period, we documented 1,247 recurrent gout attacks.

The median time between the gout attack onset and completion of the Hazard-Period Questionnaire was ** days.

As shown in **Table 2**, compared with the lowest quintile of purine intake over a 2-day period (approximately 21 oz of beef, or 17 cups of broccoli), the odds ratios (11) for recurrent gout attacks were 1.18, 1.39, 2.22 and 4.76 (approximately 85 oz of beef or 68 cups of broccoli for the highest quintile categories), respectively, with each increasing quintile (p for trend < 0.001). The exposure-effect curve, shown in **Figure 1**, indicated an apparent dose-response relationship between total purine intake and risk of recurrent gout attacks.

The impact of purine intake from animal sources on the risk of recurrent gout attacks was greater than that from non-animal sources (**Figure 2**). Compared with the lowest quintile of purine intake from animal sources, ORs of recurrent gout attacks were 1.46, 1.43, 2.00, and 2.97, respectively with each increasing quintile (P for trend < 0.001). The corresponding ORs for purine intake from non-animal sources were 1.12, 1.04, 1.39, and 1.67 (P for trend < 0.001), respectively. When we explored the relations according to cross-classification by tertiles of the two purine sources (**Table 3**), the relative effect on risk of recurrent gout attacks was greater for purine categories of animal sources than those of non-animal sources.

The effect of purine intake on the risk of recurrent gout attacks persisted across subgroups by sex, use of alcohol, diuretics, and allopurinol (all p-values for trend <0.001) (**Table 4**) and did not vary significantly by these factors (all p-values for interaction > 0.5).

**Discussion**

Although purine-rich food intake have been considered a risk factor for recurrent gout attacks, to our knowledge, this is the first large-scale study to formally test this hypothesis and quantify the magnitude of the association. We found that purine intake of more than 2300 mg (give some common food examples that may contain this much purine) over a 2-day period (highest quintile of purine intake) increases the risk of recurrent gout flares up to five times compared with purine intake of less than 1150 mg over a 2-day period. These associations were independent of other risk factors for gout such as sex, alcohol intake, and use of allopurinol or diuretics. The associations persisted across subgroups stratified by these major risk factors. We also found that the impact from animal purine sources was substantially greater than that from non-animal purine sources.

Recurrent flares are the hallmark of intercurrent gout. In our online gout study we have found that approximately two thirds of participants in our online gout study who had gout attacks in the previous year experienced at least one recurrent gout attack over one year (3). Similarly, earlier reports estimated that 60% of patients with newly diagnosed gout had a second attack within the first year, 78% had a second attack within two years, and only 7% escaped recurrence of gout over a 10-year period (2). While urate lowering therapy (ULT) (12) (e.g., allopurinol in >90% of cases in the US and Europe) can be generally effective in lowering levels of SUA and the risk of gout when used compliantly, the current practice standards limit ULT to specific indications such as frequent gout attacks, tophaceous gout, and advanced gout, primarily due to rare but serious side effects (11). Thus, when these indications are not yet met, dietary manipulation and other risk factor modifications are the only acceptable options. Similarly, these non-pharmacologic measures play an exclusive role in asymptomatic hyperuricemia and when the ULTs are successfully terminated after durable remission of gout. Furthermore, these

recommendations continue an adjunct measures to aid pharmacologic ULT regardless of the stage of gout, even when ULTs are indicated.

Intake of purine-rich foods has long been postulated to increase the risk of recurrent gout attacks. These observations are supported by metabolic experiments in animals and humans that examined the impact of artificial short-term loading of purified purine on the serum uric acid level (not gouty arthritis per se) (13-16). More recently, studies have shown that higher levels of meat/seafood consumption are associated with higher levels of serum uric acid (4), and habitually higher meat and seafood intake is strongly associated with an increased risk of incident gout (5) among individuals without gout at baseline. Our findings extend the evidence to a clinically relevant context, recurrent gout flares among patients with existing gout, and indicate that avoiding or reducing purine-rich foods, especially from animal origin, would help reduce recurrent gout attacks in these contexts.

Several features of the current study are worth noting. Identifying potential triggers for recurrent gout attacks and assessing their effects are challenging when using conventional study designs. For example, a case-control study would pose difficulties for control selection, while a cohort design would be costly and unwieldy for participants. The case-crossover study uses each case as his/her own control and is highly adaptable to examining associations of triggers with acute events. Furthermore, to help overcome recruitment challenges of conventional study designs, we used the Internet to recruit subjects with intercritical gout from the entire US. These methods allowed us to assess both exposure and disease occurrence in real-time while minimizing the potential recall bias.

Our study has some limitations. While the current study design allowed us to assess the effects of changing levels of purine intake on the risk of recurrent gout attacks, it is not ideal for examining the effects of a habitual level of purine consumption. Because dietary consumption was self-reported by questionnaire, some misclassification of exposure is inevitable. In the current study we estimated the amount of purine from various foods consumed over the 2-day period according to the serving size and number of servings of each food consumed, as well as the purine content of each food according to a previously published database. While this method is unable to provide precise estimates of absolute purine intake, it allows us to classify the purine intake over a specific time period relative to that over other time periods within the same person. Any misclassification in ranking purine intake, if it occurred, would likely be random; thus, the real effect of purine on the risk of recurrent gout attacks is probably greater than what we have observed. We did not collect data on serum uric acid levels for each study participant; thus, we were unable to assess whether purine-rich food intake over a short period would increase the risk of recurrent gout attacks even among subjects whose serum uric acid is below the threshold level. Nevertheless, when we limited our analysis to subjects who reported taking allopurinol at the baseline visit and all subsequent followup visits (n = 208), the risk of recurrent gout attacks still increased when individuals increased their purine intake.

In conclusion, these large-scale study findings indicate that acute purine intake increases the risk of recurrent gout flares up to five times. We also found that the impact from animal purine sources was substantially greater than that from non-animal purine sources. Avoiding or reducing purine-rich foods, especially from animal origin (e.g.), would help reduce the risk of recurrent gout attacks.

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Table 1. Characteristics of Participants in the Internet-based Case-Crossover Study of Gout

| Characteristics | |
|---|---|
| Sex (n, %) | |
| Men | 494(78.0) |
| Women | 39 (19.8) |
| Age (median, range) | 54(**-**) |
| Education (n, %) | |
| High School Graduate | |
| Some College/Technical School | |
| College Graduate | |
| Completed Professional or Graduate School | |
| Household Income (n, %) | |
| <25,000 | |
| 25,000-49,999 | |
| 50,000-74,999 | |
| 75,000-99,999 | |
| >100,000 | |
| Missing | |
| Race (n, %) | |
| Black | |
| White | 558(88.2) |
| Other | |
| Missing | |
| Number of days between attack date and logon (median, range) | 3 (0-24) |
| Years of Disease Duration (Median, range) | 5.0 |

Table 2. Total Purine Consumption and Risk of Recurrent Gout Attack

| Quintiles of total purine intake over past-2days | Number of control periods | Number of hazard periods | Crude OR (95% CI) | Adjusted OR (95% CI)** |
|---|---|---|---|---|
| 1 (853 mg)* | 363 | 203 | 1.0 | 1.0 |
| 2 (1303 mg) | 359 | 209 | 1.21 (0.92-1.59) | 1.18 (0.89-1.56) |
| 3 (1739 mg) | 348 | 219 | 1.43 (1.06-1.91) | 1.39 (1.03-1.88) |
| 4 (2281 mg) | 301 | 267 | 2.32 (1.72-3.13) | 2.22 (1.63-3.02) |
| 5 (3479 mg) | 218 | 349 | 4.98 (3.55-6.98) | 4.76 (3.37-6.72) |
| P for trend | | | | < 0.001 |

*Median value of purine intake over 2-day period

** Adjusted for use of alcohol, allopurinol, and diuretics

Table 3. Odds Ratios of Recurrent Gout Attacks According to Tertile Categories of Purine from Animal and Non-animal Sources

| Tertiles of Purine from Non-animal sources | | Tertiles of Purine Intake from Animal Sources | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1* | | 2 | | 3 | |
| | | Control | Hazard | Control | Hazard | Control | Hazard |
| 1 | No. Visits | 261 | 155 | 183 | 126 | 116 | 104 |
| | OR** (95% CI) | 1.0 | | 1.39 (0.98, 1.97) | | 1.99 (1.33, 2.97) | |
| 2 | No. Visits | 192 | 114 | 220 | 129 | 144 | 146 |
| | OR (95% CI) | 1.22 (0.86, 1.74) | | 1.42 (1.00, 2.03) | | 2.46 (1.69, 3.59) | |
| 3 | No. Visits | 130 | 90 | 163 | 126 | 178 | 257 |
| | OR (95% CI) | 1.45 (0.96, 2.19) | | 1.83 (1.23, 2.71) | | 3.82 (2.63, 5.55) | |

*1 represents the lowest tertile group and 3 represents the highest tertile group

**Adjusted for alcohol intake, use of diuretic and allopurinol

Table 4. Total Purine Consumption over Past 2-day and Risk of Recurrent Gout Attack by Sex, Alcohol Consumption, Use of Diuretic and Allopurinol

| Other risk factors | Quintile of purine intake* | Number of control periods | Number of hazard periods | Adjusted OR (95% CI)** | P for trend |
|---|---|---|---|---|---|
| Men | 1 (lowest) | 290 | 156 | 1.0 | <0.001 |
| | 2 | 285 | 162 | 1.11 (0.81-1.53) | |
| | 3 | 275 | 171 | 1.37 (0.97-1.93) | |
| | 4 | 235 | 212 | 2.35 (1.65-3.34) | |
| | 5 (highest) | 175 | 271 | 4.82 (3.25-7.16) | |
| Women | 1 (lowest) | 73 | 47 | 1.0 | <0.001 |
| | 2 | 74 | 47 | 1.46 (0.80-2.67) | |
| | 3 | 73 | 48 | 1.45 (0.78-2.69) | |
| | 4 | 66 | 55 | 2.86 (0.98-3.51) | |
| | 5 (highest) | 43 | 78 | 4.72 (2.28-9.78) | |
| Alcohol drinkers | 1 (lowest) | 261 | 132 | 1.0 | <0.001 |
| | 2 | 262 | 155 | 1.26 (0.90-1.76) | |
| | 3 | 247 | 141 | 1.36 (0.95-1.96) | |
| | 4 | 217 | 182 | 2.27 (1.57-3.30) | |
| | 5 (highest) | 157 | 246 | 5.13 (3.40-7.75) | |
| Alcohol abstainers | 1 (lowest) | 102 | 71 | 1.0 | <0.001 |
| | 2 | 97 | 54 | 1.02 (0.61-1.69) | |
| | 3 | 101 | 78 | 1.46 (0.86-2.48) | |
| | 4 | 84 | 85 | 2.23 (1.31-3.81) | |
| | 5 (highest) | 61 | 103 | 4.38 (2.36-8.15) | |
| Diuretic users | 1 (lowest) | 109 | 74 | 1.0 | <0.001 |
| | 2 | 101 | 67 | 1.06 (0.81-1.53) | |
| | 3 | 101 | 70 | 1.42 (0.97-1.93) | |
| | 4 | 82 | 77 | 1.76 (1.03-3.00) | |
| | 5 (highest) | 66 | 122 | 4.13 (2.26-7.54) | |
| Diuretic Non-users | 1 (lowest) | 254 | 129 | 1.0 | <0.001 |
| | 2 | 258 | 142 | 1.28 (0.91-1.80) | |
| | 3 | 247 | 149 | 1.44 (1.00-2.08) | |
| | 4 | 219 | 190 | 2.56 (1.76-3.72) | |
| | 5 (highest) | 152 | 227 | 5.30 (3.48-8.09) | |
| Allopurinol users | 1 (lowest) | 119 | 49 | 1.0 | <0.001 |
| | 2 | 114 | 59 | 1.41 (0.80-2.50) | |
| | 3 | 247 | 51 | 1.44 (0.75-2.77) | |
| | 4 | 219 | 61 | 1.70 (0.88-3.29) | |
| | 5 (highest) | 152 | 85 | 5.51 (2.57-11.8) | |
| Allopurinol Non-users | 1 (lowest) | 224 | 154 | 1.0 | <0.001 |
| | 2 | 245 | 150 | 1.05 (0.75-1.48) | |
| | 3 | 229 | 168 | 1.30 (0.90-1.86) | |
| | 4 | 204 | 206 | 2.19 (1.50-3.20) | |

| | | | | |
|---|---|---|---|---|
| | 5 (highest) | 153 | 264 | 4.42 (2.90-6.73) |

*1 represents the lowest quintile group and 5 represents the highest quintile group.
** Adjusted for alcohol intake, use of diuretic and allopurinol

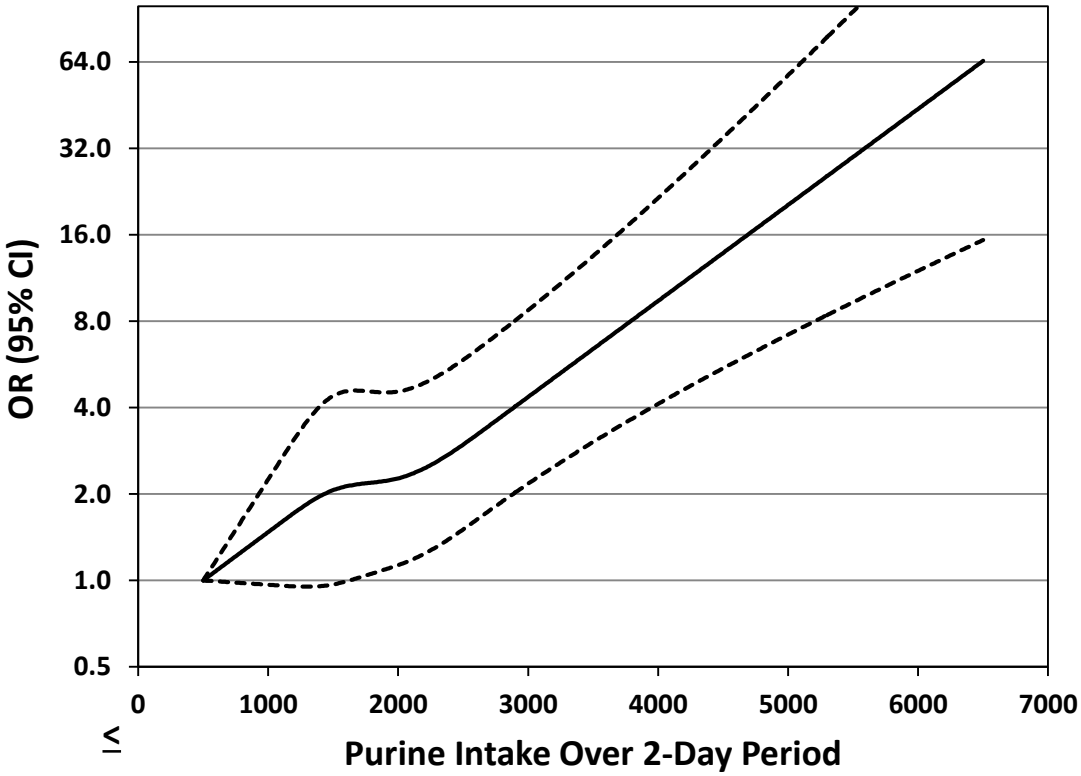


Figure 1. Estimated Odds Ratio and 95% Confidence Intervals for Recurrent Gout Attacks According to Amount of Purine Intake during the Past 2 Days

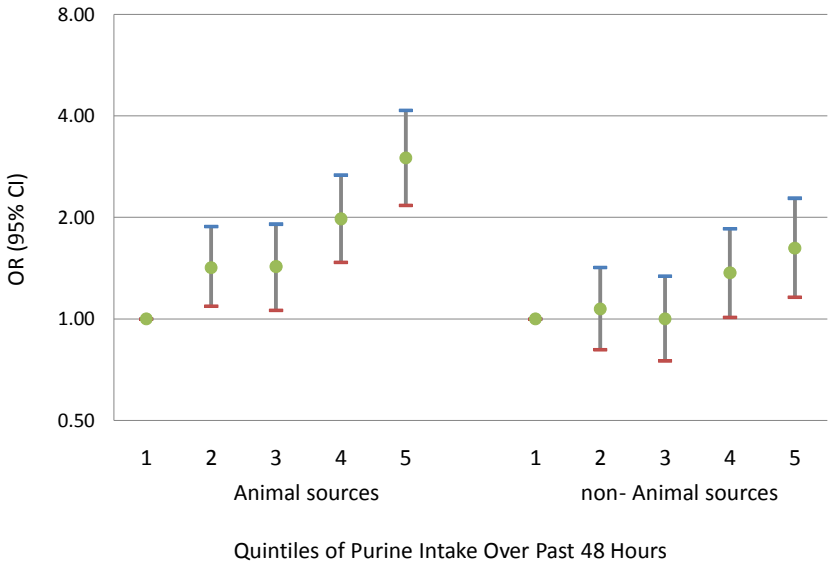


Figure 2. Estimated Odds Ratio for Recurrent Gout Attacks Related to the Source of Purine Intake

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