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Low-dose aspirin use and recurrent gout attacks

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Abstract

Objective—To examine the association between cardioprotective use of low-dose aspirin and the risk of recurrent gout attacks among gout patients.

Methods—We conducted an online case-crossover study of individuals with gout over 1 year. The following information was obtained during gout attacks: the onset dates, symptoms and signs, medications, and exposure to potential risk factors, including daily aspirin use and dosage, during the 2-day hazard period prior to the gout attacks. The same exposure information was also obtained over 2-day control periods.

Results—Of the 724 participants analysed, 40.5% took aspirin 325 mg/day during either a hazard or a control period. Compared with no aspirin use, the adjusted OR of gout attacks increased by 81% (OR=1.81, 95% CI 1.30 to 2.51) for 325 mg/day of aspirin use on two consecutive days. The corresponding ORs were stronger with lower doses (eg, OR=1.91 for 100 mg, 95% CI 1.32 to 2.85). These associations persisted across subgroups by sex, age, body mass index categories and renal insufficiency status. Concomitant use of allopurinol nullified the detrimental effect of aspirin.

Conclusions—Our findings suggest that the use of low-dose aspirin on two consecutive days is associated with an increased risk of recurrent gout attacks.

Recommended serum urate monitoring with concomitant use and dose adjustment of a urate-lowering therapy among patients with gout may be especially important to help avoid the risk of gout attacks associated with low-dose aspirin.

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INTRODUCTION

Approximately 8.3 million adults in the USA have gout,¹ and the prevalence and incidence of gout have increased over the last few decades.^{2,3} In addition to the substantial pain and morbidity caused by gout itself, a large proportion of patients with gout suffer from other comorbidities, including coronary heart disease, obesity, type 2 diabetes mellitus, dyslipidaemia and hypertension.^{4,5} While medications used to manage these comorbidities may also affect the risk of gout attacks, the data on such impacts are currently limited.

Low-dose aspirin (acetylsalicylic acid), a widely used cardioprotective medication,^{6,7} is known to affect renal handling of uric acid in an inverse dose-dependent manner. Aspirin doses up to 1–2 g/day reduce uric acid excretion, contributing to hyperuricaemia, whereas higher doses are uricosuric.⁸ The commonly employed doses in the USA, such as 325 mg ('full strength') or 81 mg ('baby aspirin'), are within the urate retentive range and thus could contribute to the risk of gout. Given the substantial burden of cardiovascular comorbidities among gout patients,⁵ the prevalence of cardioprotective aspirin use could be considerable. Indeed, in a recent evaluation of gout patients in the UK, approximately one-third of gout patients used low-dose aspirin either currently or in the past.⁹ This may in fact be an underestimate of the true prevalence of low-dose aspirin use in the USA, given the availability of low-dose aspirin over the counter without a prescription. Furthermore, gout patients may be at an even higher risk of low-dose aspirin-related urate retention, given gout's strong association with chronic kidney disease.^{5,10} However, to date, no study has assessed the impact of aspirin use on the risk of gout attacks.

In this study, we used a case-crossover design to examine the association between cardioprotective use of low-dose aspirin and the risk of recurrent gout attacks as well as its potential modification by allopurinol use and other known gout risk factors.

METHODS

Study design

Since February 2003, we have conducted an internet-based case-crossover study (ie, Boston University Online Gout Study) with the primary aim of investigating purported triggers for recurrent gout attacks.¹¹ As described previously, eligible participants were followed for 1 year and asked to complete an online hazard period questionnaire as soon as they experienced a recurrent gout attack (ie, hazard period). Over the 1-year follow-up, the same questionnaire was also administered every 3 months during the intercritical period (ie, control periods) for each participant. The frequency of each potential risk factor occurring during the hazard period was then compared with that occurring during the control periods. With this study design, each participant serves as his or her own control, and self-matching eliminates confounding by risk factors that are constant for an individual but that would differ between study subjects during the study period (eg, genetics, sex, race, education). Such a design has been successfully utilised to evaluate associations between transient exposures and the onset of acute events,^{12–16} including studies of pharmacovigilance.^{17–19}

Subject recruitment

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 (<http://www.Google.com>) by linking an advertisement to the search term 'gout'. Individuals who clicked on the study advertisement were directed to the study website where they were asked to provide the following details: sociodemographic information, gout-related data (eg, diagnosis of initial gout attack, age of onset, medication

used for treatment of gout and the number of gout attacks in the last 12 months), history of other diseases (eg, renal disease) and medication use.

Eligible participants were required 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 USA, provide informed consent and agree to release medical records pertaining to gout diagnosis and treatment. To confirm a diagnosis of gout, we obtained medical records pertaining to the participant's gout history and/or a checklist of the features listed in the American College of Rheumatology (ACR) Preliminary Classification Criteria for Gout²⁰ completed by the subject's physician. Two rheumatologists (DJH and TN) reviewed all medical records and checklists and determined whether the participants had a diagnosis of gout according to the ACR criteria. The study was approved by the Institutional Review Board of Boston University Medical Campus.

Ascertainment of recurrent gout attacks

Data were collected regarding the onset date of the recurrent gout attack, anatomical location of the attack, clinical symptoms and signs (maximal pain within 24 h or redness), and medications used to treat the attack (eg, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids). This method of assessing gout attacks is consistent with the approaches used in acute and chronic gout trials.^{21–25} We also performed sensitivity analyses by restricting the cases to those who fulfilled ACR classification criteria for gout, as well as to those who had a gout attack involving the first metatarsophalangeal joint, experienced typical clinical symptoms and signs (ie, maximal pain within 24 h or redness), and were treated with at least one anti-gout medication (as listed above).

Ascertainment of aspirin intake

Participants were queried about the presence of a set of potential risk factors during the 2-day period prior to the gout attack (ie, hazard period), and during the following pre-specified control periods. Of note, aspirin was one of the hypothesised exposures considered to be potentially relevant to the risk of gout attacks since the conception of the current study. During the 2-day hazard periods, all participants were asked whether they took aspirin on a daily basis to prevent heart disease or stroke. If the answer was 'yes', they were further queried as to whether they took aspirin on each of the prior 2 days (ie, yesterday and the day before yesterday), the dose (ie, 81, 162, 325, 500, 650, 800, 975 mg and other doses) and the number of tablets taken daily. The same exposure data were also collected at the following time points (ie, control periods, four in total): for those subjects who entered the study during an intercritical period, at study entry and at 3, 6 and 9 months of follow-up; for those subjects who entered the study at the time of a gout attack, at 3, 6, 9 and 12 months of follow-up. Other potentially time-varying exposures that could be pertinent to gout attack risk were also assessed in the same manner.

Statistical analysis

We examined the association between aspirin use and the risk of recurrent gout attacks using conditional logistic regression. In a multivariable regression model, we adjusted for purine intake as well as use of alcohol, allopurinol, colchicine, NSAIDs and diuretics. While our primary analysis focused on aspirin doses of 325 mg/day, we also divided daily aspirin use into the following alternative categories: 100, 101–500 and 501–999 mg. Doses 1000 mg/day were only used during 14 periods (ie, nine hazard and five control periods) and thus did not allow meaningful analyses. Furthermore, these higher doses are not typically used for cardiovascular protection, but instead for analgesic or anti-inflammatory purposes, which could lead to potentially intractable confounding by indication (ie, for early signs of gout attacks). Thus, we excluded these 14 periods from our analysis.

We assessed potential subgroup effects according to sex, age (<55 years vs ≥55 years), obesity (body mass index (BMI) <30 kg/m² vs BMI ≥30 kg/m²) and renal insufficiency (yes vs no). We tested for effect modification by each of these factors by adding interaction terms to the final multivariable regression models. We also evaluated the potentially synergistic effect of concomitant consumption of alcoholic beverages (yes vs no) as well as the use of allopurinol (yes vs no), diuretics (yes vs no), NSAIDs (yes vs no) and colchicine (yes vs no).

RESULTS

There were 724 subjects with gout who completed both hazard period and control period questions. Of them, 614 (84.8%) participants met the ACR Preliminary Classification Criteria for Gout. Subjects were recruited from 49 states and the District of Columbia. The characteristics of the participants are presented in table 1. The average age of the participants was 54 years. Participants were predominantly men (78%), white (89%) and over half of them had received a college education. At the baseline, the mean BMI was 30.6 and 18.4% of the subjects reported renal insufficiency. About 51% of the participants consumed alcohol, 29% used diuretics, 47% took allopurinol, 64% used NSAIDs and 30% took colchicine during either hazard or control periods. During the 1-year follow-up, 43.5% of the subjects reported aspirin use, constituting 1016 hazard or control periods. Of those, 98.6% (n=1002) reported use of aspirin <1000 mg/day, with 40.5% of the subjects using aspirin ≥325 mg/day over the 2-day hazard or control period and 23.1% using aspirin <81 mg/day.

During the follow-up period, we documented 1434 recurrent gout attacks. Most gout attacks occurred in the lower extremity (92%), particularly in the first metatarsophalangeal joint, and had features of either maximal pain within 24 h or redness (99%). Approximately 90% of the gout attacks were treated with colchicine, NSAIDs, systemic corticosteroids, intra-articular corticosteroid injections or a combination of these medications.

As shown in table 2, compared with no use, use of aspirin ≥325 mg/day in the prior two consecutive days was associated with an 81% higher risk of gout attacks (OR=1.81, 95% CI 1.30 to 2.51). The association between aspirin use and risk of recurrent gout attacks increased as the aspirin dose decreased. For example, the ORs for recurrent gout attacks were 1.94, 1.64 and 1.55 for aspirin use 100, 101–500 and 501–999 mg/day on the prior two consecutive days, respectively. However, the use of aspirin for only 1 day over the prior 2-day period was not associated with the risk of gout attacks (see web appendix table 1). In addition, compared with no use, the use of aspirin <81 mg/day on the prior two consecutive days was associated with a 91% higher risk of gout attacks (OR=1.91, 95% CI 1.30 to 2.82).

When we limited the analysis to participants who met to the ACR Preliminary Classification Criteria for Gout (n=614), the effect estimates did not change significantly. The multivariable OR of recurrent gout attacks for aspirin use ≥325 mg/day on two consecutive days was 1.85 (95% CI 1.28 to 2.66). The effect of aspirin use ≥325 mg/day on two consecutive days was stronger (OR=2.96, 95% CI 1.50 to 5.86) when the analysis was restricted to participants whose gout attacks involved the first metatarsophalangeal joint, who experienced typical clinical symptoms and signs (ie, maximal pain within 24 h or redness), and who were treated with at least one anti-gout medication (n=247).

The association between aspirin use ≥325 mg/day on two consecutive days and the risk of recurrent gout attacks persisted across subgroups by sex, age and BMI categories (table 3). Such an effect appeared more pronounced among participants who had self-reported renal insufficiency, although the interaction term was not statistically significant probably due to the relatively small number of individuals reporting renal insufficiency (n=133).

Table 4 presents the combined effect of aspirin use (325 mg/day on two consecutive days) and various time-varying gout-related risk factors on the risk of gout attacks. The risk of gout attacks was much higher when aspirin was used concomitantly with high purine intake and diuretic use, whereas the increased risk of gout with aspirin use was nullified by concurrent allopurinol use.

DISCUSSION

In this large prospective case-crossover study, we found that the use of low-dose aspirin was associated with a higher risk of recurrent gout attacks. This association increased as the dose decreased, and the commonly used cardiovascular doses (325 mg/day or 81 mg/day) were associated with an approximately twofold higher risk of recurrent gout attacks. These associations were independent of other risk factors and persisted across subgroups stratified by these major risk factors.

Low-dose aspirin is widely used as a public health strategy for preventing coronary artery disease. Nearly one-third of middle-aged Americans (approximately 50 million people) regularly take low-dose aspirin to prevent cardiovascular disease,²⁶ a proportion similar to that noted in patients with gout.⁹ In the late 1950s, Yu and Gutman²⁷ found that high doses of aspirin use (>3 g/day) were uricosuric, whereas lower doses (1–2 g/day) caused urate retention. In the past few years, potential mechanisms behind these dual effects of salicylate involving the recently identified renal urate transporter, URAT1, have been described.²⁸ *cis*-Inhibition of URAT1 by high doses of salicylate²⁹ explains the high-dose uricosuric effect, similar to the effects of other uricosuric agents (eg, probenecid and losartan).^{29,30} In contrast, low-dose urate retentive effects reflect a *trans*-stimulation of URAT1 by intracellular salicylate, which is evidently driven by the Na⁺-anion transporter,³¹ similar to the effects of lactate or pyrazinamide.^{29,30} Caspi *et al*³² found that low doses of salicylate (75, 150, and 325 mg daily) decreased urinary urate excretion (by 1.35, 0.85 and 0.65 ml/min) and increased serum urate levels (by 0.27, 0.21 and 0.04 mg/dl, respectively). The inverse dose–response relationship in this study (ie, larger effect on gout risk with lower aspirin dose) is in agreement with these physiological study data.³² Together, these findings support that low-dose aspirin use contributes to an increased risk of recurrent gout attacks and that this impact is even higher as the dosage is further decreased.

Nevertheless, we do not advocate that patients with gout should stop or alter their use of low-dose aspirin for prevention of cardiovascular disease. Instead, physicians and patients with gout should be aware of such potential side effects and continue to monitor levels of serum uric acid closely when an individual is taking low-dose aspirin. Interestingly, we observed that the effect of low-dose aspirin on recurrent gout attack was neutralised by concomitant use of allopurinol. Harris *et al*³³ also reported that serum urate levels and 24-hour urinary urate excretion did not change significantly when patients with gout received 325 mg of aspirin daily either while taking probenecid at the same time or 6 h after taking probenecid. Thus, urate-lowering agents (eg, either xanthine oxidase inhibitors or uricosuric agents) may minimise the hyperuricaemic effects conferred by low-dose aspirin use.

There are several noteworthy strengths of our study. Using conventional study designs, such as case–control study or cohort study, to identify potential triggers for recurrent gout attacks are challenging. To address this issue, we conducted a case-crossover study to examine the relationship between a set of potential triggers, including aspirin use, and the risk of recurrent gout attacks. This study design is highly adaptable to assess the effect of transient exposure as a trigger for acute event onset.³⁴ In a case-crossover study, each case serves as his/her own control, and self-matching minimises control selection bias and removes the confounding effects of the time-invariant factors. Furthermore, to overcome challenge of

subject recruitment, we used the internet to recruit subjects with gout from across the entire USA. All these approaches allowed us to assess both exposure and disease occurrence in real time while minimising the potential for recall bias.

Our study has some limitations. First, we only assessed the effect of aspirin use over the prior 2 days. Therefore, we were unable to determine the potential effects of low-dose aspirin use over the longer term. Second, because of the nature of the study design, we could only assess the effect of intermittent, but not continuous, low-dose aspirin use on the risk of recurrent gout attacks. Nonetheless, given that adherence to chronic cardioprotective medications such as aspirin is suboptimal,^{35,36} these results demonstrate clinically the relevant effects for typical gout patients in the community. Third, few participants in our study took high-dose aspirin (ie, >1000 mg/day); thus, we were unable to assess the potential effect of high-dose aspirin use on the risk of recurrent gout attacks. Fourth, we did not collect data on levels of serum urate or urinary urate excretion for study participants; thus, we were unable to assess whether the increased risk of gout attacks observed with low-dose aspirin use was operating through its impact on these factors. However, our finding that concomitant use of allopurinol, but not colchicine, reduces the risk of gout attacks when using low-dose aspirin indicates that aspirin may trigger gout attacks through its effect on serum urate levels. Fifth, the accuracy of recall of low-dose aspirin use over the previous 2-day period, especially if it varies according to the severity of the gout attacks, may jeopardise the validity of the study findings. However, when we limited our analysis to gout attacks involving the first metatarsophalangeal joint, treated with at least one anti-gout medication, the results did not change significantly. Finally, although the characteristics of our study participants may not be representative of gout patients in the USA, the biological effects of low-dose aspirin use on gout attacks should be similar.

In conclusion, our study findings suggest that low-dose aspirin use is associated with an almost twofold increased risk of recurrent gout attacks. Given the substantial cardiovascular comorbidities associated with gout, the use of low-dose aspirin is likely to be unavoidable in the majority of patients. As such, ongoing serum urate monitoring, as warranted for all gout patients, with concomitant use and dose adjustment of a urate-lowering therapy may help avoid the risk of gout attacks associated with low-dose aspirin use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of 724 participants in the internet-based case-crossover study of gout

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, %)	
<25000	58 (8.0)
25000–49999	141 (19.5)
50000–74999	133 (18.4)
75000–99999	106 (14.6)
>100000	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)
Alcoholic beverage intake reported (n, %)	474 (51.0)
Diuretic users (n, %)	209 (28.9)
Allopurinol users (n, %)	337 (46.7)
Nonsteroidal anti-inflammatory drug users (n, %)	461 (63.7)
Colchicine users (n, %)	214 (29.6)
Self-reported renal insufficiency	133 (18.4)

BMI, body mass index.

Table 2

Use of aspirin on two consecutive days and risk of recurrent gout attacks

Daily dose of aspirin over 2 days	Number of control periods	Number of hazard periods	Crude OR (95% CI)	Adjusted OR (95% CI)*
Primary exposure categories				
None	1339	963	1.0 (reference)	1.0 (reference)
325 mg	493	377	2.09 (1.53 to 2.85)	1.81 (1.30 to 2.51)
>325 mg [†]	21	19	1.98 (0.79 to 4.94)	1.69 (0.62 to 4.59)
Alternative exposure categories				
None	1339	963	1.0 (reference)	1.0 (reference)
100 mg	333	240	2.05 (1.43 to 2.95)	1.94 (1.32 to 2.85)
101–500 mg	165	139	2.17 (1.41 to 3.36)	1.64 (1.03 to 2.60)
>500 mg [†]	16	17	2.03 (0.73 to 5.62)	1.55 (0.51 to 4.75)

* Adjusted for use of alcohol, purine intake, diuretics, allopurinol, NSAIDs and colchicine.

[†] Limited to aspirin exposure of <1000 mg daily (see text for details).

Table 3

Aspirin use (325 mg/day) on two consecutive days and risk of recurrent gout attacks according to sex, age, BMI and status of renal function

Risk factors	Aspirin use (325 mg/day)over 2 days*	Number of control periods	Number of hazard periods	Adjusted OR (95% CI) [†]	p for interaction
Sex					0.878
Men	No	1060	757	1.00 (reference)	
	Yes	400	301	1.85 (1.27 to 2.69)	
Women	No	279	206	1.00 (reference)	
	Yes	93	76	1.57 (0.67 to 3.72)	
Age (years)					0.182
<55	No	716	529	1.00 (reference)	
	Yes	100	106	2.50 (1.44 to 4.33)	
55	No	623	434	1.00 (reference)	
	Yes	393	271	1.53 (0.98 to 2.37)	
BMI (kg/m ²)					0.401
< 30	No	616	419	1.0 (reference)	
	Yes	261	163	1.66 (1.04 to 2.63)	
30	No	723	544	1.00 (reference)	
	Yes	232	214	2.26 (1.34 to 3.78)	
Renal insufficiency					0.312
No	No	1244	896	1.00 (reference)	
	Yes	437	326	1.73 (1.21 to 2.47)	
Yes	No	95	67	1.00 (reference)	
	Yes	56	51	3.42 (0.95 to 12.3)	

* Low-dose aspirin (325 mg/day) use on each of the prior 2 days vs no use.

[†] Adjusted for purine intake and use of alcohol, diuretics, allopurinol, colchicine and NSAIDs.
BMI, body mass index.

Table 4

Aspirin use (≥ 325 mg/day) on two consecutive days and risk of gout attacks according to time-varying risk factors

Risk factors over 2 days	Aspirin use (≥ 325 mg/day) over 2 days*	Number of control periods	Number of hazard periods	Adjusted OR (95% CI) [†]
Purine intake				
1.7 g (low)	No	773	413	1.00 (reference)
	Yes	272	139	1.79 (1.19 to 2.71)
>1.7 g (high)	No	566	550	2.20 (1.76 to 2.77)
	Yes	221	238	4.40 (2.98 to 6.50)
Alcohol drinking				
No	No	845	576	1.00 (reference)
	Yes	300	223	1.84 (1.23 to 2.76)
Yes	No	494	387	1.35 (1.03 to 1.77)
	Yes	193	154	2.41 (1.56 to 3.73)
Diuretic use				
No	No	1162	766	1.0 (reference)
	Yes	325	237	2.28 (1.56 to 3.32)
Yes	No	177	197	4.59 (2.81 to 7.50)
	Yes	168	140	4.16 (2.29 to 7.55)
Allopurinol use				
No	No	916	728	1.00 (reference)
	Yes	314	272	1.79 (1.24 to 2.61)
Yes	No	423	235	0.45 (0.33 to 0.63)
	Yes	179	105	0.89 (0.55 to 1.44)
Colchicine use				
No	No	1148	847	1.00 (reference)
	Yes	422	333	1.77 (1.25 to 2.50)
Yes	No	191	116	0.66 (0.45 to 0.96)
	Yes	71	44	1.79 (0.91 to 3.50)
NSAID use				
No	No	963	682	1.00 (reference)
	Yes	401	298	1.77 (1.23 to 2.53)
Yes	No	381	283	1.05 (0.80 to 1.35)
	Yes	99	89	2.22 (1.35 to 3.66)

* Low-dose aspirin (≥ 325 mg/day) use for each of the prior 2 days vs no use.

[†] Adjusted for purine intake and use of alcohol, diuretics, allopurinol, colchicine and non-steroidal anti-inflammatory drugs (NSAIDs) in separate models for corresponding risk factors.