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Recent Diuretic Use and the Risk of Recurrent Gout Attacks: The Online Case-Crossover Gout Study

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ABSTRACT. ***Objective.*** To assess several putative risk factors, including thiazide and loop diuretics use, thought to trigger recurrent gout attacks.

Methods. We conducted an internet-based case-crossover study involving subjects who had a gout attack within the past year. Patients were recruited online and asked to provide access to medical records. Data were obtained on specific diuretic use on each day over the 2-day period prior to an acute gout attack (hazard period) and on each day of 2 days during the intercritical period (control period). We examined the relation of all diuretic use and use of specific diuretics, i.e., thiazide and loop, to the risk of recurrent gout attacks using a conditional logistic regression model adjusting for alcohol consumption and purine intake.

Results. One hundred ninety-seven subjects completed both control and hazard period questionnaires. Participants were predominantly male (80%) and over half had a college education. The median time between onset of gout attack and logging on to the website was 2 days. Adjusting for alcohol consumption and purine intake, the odds ratio (OR) for recurrent gout attacks from all diuretic use over the last 48 h was 3.6 (95% confidence interval 1.4–9.7). OR of recurrent gout attacks were 3.2 and 3.8 for use of thiazide and loop, respectively.

Conclusion. Recent use of diuretics is associated with a significantly increased risk for recurrent gouty arthritis. The increased risk of gout attacks from either thiazide or possibly loop diuretic therapies represents an important modifiable risk factor in patients with gout. (First Release June 1 2006; J Rheumatol 2006;33:1341–5)

Key Indexing Terms:
DIURETICS GOUT TRIGGERS

Gout affects about 8.4 per 1000 persons in the US[1]; epidemiologic data obtained from the last 4 decades are consistent with an increasing incidence and prevalence of gout in Western industrialized countries[2]. Although much is known about the pathophysiology of gout and clinically effective drug treatments are available, many patients with gout have recurrent attacks[3,4]. These attacks cause progressive disability and can lead to cumulative joint damage[5]. While a central therapeutic strategy in management of gout is avoidance of triggering events, investigations have concentrated on risk factors for initial occurrence of gout[3,6-10] and few have explored factors that trigger recurrent attacks among individuals already diagnosed with gout.

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The association between hyperuricemia and diuretic therapy has been known since 1958[11-13]. Shortly after discovery of the thiazide class of diuretics, these medications were observed to raise serum uric acid levels. A similar effect was also later found for loop diuretics[12]. Diuretics raise uric acid levels through a combination of volume depletion and decreased renal tubular secretion of uric acid[14]. In a retrospective cohort study of enrollees in the New Jersey Medicaid program, Gurwitz, *et al*[14] found a 2-fold increased risk for initiation of anti-gout medication in patients receiving thiazide diuretics. In a small case-control study of hypertensive patients who developed gout, gout was more strongly related to the use of loop diuretics than thiazides[15]. While knowledge of the association with hyperuricemia is clear, the relation of diuretic use as well as use of specific diuretics, such as thiazide and loop, to the risk of recurrent gout attacks has not been formally investigated, and the magnitude of association, if existing, is unknown.

In addition to the burden of gout-related arthritis itself, patients with gout often have comorbidities including hypertension and coronary heart disease[16]. Further, hypertension itself is an independent risk factor for the development of gout[17]. Several investigators have hypothesized that significant increases over the last 2 decades in the prevalence of hypertension and concomitant diuretic therapy may contribute to the increased prevalence and incidence of gout in Western

countries[18-20]. The Joint National Commission Seventh Report on Prevention, Detection, Evaluation, and Treatment of Hypertension recommends thiazide-type diuretics as initial therapy in most patients either alone or in combination with another agent[21]. Because of the favorable cost profile and efficacy, thiazide diuretics are commonly prescribed, ranking seventh among the most prescribed medications in the US in 2003[22], and this number does not include the use of thiazides in combination therapy. Thus, both increasing prevalence of hypertension[20] and use of thiazide diuretic prescriptions are likely to lead to further increases in recurrent gout attacks.

Considering the relatively high prevalence of hypertension among gout patients and the widespread use of diuretics for the treatment of hypertension, we conducted an internet-based case-crossover study to assess the relation of diuretic use to the risk of recurrent gout attacks and evaluated whether the effect varies according to types of diuretic use. The case-crossover study uses each subject as his/her own control and compares the frequency of exposure to a suspected precipitating factor immediately prior to disease onset (hazard period) to that during the control periods. Self-matching of each subject eliminates bias in control selection and removes confounding effects of factors that are constant over time. Thus, it is an optimal study design for examining the effect of risk factors triggering recurrent attacks, such as repeated gout attacks.

MATERIALS AND METHODS

Study design. We constructed a website for this study (https://dcc2.bumc.bu.edu/GOUT) on an independent secure server within the Boston University School of Medicine 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 US, and be willing to release medical records pertaining to gout diagnosis and treatment.

Questionnaires. Eligible subjects were asked to complete the following questionnaires: (1) sociodemographic questionnaire: name, age, sex, home address, home and work phone number, e-mail address, date of birth, years of education, and household income; (2) medical history questionnaire: medication use, self-reported comorbidities, and history of gout attacks; (3) control-period questionnaire: frequency and quantity of potential risk factors, including all medications taken, for each day over the preceding 2-day period during the intercritical gout period. The questionnaire was administered at study entry, and at 3, 6, and 9 months of followup. Subjects were asked to report the occurrence of a gout attack within 48 hours after its onset and complete (4) a hazard-period questionnaire: date of recurrent gout attack, clinical symptoms, medication used to treat the recurrent gout attack, and frequency and quantity of potential risk factors, including all medications taken, for each 24-hour period over the 48 hours prior to the attack. As part of the medical history participants were asked, 'Did you take any of the following diuretics ('water pills') yesterday or the day before yesterday?" They were then provided with different options to check on the website, including: (1) hydrochlorothiazide or thiazide for hypertension (e.g., Dyazide, Esidrix, Hydrodiuril); (2) furosemide ("loop" diuretics) for congestive heart failure (e.g., Lasix); (3) amiloride, spironolactone, or triamterene (e.g., Midamor, Aldactone, Dyrenium); or (4) other diuretics (please specify).

Diagnosis of gout, and assessment of risk factors. We obtained medical records pertaining to the participant's gout history and/or a checklist of gout symptoms completed by the subject's physician. To confirm a subject's diagnosis of gout, we used information abstracted from medical records or the checklist, and data collected from the questionnaires submitted by study participant. A rheumatologist reviewed all medical records and the checklist information and assessed whether the subject had a diagnosis of gout by a physician, and a history of gout according to American College of Rheumatology (ACR) criteria for gout[23].

Self-reported acute gout attacks were defined on the basis of: (1) moderate to severe joint pain developed within a 24-hour period; (2) 3 or fewer joints involved at time of the acute attack; (3) redness observed over joints; (4) joint(s) feels warm or swollen; and (5) attack requires specific therapy, e.g., a nonsteroidal antiinflammatory drug, or colchicine. These modified criteria are based on criteria published by the ACR[23].

We also assessed a set of other putative risk factors, including alcohol consumption and total amount of purine intake. 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, i.e., 12-ounce bottle or can of beer; 5-ounce glass of wine; and 1–1.5 ounces of spirits. Total purine intake from food for each day over 2-day period was estimated using established food purine contents[24].

Statistical analysis. Using a conditional logistic regression model, we examined the relation of all diuretic use over the 2-day period to the risk of recurrent gout attacks while adjusting for alcohol consumption and purine intake using well described methods[25]. Data on diuretic use, purine consumption from food, and alcohol intake were collected during the same time period at each hazard and control period. In addition, we also evaluated the effect of specific type of diuretic use, i.e., thiazide or loop class, on the risk of recurrent gout attacks.

RESULTS

Of 197 subjects who completed both hazard-period and control-period questionnaires, 179 (91%) subjects fulfilled the ACR criteria for gout. One hundred eighty-six 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 163 (94.8%) met ACR criteria for gout.

Characteristics of the 197 participants who completed both hazard-period and control-period questionnaires are presented in Table 1. The average age of participants was 52 years. Participants were predominantly male (80%) and Caucasian (88%), and over half had a college education. Subjects were recruited from 40 states and the District of Columbia. During the one-year followup period, 321 recurrent gout attacks occurred among participants. The median time between the date of the gout attack and date of completion of hazard-period questionnaire was 2 days. All participants included in this analysis completed at least one control-period questionnaire. The mean number of control-period questionnaires completed was 2.4 (SD 1.4, range 1–5) and hazard period questionnaires was 1.7 (SD 1.1). Among the subset who took diuretics, the

Table 1. Characteristics of participants in the Internet-based case-crossover study of gout, 2003–04.

Characteristics	N	%, Mean, or Median
Sex, %		
Men	158	80.2
Women	39	19.8
Age, median (range)	197	52 (29–83)
BMI, median (range)	196**	30 (22–40)
Education, %		
High school graduate/GED	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, %		
< 20,000	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, %		
African American	2	1.0
Caucasian	174	88.3
Other	16	8.1
Missing	5	2.5
No. of days between attack date and logon, median (range)	321*	2 (0–24)
Years of disease duration, median (range)	196†	8.2 (0–36)
Regular alcohol consumption, %	197	73.6
Self-report comorbidities, %		
Heart attack	5	2.6
Heart failure	6	3.1
Hypertension	92	46.9
Kidney problem	16	8.2
Tophus	64	32.7
Crystal diagnosis	37	19.0

* 321 hazard visits contributed by 197 subjects. ** One subject did not provide the data on BMI or years of disease duration. BMI: body mass index.

mean number of control-period questionnaires completed was 2.4 (SD 1.5) and hazard period questionnaires was 1.6 (SD 0.9). About 33% of subjects had tophus, 19% had crystal in their affected joint, and 50% of subjects' medical records indicated that the participants had hyperuricemia.

During the followup period, 141 subjects did not take any diuretic medication over either hazard or control period and 56 subjects used at least one type of diuretic. Of these, 14 used only loop diuretics, 39 used only thiazides, and 3 used both loop and thiazide diuretics. Since subjects who did not use any type of diuretic during the followup period would not contribute informative data on the effect of diuretic use, we excluded these subjects from the analyses. We limited our analyses to the remaining 56 subjects who used at least one type of diuretic during the study period.

As shown in Table 2, the odds ratio (OR) of recurrent gout attacks for any type of diuretic use over last 48 hours was 3.6 (95% CI 1.4–9.7). When the effect of a specific type of diuretic use was assessed separately, thiazide use alone had more than 3-fold increased risk for recurrent gout attacks (OR 3.2, 95% CI 1.1–9.5). A similar effect was also observed for loop diuretic use (OR 3.8, 95% CI 0.3–51.0); however, the number of subjects using loop diuretics was relatively small and the CI of the point estimate was wide.

DISCUSSION

Our results suggest that recent use of diuretics within 48 hours is associated with a significantly increased risk of recurrent gout attacks among persons with preexisting gout. Such an effect was observed for both thiazide and loop diuretics, although the effect for the latter was not statistically significant. While the association of diuretics with hyperuricemia has been known for years, this is the first study to find and quantify the effect of diuretics on the risk of recurrent gout attacks.

Many persons with gout continue to have recurrent gout attacks[3,4]. These attacks are painful, increase functional limitation, and can potentially lead to cumulative joint damage[5]. Both prevalence and incidence of gout have increased over the last 2 decades in industrialized countries[2]. One explanation

Table 2. Association between any diuretic use as well as specific type of diuretic use over the last 48 hours and risk of recurrent gout attacks.

Diuretics Use	Control Periods	Hazard Periods	Adjusted OR* (95% CI)
		Loop or Thiazide or Both (n = 56)	
Neither type	37	11	1.0
Any type	89	78	3.6 (1.4–9.7)
		Thiazide Only (n = 39)	
No	29	9	1.0
Yes	57	49	3.2 (1.1–9.5)
		Loop Only (n = 14)	
No	8	2	1.0
Yes	29	23	3.8 (0.3–51.0)

* Adjusted for alcohol consumption and purine intake.

for such an increase is the increases in the prevalence of hypertension and concomitant diuretic therapy[18-20]. For instance, the prevalence of hypertension in the US has increased from 25.0% during 1991-98 to 28.7% during 1999-2000[20]. Recently, the Joint National Commission 7th Report on Prevention, Detection, Evaluation and Treatment of Hypertension recommended thiazide-type diuretics as initial therapy in most patients either alone or in combination with another agent[21]. Since hypertension impairs urate secretion and promotes hyperuricemia[26], the association between hypertension and gout is further compounded by the administration of diuretic therapy. Clarification of the effect of diuretic use on the risk of recurrent gout attacks has important clinical implications. We hypothesize that abrupt changes in diuretic use may lead to acute increases in uric acid concentration, thus increasing the appropriate conditions for crystal formation or precipitation and modulating their phlogistic potential through perturbation of the local synovial microenvironment[27].

There are a number of alternative effective agents for the treatment of hypertension and congestive heart failure in persons with gout that are unlikely to predispose to recurrent gout attacks. Clinicians have ample ability to individualize management for special populations[28] and could reduce the risk of gout attacks by avoiding the use of diuretics in persons with preexisting gout. In our study, about 28% of participants with a history of gout were taking diuretics, and the effect of these diuretics on recurrent gout attacks was not trivial.

Several characteristics of our study are noteworthy. First, studying the triggering effect of diuretics on the risk of recurrent gout attacks is challenging. Neither case-control nor cohort studies are ideal study designs for such research questions. In our study, we applied 2 innovative approaches, a case-crossover study design and use of the Internet, to examine whether diuretic use could trigger recurrent gout attacks. The case-crossover study design uses each subject as his/her own control and compares the frequency of exposure to a suspected precipitating factor immediately prior to disease onset to that during the control periods. Self-matching of each subject eliminates bias in control selection and removes confounding effects of factors that are constant over time. Second, using the Internet as a medium, we were able to reach patients with gout in the entire US. Indeed, participants in our study were recruited from 40 states and the District of Columbia. Further, we showed that the majority of subjects' history of gout could be verified by their medical records and these subjects can be efficiently followed over time. Third, we showed that both risk factors and disease occurrence can be assessed in real time, which should minimize the potential recall bias.

Our study has some limitations as well. We did not collect information on dosages of medications used; we were unable to assess a dose-response relationship between diuretic use and risk of recurrent gout attacks. Also, the number of subjects using diuretics in our study was relatively small; this was especially the case for loop users.

While we used validated questionnaires to assess risk factors for gout, including diuretic use, 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. Thus, we postulate that the true effect of diuretics may actually be larger than we observed.

There are other potential important confounders that could have varied between control and hazard periods including adiposity (e.g., weight and body mass index) and use of other medications known to affect serum urate levels (e.g., beta-blockers, low-dose aspirin use, and allopurinol). Further, our study design was not immune to "confounding by indication" for diuretic use, such as developing or worsening of hypertension, congestive heart failure, and renal insufficiency, that may also trigger recurrent gout attacks. While it is possible these risk factors may occur differently during the hazard period compared to the control period, we believed the frequency of these risk factors, such as congestive heart failure or renal insufficiency, would be very low in our study participants. Developing or worsening of hypertension is likely to be a

chronic process and could therefore occur during either a hazard or control period.

In summary, we found that recent use of thiazide and possibly loop diuretics was associated with a significantly increased risk for recurrent gouty arthritis. Despite the well known association of gout and diuretics, a relatively large proportion of our patient population with preexisting gout was prescribed this class of antihypertensive therapy. Given the wide availability of alternative effective agents for the treatment of hypertension and congestive heart failure, clinicians have ample ability to individualize management for this population, and could reduce risk of recurrent gout attacks by avoiding the use of thiazide and possibly loop diuretics in persons with preexisting gout.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778-99.
2. Bieber JD, Terkeltaub RA. Gout: on the brink of novel therapeutic options for an ancient disease. Arthritis Rheum 2004;50:2400-14.
3. Gutman AB. The past four decades of progress in the knowledge of gout, with an assessment of the present status. Arthritis Rheum 1973;16:431-45.
4. Terkeltaub RA. Clinical practice. Gout. N Engl J Med 2003;349:1647-55.
5. Wallace SL, Singer JZ. Review: systemic toxicity associated with the intravenous administration of colchicine — guidelines for use. J Rheumatol 1988;15:495-9.
6. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. JAMA 1991;266:3004-7.
7. Hochberg MC, Thomas J, Thomas DJ, Mead L, Levine DM, Klag MJ. Racial differences in the incidence of gout. The role of hypertension. Arthritis Rheum 1995;38:628-32.
8. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.
9. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004;363:1277-81.
10. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093-103.
11. Oren B, Rich M, Belle M. Chlorothiazide (Diuril) as a hyperuricacidemic agent. JAMA 1958;168:2128-9.
12. Laragh JH, Cannon PJ, Stason WB, Heinemann HO. Physiologic and clinical observations on furosemide and ethacrynic acid. Ann NY Acad Sci 1966;139:453-65.
13. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742-8.
14. Gurwitz JH, Kalish SC, Bohn RL, et al. Thiazide diuretics and the initiation of anti-gout therapy. J Clin Epidemiol 1997;50:953-9.
15. Waller PC, Ramsay LE. Predicting acute gout in diuretic-treated hypertensive patients. J Hum Hypertens 1989;3:457-61.
16. Rott KT, Agudelo CA. Gout. JAMA 2003;289:2857-60.
17. Grodzicki T, Palmer A, Bulpitt CJ. Incidence of diabetes and gout in hypertensive patients during 8 years of follow-up. The General Practice Hypertension Study Group. J Hum Hypertens 1997;11:583-5.
18. Izzo JL Jr. Hypertension in the metabolic syndrome and diabetes: pathogenesis, clinical studies, and treatment. J Clin Hypertens 2003;5 Suppl 4:3-10.
19. Salvetti A, Ghiadoni L. Guidelines for antihypertensive treatment: an update after the ALLHAT study. J Am Soc Nephrol 2004;15 Suppl 1:S51-S54.
20. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA 2003;290:199-206.
21. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
22. Mosby's Drug Consult. Top 200 most prescribed drugs of 2003. New York: Elsevier; 2003. [Internet]. Available from: http://www.mosbysdrugconsult.com/DrugConsult/Top_200/. Accessed April 6, 2006.
23. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
24. Wolfram G, Colling M. [Total purine content in selected foods.] Z Ernahrungswiss 1987;26:205-13.
25. Greenland S. A unified approach to the analysis of case-distribution (case-only) studies. Stat Med 1999;18:1-15.
26. Tykarski A. Evaluation of renal handling of uric acid in essential hypertension: hyperuricemia related to decreased urate secretion. Nephron 1991;59:364-8.
27. Malawista SE, Van Blaricom G, Cretella SB, Schwartz ML. The phlogistic potential of urate in solution: studies of the phagocytic process in human leukocytes. Arthritis Rheum 1979;22:728-36.
28. Ferdinand KC. Recommendations for the management of special populations: racial and ethnic populations. Am J Hypertens 2003;16(11 Pt 2):50S-54S.