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Increased Risk of Recurrent Gout Attacks with Hospitalization

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Abstract

Background—While anecdotal evidence suggests that risk of recurrent gout attack increases with hospitalization, no study has formally tested this hypothesis.

Methods—We conducted an online case-crossover study of individuals with gout. We obtained information on gout attacks over a one-year period, including: onset date, symptoms and signs, medications, and exposure to potential risk factors, including hospitalization, during the 2-day hazard period prior to each gout attack. The same exposure information was also obtained over 2-day intercritical gout control periods. We performed conditional logistic regression to examine the relationship of hospitalization with recurrent gout attacks and whether such a relationship was modified by concomitant use of anti-gout medications.

Results—Of 724 participants (mean age 54.5 years, 78.5% male), 35 hospitalizations occurred during either a hazard or control period. The adjusted odds of gout attacks was increased 4-fold with hospitalization (OR 4.05, 95% confidence interval: 1.78–9.19) compared with no hospitalization. The effect of hospitalization tended to attenuate with use of allopurinol, colchicine, or NSAIDs, but not statistically significantly.

Conclusions—Our study confirmed that the risk of gout attacks increases among gout patients during hospitalization. Appropriate measures should be considered for prevention of gout attacks during hospitalization for patients with pre-existing gout.

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Introduction

Approximately 8.3 million adults in the US have gout,¹ with gout incidence increasing in recent decades.² Although the pathophysiology of gout is well understood and effective preventive therapies exist, many patients still experience recurrent gout attacks attributed to various triggers.

Hospitalization has been anecdotally recognized by clinicians as a potential trigger for gout attacks.³ Indeed, hospitalization may be associated with an increased risk of recurrent gout attacks through several mechanisms, including fluid shifts, alterations in pH, tissue hypoxia, changes in renal urate handling, and initiation or discontinuation of medications. As a substantial proportion of gout patients are hospitalized annually for any cause,⁴ hospitalization could potentially serve as a marker for an increased risk of recurrent gout attacks among these patients. Confirming such an association and determining the magnitude of effect of hospitalization on recurrent gout attacks would provide impetus for the study of prophylactic medication use when persons with pre-existing gout are hospitalized. Such findings would also have financial implications in their potential to reduce the length of hospital stay and other costs associated with gout attacks.⁵ To address these issues, we conducted an online case-crossover study and examined the relationship between hospitalization and risk of recurrent gout attacks.

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”. Individuals who clicked on the advertisement were directed to the study website and were asked about socio-demographic information, gout-related data (e.g., diagnosis of initial gout attack, age of onset, medications for treatment of gout, and number of gout attacks in the last 12 months), history of other diseases, and medication use.

Participants were required to have had a gout attack within the past 12 months, be at least 18 years of age, reside in the U.S., provide informed consent, indicate if gout was diagnosed by a physician, and agree to release medical records pertaining to gout diagnosis and treatment. To confirm the diagnosis of gout, we obtained medical records pertaining to the participant's gout history and/or a checklist of the American College of Rheumatology (ACR) Preliminary Classification Criteria for Gout,⁷ as completed by the participant's physician. Two rheumatologists (DJH, TN) reviewed all medical records and the checklists and determined whether the participants met ACR criteria. The study was approved by the Institutional Review Board of Boston University Medical Campus.

Ascertainment of risk factors

Participants were queried about potential risk factors during the 2-day period prior to the gout attack (hazard period), and during four pre-specified control-periods at 3-month intervals during the year 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. Risk factors included dietary aspects, medications and hospitalizations. Participants were specifically asked if they were hospitalized during either hazard or control periods. If the answer was “yes”, they were asked to indicate the primary reason for hospitalization.

Statistical analysis

We examined the relationship of hospitalization with risk of recurrent gout attacks using conditional logistic regression. In a multivariable model, we adjusted for the following time-varying potential confounders: alcohol consumption, purine intake, and use of diuretics, allopurinol, colchicine, and NSAIDs. We also determined the effect of hospitalization on risk of recurrent gout attack according to use of allopurinol, colchicine, and/or NSAIDs, after adjustment for potential confounders.

Results

We analyzed 724 persons with gout who completed both hazard and control period questionnaires. Of them, 614 (84.8%) met the ACR Preliminary Classification Criteria for gout, and 93 (12.8%) had a previous synovial fluid analysis confirming monosodium urate crystals. Participants were recruited from 49 states and the District of Columbia. The average age of the participants was 54 years. Participants were predominantly men (78%), white (89%), and college educated (55%). Allopurinol was used by 47%, colchicine by 30%, and NSAIDs by 64% of subjects during either a hazard or control period (Table 1).

Over the one-year follow-up period, 35 hospitalizations occurred; 24 during hazard periods and 11 during control periods. Two participants were hospitalized due to a gout attack, and were therefore excluded from the analysis. Of the remaining hospitalizations, 9 were for surgery, 8 for acute infections, 7 for cardiovascular conditions, 5 for other reasons, and a reason for hospitalization was not indicated in 4 cases (Appendix Table 1). Compared with no hospitalization, the multivariable adjusted odds of recurrent gout attacks was increased 4-fold with hospitalization (odds ratio [OR] 4.05, 95% confidence interval [CI] 1.78–9.19) (Table 2). The association between hospitalization and the risk of recurrent gout attack tended to attenuate with use of allopurinol, colchicine, and/or NSAIDs, albeit not reaching statistical significance due to the small number of hospitalizations that limited our ability to perform a stratified analysis according to gout medication use (Table 2). Sensitivity analyses, including (i) adjustment for cherry intake and aspirin use, and (ii) restriction to subjects who met ACR classification criteria for gout, did not change results (OR 4.39, 95% CI 1.91–10.07, and OR 4.88, 95% CI 1.91–12.32, respectively)

Discussion

Although hospitalization has been anecdotally associated with recurrent gout attacks, this study is the first, to our knowledge, to formally demonstrate this association. Our study found that risk of acute gout attack was increased 4-fold with hospitalization. These findings are noteworthy because up to 18% of gout patients are hospitalized each year (all causes), making hospitalization an important potential exposure at the population level.⁴ Because gout attacks have the potential to prolong hospital stay,⁸ there is great potential to reduce healthcare costs by treating hospitalized patients with pre-existing gout with prophylactic medications, if our findings are replicated in other studies.

Hospitalization is likely to be associated with recurrent gout attacks through two potential pathways: (1) the condition that prompted hospitalization, and/or (2) the events and treatments that occurred during the hospitalization; however both pathways may have similar pathophysiology. Both acute illness, or treatment during hospitalization may cause volume depletion or acidosis, that may promote urate crystallization.⁹ Similarly, fluid shifts may result in changes to renal urate handling and serum urate.¹⁰ Tissue hypoxia, as a result of pulmonary or cardiovascular conditions, may decrease urate excretion.¹¹ Use of medications to treat co-existing conditions during a hospitalization (e.g., diuretics and low-dose aspirin) or discontinuation of medications used for gout attack prophylaxis and/or

urate-lowering, due to real/perceived contraindication or medical error, may also increase gout attacks.

Few studies have examined the association between hospitalization and risk of recurrent gout attacks. Two studies reported a modest risk of recurrent gout attacks among patients who had undergone surgery (17% and 33%, respectively), but risk due to hospitalization for non-surgical causes was not reported.^{12,13} In a study of gout attacks during hospitalizations for any reason, a gout attack occurred *after* admission in 69% of patients with a history of gout, however a clear gout trigger during hospitalization was identified in only a minority of patients.¹⁴ These findings suggest that many gout patients may benefit from use of prophylactic medications to reduce risk of acute attacks during hospitalization. Our findings support the potential for prophylaxis with colchicine or NSAIDs, or pre-existing use of allopurinol to lower the risk of recurrent gout attack associated with hospitalization, similar to findings in post-surgical patients.¹⁵ However, the effectiveness of such strategies will need to be tested specifically.

Several strengths of this study are worth noting. Because the case-crossover design uses each case as his/her own control, it minimizes control selection bias, eliminates time-invariant confounders between individuals, and allows examination of potential triggers with short induction times. Secondly, we used the internet as a platform to recruit subjects with gout from across the U.S. and to collect information on hospitalization and gout attacks in real-time, while minimizing the potential for recall bias and making the study more efficient.

Our study has some limitations. Individual reasons for hospitalization occurred at relatively low frequencies in our study, which did not allow for meaningful assessment of risk associated with each individual condition. However, our findings are consistent with the limited literature suggesting that recurrent gout attack risk is increased in the post-operative period.¹⁵ Additionally, subjects may inaccurately report use of gout-related medications during hospitalizations, which would tend to bias study findings toward the null. The low frequencies of allopurinol, colchicine and NSAID use during hospitalization limited our ability to infer any risk reduction with these medications. Finally, our study participants may not be demographically representative of all gout patients in the US, though the biologic effects of conditions leading to hospitalization or events during hospitalization should be similar to those in the general population.

In conclusion, our study findings suggest that hospitalization is associated with more than 4-fold risk of recurrent gout attacks. Given the morbidity and costs associated with gout attacks occurring in hospital, including increased length-of-stay, consideration should be given to use of appropriate measures to prevent and promptly manage gout attacks when gout patients are hospitalized. Akin to the provision of deep venous thrombosis prophylaxis to at-risk patients during hospitalization, further study is warranted regarding the risk/benefit ratio and cost-effectiveness of gout prophylaxis in hospitalized patients with pre-existing gout who are at great risk for recurrent gout attacks.

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Clinical Significance

- Hospitalization is common among patients with pre-existing gout
- Risk of acute gout attack was increased 4-fold with hospitalization (any cause)
- Risk of acute gout attack with hospitalization may be reduced with use of NSAIDs, colchicine, or pre-existing allopurinol use

Table 1

Characteristics of 724 Participants in the Internet-Based Case-Crossover Study of Gout* During either hazard or control periods.

Characteristics	N=724
Sex (n, %)	
Men	568 (78.4)
Age (median, range)	54 (21–88)
Education (n, %)	
Less than High School Graduate	14 (1.9)
High School Graduate	66 (9.1)
Some College/Technical School	223 (30.8)
College Graduate	175 (24.2)
Some Professional/Graduate School	78 (10.8)
Completed Professional or Graduate School	168 (23.2)
Household Income (n, %)	
<\$25,000	58 (8.0)
25,000–49,999	141 (19.5)
50,000–74,999	133 (18.4)
75,000–99,999	106 (14.6)
>100,000	186 (25.7)
Refused to Answer	100 (13.8)
Race (n, %)	
Black	20 (2.8)
White	642 (88.7)
Other	53 (7.3)
Refused to Answer	9 (1.2)
BMI (kg/m ² , median, range)	30.6 (14.7, 69.9)
Years of Disease Duration (median, range)	5 (0–51)
Allopurinol Users* (n, %)	337 (46.7)
Nonsteroidal Anti-Inflammatory Drug Users* (n, %)	461 (63.7)
Colchicine Users* (n, %)	214 (29.6)
Diuretic Users* (n, %)	209 (28.9)
Alcohol drinkers* (n, %)	474 (51.0)

* During either hazard or control periods.

Table 2

Risk of recurrent gout attacks with hospitalization and medication use in the prior two days.

Overall Sample				
Hospitalization in prior 2 days		Control periods (N)	Hazard periods (N)	Adjusted OR* (95% CI)
No		1935	1410	1.00 (referent)
Yes		10	23	4.05 (1.78–9.19)
According to Gout-Related Medication Use				
Hospitalization in prior 2 days	Anti-Gout Medication use in prior 2 days [†]	Control periods (N)	Hazard periods (N)	Adjusted OR* (95% CI)
No	No	904	710	1.00 (referent)
	Yes	1031	700	0.79 (0.64–0.97)
Yes	No	7	17	4.52 (1.71–11.86)
	Yes	3	6	3.03 (0.65–14.21)

* Adjusted for alcohol consumption, purine intake and use of diuretics.

[†] Including NSAIDs, colchicine and allopurinol, combined

Appendix Table 1

Primary reason for hospitalization during the 2-day period prior to gout attack, or control period

Primary reason for hospitalization	Total N(%)
Surgery	9 (28.1%)
Musculoskeletal conditions	5 (15.6%)
Abdominal	3 (9.4%)
Cancer	1 (3.1%)
Infections	8 (25.0%)
Cellulitis/ superficial	2 (6.3%)
Gastrointestinal	2 (6.3%)
Unknown site	4 (12.5%)
Cardiovascular	7 (21.2%)
Arrhythmia	2 (6.3%)
Myocardial infarction	1 (3.1%)
Stroke	1 (3.1%)
Syncope	1 (3.1%)
Ischemic colitis	1 (3.1%)
Deep venous thrombosis	1 (3.1%)
Other [*]	5 (15.6%)
Not indicated	4 (12.5%)

^{*} Other reasons included: Nephrolithiasis, vertigo, pneumothorax, and pain not otherwise specified