Associations between urate-lowering therapy and the risk of type 2 diabetes mellitus

Hsin-Wen Chang¹,², Ya-Wen Lin¹,², Ming-Hung Lin³, Yu-Ching Lan⁵*, Ruey-Yun Wang¹*⁶

¹ Department of Public Health, China Medical University, Taichung, Taiwan, ² Center for General Education, Hsuan Chuang University, Hsinchu City, Taiwan, ³ School of Nursing, College of Health Care, China Medical University, Taichung, Taiwan, ⁴ Department of Pharmacy, Tajen University, Pingtung, Taiwan, ⁵ Department of Health Risk Management, China Medical University, Taichung, Taiwan

* These authors contributed equally to this work.
* rywang@mail.cmu.edu.tw, rywang0812@gmail.com (RYW); yclan@mail.cmu.edu.tw (YCL)

Abstract

Background
Gout is independently associated with increased risk of type 2 diabetes mellitus (T2DM). Urate-lowering therapy (ULT) might be beneficial in lowering the risks of T2DM. Therefore, we conducted a nested case-control study to evaluate the associations between ULT and T2DM.

Methods
This study retrieved the data of 29,765 gout patients from the period of 1998–2010 by using data from Taiwan’s National Health Insurance Research Database. Controls (n = 59,530) were matched at a 1:2 ratio by age, sex, and region. Multivariate Cox proportional hazards regression were performed to examine the dose-dependent relationship between ULT and T2DM.

Results
The adjusted Hazard ratio (HR) for the association of T2DM with allopurinol or benzbromarone exposure was 1.17 (95% confidence interval (CI) 1.07–1.28) and 1.09 (95% CI 1.03–1.15), respectively. The HR for the cumulative allopurinol dose was 0.87 (95% CI 0.71–1.07) for patients with dose ≤1.3 mg/day and was 1.31 (95% CI 1.13–1.52) for those with a dose >15.2 mg/day. Similarly, the HR for the cumulative benzbromarone dose was 0.85 (95% CI 0.75–0.96) for patients with a dose ≤1.3 mg/day and 1.42 (95% CI 1.30–1.55) for patients with a dose >9.4 mg/day, respectively. Moreover, the average exposure dose of >100 mg/day for allopurinol and >100 mg/day for benzbromarone was associated with a 1.28-fold (95% CI 1.11–1.48) and 1.47-fold (95% CI 1.23–1.76) T2DM risk respectively. The HR for patients in aged >50 years group with cumulative dose ≤1.3 mg/day of allopurinol or benzbromarone had lower risk of T2DM (HR = 0.74, 95% CI 0.58–0.94 for allopurinol; HR = 0.79, 95% CI 0.69–0.90 for benzbromarone).
Conclusion

Gout patients with prolonged ULT and a high dose of ULT were associated with a significant increase in T2DM risk. Although gout patients with age greater than 50 years and a lower dose of ULT may be beneficial in lowering T2DM risk, further clinical studies need to be confirmed these associations.

Introduction

The prevalence of diabetes in the WHO report was estimated to be 422 million peoples throughout the world [1]. Uric acid level and hyperuricemia are one of the underlying pathways of gout and a well-studied risk factor for gout [2]. Several studies have investigated that the serum uric acid levels and gout are associated with the metabolic syndrome[3] and have an independent impact on the risk of cardiovascular disease [4, 5] and developing type 2 diabetes mellitus (T2DM)[6, 7]. Randomized trials have reported that lowering uric acid by using allopurinol improves insulin resistance in asymptomatic hyperuricemic individuals [8, 9], and similar improvement in insulin resistance has been observed with the use of benzbromarone as urate-lowering therapy (ULT)[10]. Although ULT might be beneficial in lowering T2DM risk, observational studies have demonstrated that gout may be independently associated with an increased risk of T2DM [11, 12]. The association between ULT and serum uric acid are still controversial in T2DM.

Allopurinol, a xanthine oxidase inhibitor has been approved worldwide to first-line treatment for gout patients with asymptomatic hyperuricemia and comorbid renal or cardiovascular diseases[13]. Xanthine oxidase inhibitors block the synthesis of uric acid and can be used regardless of whether urate is overproduced [14]. Uricosuric drugs including probenecid, sulfinpyrazone, and benzbromarone, which are second-line therapies for gout, block renal tubular urate reabsorption [14, 15]. Uricosuric drugs predominantly act on urate anion exchanger 1—an organic anion transporter—to prevent the reuptake of uric acid at the proximal renal tubule, thus increasing the renal excretion of uric acid[16, 17]. Benzbromarone (not available in the United States) may be prescribed to patients with mild-to-moderate renal insufficiency but is potentially hepatotoxic, whereas probenecid and sulfinpyrazone are generally ineffective in patients with renal impairment[14]. Uricosuric agents are more commonly prescribed than are xanthine oxidase inhibitors[18]. Owing to this study, a higher proportion of gout patients in Taiwan are using benzbromarone (approximately 84.8%, n = 25 254) than allopurinol (57.8%, n = 17 199).

To determine whether long-term or excessive ULT protects against T2DM risk, we retrospectively analyzed data from a population-based database of Taiwan and evaluated the relationship between ULT and T2DM risk.

Material and methods

Data source and study population

Data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD), which was established in 1995 and collects all claims of those insured under the National Health Insurance (NHI) program. The program covers more than 98% of the total population (23,000,000) and has contracted with 97% of the hospitals and clinics in Taiwan[19]. For this analysis, we used data from Longitudinal Health Insurance
Database 2010 (LHID2010), which is a nationwide database including the claims data of 1 million individuals randomly selected from all insurants in the NHIRD. We conducted a nested case-control study by using data from the NHIRD for the period between January 1998 and December 2010. The diagnoses in the NHIRD are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic (ICD-9-CM). The diagnoses in the claims data of the NHIRD are primarily used for administrative purposes, and anonymity of the data is ensured by assigning identification numbers. The study protocols were reviewed and approved by the China Medical University Ethics Review Committee.

Inclusion and exclusion criteria

The inclusion criteria were patients newly diagnosed with gout and age ≥20 years, and the study population was followed up for 13 years. The exclusion criteria were age >100 years and age <20 years, type 1 diabetes (250.x1 or 250.x3, with x = 0–9), type 2 diabetic patients with clinic visits <3 and no antidiabetic therapy, gout patients with clinic visits <3 and inhibiting or increasing uric acid therapy, gout patients with clinic visits <3 and no inhibiting or increasing uric acid therapy, patients diagnosed with T2DM before December 31, 1998, patients diagnosed with gout before January 1, 1998, and after January 1, 2010, prior diagnosis of T2DM and the first diagnosis date for gout until the index date of T2DM <1 year. The more detailed information was presented in Fig 1.

Ascertainment of gout

This study comprises 29 765 gout patients and 59 530 controls (matched at a 1:2 ratio). The primary case definition of gout was having a physician-recorded primary diagnosis (ICD-
9-CM 274.x) at an outpatient or inpatient visit. To evaluate the robustness of gout case ascertainment, gout was defined as ≥3 clinic visits with ULT. The agents for ULT inhibited uric acid production (allopurinol, Anatomic Therapeutic Chemical code M04AA01), and those for ULT increased uric acid excretion (probenecid, M04AB01; sulfinpyrazone, M04AB02; and benzbromarone, M04AB03).

We calculated the cumulative exposure dose for ULT, which was derived by dividing the total exposure dose for ULT by the total follow-up days (by the first treatment date for gout among gout patients until the index date of T2DM or to the study end with no events). Simultaneously, we calculated the annual exposure day, which was derived by dividing the total exposure days of ULT by the total follow-up time, and the average exposure dose for ULT, which was derived by dividing the total exposure dose for ULT by the total exposure days. We classified the cumulative exposure dose for allopurinol into the following categories according to the quartile method: none, >0–1.3, >1.3–4.2, >4.2–15.2, and >15.2, and that for benzbromarone was categorized as follows: none, >0–1.3, >1.3–3.4, >3.4–9.4, and >9.4. In addition, the quartile method was adopted to classify the annual exposure days for allopurinol (none, >0–2.5, >2.5–8.8, >8.8–37.0, and >37.0) and benzbromarone (none, >0–6.6, >6.6–17.6, >17.6–49.1, and >49.1). We classified the average exposure dose for allopurinol in the following categories: none, >0–50, >50–100, and >100, and that for benzbromarone was categorized as follows: none, >0–100, >100–200, >200–300, and >300, and for benzbromarone.

T2DM outcome assessment
T2DM events were defined as a new occurrence of T2DM events (ICD-9-CM code 250.x0 or 250.x2, with x = 0–9). T2DM was defined as ≥3 clinic visits and antidiabetic treatment. The oral antidiabetic agents were metformin (A10BA), sulfonylureas (A10BB), meglitinides (A10BX), thiazolidinediones (A10BG), and α-glucosidase inhibitor (A10BF). The insulin injection agents were rapid-acting (A10AB), intermediate-acting (A10AC), long-acting (A10AE), and combination (A10AD).

Assessment of covariates
From the NHIRD, we collected data on the demographic characteristics of age, sex, and region, as well as the comorbidities of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, rheumatologic disease, renal disease, and alcohol-related diseases, with diagnoses coded according to ICD-9-CM.[20]

Statistical analyses
Continuous variables are presented as mean (standard deviation) or median (interquartile range), and categorical variables are presented as frequencies (percentages). Continuous and categorical variables were analyzed using a t-test or chi-square test for comparisons between gout patients and controls. The dose-response relationship and the annual exposure day for ULT were measured. Moreover, the relationship between diverse exposure doses for ULT and the risk of T2DM was analyzed using the Cox proportional hazards model. Multivariate models were adjusted for the covariates of age group, sex, region, and comorbidities. We also conducted subgroup analyses of gout patients on ULT by sex or age to examine their influence. To assess the robustness of our findings, sensitivity analyses were performed by simultaneously altering the relative risk of the dose-response relationship between ULT doses and the T2DM risk. P values of less than 0.05 were regarded as significant. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).
Results

Baseline characteristics of study subjects

We presented the baseline characteristics of gout patients and controls in the Table 1. The mean age was 47.3 years among the gout patients. Thus, we adopted age \( \leq 50 \) years and age

| Table 1. Characteristics of subjects with gout and controls. |
|-----------------|-----------------|-----------------|
|                 | Gout            | Controls        | P value          |
| N               | 29765           | 59530           |                 |
| Type 2 diabetes, n(%) | 3940 (13.2) | 6334 (10.6) | <0.0001         |
| Oral anti-diabetic therapy (ATC code), n(%) | | | |
| Metformin (A10BA) | 3540 (11.9) | 5753 (9.7) | <0.0001         |
| Sulfonylureas (A10BB) | 3222 (10.8) | 5675 (9.5) | <0.0001         |
| Meglitinides (A10BX) | 599 (2.0) | 1173 (2.0) | 0.6714          |
| Thiazolidinediones (A10BG) | 623 (2.1) | 1534 (2.6) | <0.0001         |
| α-glucosidase inhibitor (A10BF) | 825 (2.8) | 1695 (2.8) | 0.3202          |
| Insulin injection therapy (ATC code), n(%) | | | |
| Rapid-acting (A10AB), | 484 (1.6) | 960 (1.6) | 0.8807          |
| Intermediate-acting (A10AC) | 89 (0.3) | 276 (0.5) | 0.0003          |
| Combination (A10AD) | 61 (0.2) | 205 (0.3) | 0.0003          |
| Long-acting (A10AE) | 60 (0.2) | 183 (0.3) | 0.0042          |
| Age mean(SD), years | 55.4 (16.2) | 55.3 (16.1) | 0.2865          |
| Gout diagnosis age (SD), years | 47.3 (15.9) | | |
| Age group, n(%) | | | |
| 20 to 30 | 1542 (5.2) | 3158 (5.3) | |
| >30 to 40 | 4161 (14.0) | 8370 (14.1) | |
| >40 to 50 | 5794 (19.5) | 11466 (19.3) | |
| >50 to 60 | 7187 (24.1) | 14459 (24.3) | |
| >60 to 70 | 4702 (15.8) | 9450 (15.9) | |
| >70 to 80 | 4001 (13.4) | 7934 (13.3) | |
| >80 | 2378 (8.0) | 4693 (7.9) | 0.9353          |
| Gender, n(%) | | | |
| Men | 24561 (82.5) | 48995 (82.3) | |
| Women | 5204 (17.5) | 10535 (17.7) | 0.4303          |
| Region, n(%) | | | |
| Northern | 13788 (46.3) | 27669 (46.5) | |
| Central | 7177 (24.1) | 13936 (23.4) | |
| Southern | 7686 (25.8) | 15909 (26.7) | |
| Eastern | 825 (2.8) | 1487 (2.5) | |
| Offshore islets and other | 289 (1.0) | 529 (0.9) | 0.9423          |
| Comorbidities, n(%) | | | |
| Myocardial infarction | 377 (1.3) | 451 (0.8) | <0.0001         |
| Congestive heart failure | 2256 (7.6) | 2121 (3.6) | <0.0001         |
| Peripheral vascular disease | 1448 (4.9) | 1604 (2.7) | <0.0001         |
| Cerebrovascular disease | 3580 (12.0) | 4982 (8.4) | <0.0001         |
| Rheumatologic disease | 1303 (4.4) | 982 (1.6) | <0.0001         |
| Renal disease | 2162 (7.3) | 1285 (2.2) | <0.0001         |
| Alcohol-related diseases | 838 (2.8) | 598 (1.0) | <0.0001         |

SD: standard deviation; Comorbidities were defined as \( \geq 3 \) outpatient claims.

Continuous and categorical variables were analyzed using a \( t \) test and chi-square test for comparisons between gout patients and controls.

https://doi.org/10.1371/journal.pone.0210085.t001
Table 2. Only allopurinol or benzbro marone use in gout patients.

|                              | Inhibiting uric acid production M04AA01 (Allopurinol) | Increasing uric acid excretion M04AB03 (Benzbromarone) |
|------------------------------|-----------------------------------------------------|--------------------------------------------------------|
|                              | Total type 2 diabetes Non-type 2 diabetes              | Total type 2 diabetes Non-type 2 diabetes              |
| Males, n                     | 3182 375 2807                                        | 9787 975 8812                                         |
| Follow-up duration, median(IQR), years | 6.5 (3.6–9.2) 4.5 (2.5–6.8) 6.7 (3.8–9.4) <0.0001 | 6.7 (3.6–9.4) 4.4 (2.5–6.8) 7 (3.9–9.5) <0.0001 |
| Total clinic visits, median(IQR), frequencies | 3 (2–8) 4 (2–11) 3 (1–8) 0.0028 | 4 (2–10) 5 (2–13) 4 (2–10) 0.0002 |
| Total drug use, median (IQR), days | 43 (14–147) 56 (14–180) 42 (14–141) 0.0316 | 90 (30–224) 97 (30–280) 88.5 (30–219) 0.0683 |
| Total drug tablets, median (IQR), quantities | 70 (28–212) 90 (30–294) 65 (28–203) 0.0040 | 97 (42–252) 115 (42–341) 93 (42–248.5) 0.0070 |
| Total dosage, median (IQR), mg | 7650 (2800–22700) 9100 (3000–29900) 7000 (2800–22400) 0.0096 | 6000 (2800–15600) 7000 (2800–2050) 6000 (2800–15100) 0.0178 |
| Total dosage(mg) /Follow-up duration (years<365 days) | 4.2 (1.3–15.1) 7.6 (2.3–24.7) 3.8 (1.3–14) <0.0001 | 3.3 (1.2–9.1) 5.2 (1.8–14.7) 3.1 (1.2–8.6) <0.0001 |
| Total drug use(day)/Follow-up duration (years) | 8.6 (2.6–36.3) 14.4 (4.6–56.1) 8.1 (2.3–33.8) <0.0001 | 17.2 (6.5–48) 26.8 (8.9–76.7) 16.5 (6.3–45.3) <0.0001 |
| Total dosage(mg)/Total drug use(day) | 200 (100–300) 200 (100–300) 200 (100–300) 0.3930 | 63.7 (50–100) 67.6 (50–100) 63.5 (50–100) 0.0291 |
| Females, n | 911 176 735 | 2536 507 2029 |
| Follow-up duration, median(IQR), years | 6.5 (3.4–9.2) 3.9 (2.2–6.4) 7.1 (4.1–9.6) <0.0001 | 6.5 (3.5–9.1) 4.1 (2.2–6.3) 7.1 (4–9.5) <.0001 |
| Total clinic visits, median(IQR), frequencies | 4 (2–9) 4 (2–14.5) 4 (1–8) 0.0651 | 4 (2–10) 5 (2–12) 4 (2–9) 0.0648 |
| Total drug use, median (IQR), days | 53 (14–168) 52.5 (16.5–233) 53 (14–152) 0.1744 | 90 (36–235) 91 (35–266) 90 (37–229) 0.6038 |
| Total drug tablets, median (IQR), quantities | 79 (28–240) 84 (28–383.5) 78 (24–212) 0.0574 | 107 (44–261) 116 (42–300) 105 (44–250) 0.2896 |
| Total dosage, median (IQR), mg | 8400 (2800–25200) 8700 (2800–38350) 8400 (2700–22400) 0.0762 | 6250 (2900–16300) 6750 (3000–17200) 6000 (2900–15600) 0.5745 |
| Total dosage(mg) /Follow-up duration (years<365 days) | 4.3 (1.2–16.1) 7.5 (1.8–31.8) 3.8 (1.1–13.7) <0.0001 | 3.8 (1.3–10.1) 5.6 (2.2–15.1) 3.4 (1.2–9.3) <0.0001 |
| Total drug use(day)/Follow-up duration (years) | 9.3 (2.3–39.3) 13.6 (3.8–87) 8.5 (2.1–34.4) 0.0001 | 19.7 (7.1–55.1) 29 (11.1–82.2) 17.3 (6.4–47.8) <0.0001 |
| Total dosage(mg)/Total drug use(day) | 183.3 (100–300) 200 (100–277.2) 180 (100–300) 0.9179 | 56.3 (50–100) 54.9 (50–100) 56.3 (50–100) 0.9299 |
| Combined group, n | 4093 551 3542 | 12323 1482 10841 |
| Follow-up duration, median(IQR), years | 6.5 (3.5–9.2) 4.3 (2.5–6.7) 6.8 (3.8–9.4) <0.0001 | 6.7 (3.6–9.3) 4.2 (2.4–6.6) 7 (3.9–9.5) <0.0001 |
| Total clinic visits, median(IQR), frequencies | 3 (2–8) 4 (2–13) 3 (1–8) 0.0004 | 4 (2–10) 5 (2–12) 4 (2–9) <0.0001 |
| Total drug use, median (IQR), days | 45 (14–150) 56 (15–201) 42 (14–144) 0.0116 | 90 (32–224) 95 (31–271) 90 (33–222) 0.0314 |
| Total drug tablets, median (IQR), quantities | 70 (28–221) 90 (28–329) 69 (28–207) 0.0007 | 98 (42–254) 116 (42–325) 96 (42–242) 0.0022 |
| Total dosage, median (IQR), mg | 7900 (2800–23800) 9000 (3000–33000) 7400 (2800–22400) 0.0021 | 6000 (2800–15700) 7000 (2800–19000) 6000 (2800–15300) 0.0118 |
| Total dosage(mg) /Follow-up duration (years<365 days) | 4.2 (1.3–15.2) 7.6 (2.1–26.8) 3.8 (1.2–13.9) <0.0001 | 3.4 (1.3–9.4) 5.4 (1.9–14.9) 3.2 (1.2–8.7) <0.0001 |
| Total drug use(day)/Follow-up duration (years) | 8.8 (2.5–37) 13.8 (4.2–59.2) 8.2 (2.3–33.8) <0.0001 | 17.6 (6.6–49.1) 27.7 (9.7–77.7) 16.6 (6.3–45.9) <0.0001 |
| Total dosage(mg)/Total drug use(day) | 200 (100–300) 200 (100–300) 197.9 (100–300) 0.5660 | 62.5 (50–100) 63 (50–100) 62.5 (50–100) 0.1631 |

IQR: interquartile range.

Continuous variables were analyzed using a t test for comparisons between type 2 diabetes and non-type 2 diabetes among gout patients.

https://doi.org/10.1371/journal.pone.0210085.t002

>50 years to classify age-specific subgroups for further analysis in this study. We listed only allopurinol and benzbro marone exposure and overall exposure to each agent stratified by T2DM and non- T2DM in Table 2.
The relative risk for of T2DM with allopurinol or benzbromarone use

As shown in Table 3 and S1 Table, the hazard ratio (HR) for the relationship of T2DM with allopurinol or benzbromarone use was 1.17 (95% CI 1.07–1.28) or 1.09 (95% CI 1.03–1.15).

Table 3. Association between allopurinol or benzbromarone use and risk of developing type 2 diabetes.

| Type 2 diabetes | Total people, n | Adjusted HR (95% CI) | P value |
|-----------------|-----------------|----------------------|---------|
| Allopurinol (M04AA01) | | | |
| Cumulative exposure dose' | | | |
| Non use | 6334 (10.64) | 59530 | 1.00 |
| Use, mg/day | | | |
| >0 to 1.3 | 89 (8.73) | 1019 | 0.87 (0.71–1.07) | 0.1908 |
| >1.3 to 4.2 | 119 (11.58) | 1028 | 1.12 (0.93–1.34) | 0.2293 |
| >4.2 to 15.2 | 156 (15.26) | 1022 | 1.30 (1.11–1.53) | 0.0012 |
| >15.2 | 187 (18.26) | 1024 | 1.31 (1.13–1.52) | 0.0003 |
| Increasing uric acid excretion | 1501 (11.94) | 12566 | 1.09 (1.03–1.15) | 0.0036 |
| Combination therapy | 1647 (12.57) | 13106 | 1.03 (0.98–1.09) | 0.2693 |
| Benzbromarone (M04AB03) | | | |
| Cumulative exposure dose | | | |
| Non use | 6334 (10.64) | 59530 | 1.00 |
| Use, mg/day | | | |
| >0 to 1.3 | 270 (8.51) | 3174 | 0.85 (0.75–0.96) | 0.0092 |
| >1.3 to 3.4 | 297 (9.84) | 3018 | 0.96 (0.85–1.08) | 0.4706 |
| >3.4 to 9.4 | 374 (12.26) | 3050 | 1.08 (0.97–1.20) | 0.1404 |
| >9.4 | 541 (17.56) | 3081 | 1.42 (1.30–1.55) | <0.0001 |
| Allopurinol | 551 (13.46) | 4093 | 1.17 (1.07–1.28) | 0.0004 |
| Probenecid or Sulfinpyrazone | 19 (7.82) | 243 | 0.76 (0.48–1.19) | 0.2231 |
| Combination therapy | 1647 (12.57) | 13106 | 1.03 (0.98–1.09) | 0.2594 |
| Sensitivity analysis † | | | |
| Allopurinol (M04AA01) | | | |
| Cumulative exposure dose | | | |
| Non use | 6334 (10.64) | 59530 | 1.00 |
| Use, mg/day | | | |
| >0 to 1.3 | 379 (9.35) | 4055 | 0.89 (0.80–0.99) | 0.0309 |
| >1.3 to 4.2 | 464 (10.81) | 4292 | 0.99 (0.90–1.09) | 0.8522 |
| >4.2 to 15.2 | 627 (14.05) | 4464 | 1.16 (1.07–1.26) | 0.0003 |
| >15.2 | 728 (16.59) | 4388 | 1.16 (1.07–1.25) | 0.0003 |
| Other | 1501 (11.94) | 12566 | 1.09 (1.03–1.15) | 0.0034 |
| Benzbromarone (M04AB03) | | | |
| Cumulative exposure dose | | | |
| Non use | 6334 (10.64) | 59530 | 1.00 |
| Use, mg/day | | | |
| >0 to 1.3 | 542 (9.04) | 5997 | 0.86 (0.79–0.94) | 0.0006 |
| >1.3 to 3.4 | 615 (10.3) | 5969 | 0.95 (0.87–1.03) | 0.2200 |
| >3.4 to 9.4 | 828 (12.63) | 6558 | 1.08 (1.00–1.16) | 0.0491 |
| >9.4 | 1128 (16.76) | 6730 | 1.29 (1.21–1.38) | <0.0001 |
| Other | 586 (12.99) | 4511 | 1.14 (1.05–1.24) | 0.0029 |
| Sensitivity analysis 2‡ | | | |
| Allopurinol (M04AA01) | | | |

(Continued)
respectively. We found that T2DM risk was higher in allopurinol or benzbromarone users than in nonuser controls. Compared with nonuser controls, the HR for the cumulative allopurinol dose was 0.87 (95% CI 0.71–1.08) for patients on ≤1.3 mg/day and were 1.31 (95% CI 1.13–1.52) for those on >1.3 mg/day. Similarly, the HR for the cumulative benzbromarone dose was 0.85 (95% CI 0.75–0.96) for patients on ≤1.3 mg/day and 1.42(95% CI 1.30–1.55) for those on >9.4 mg/day. In sensitivity analysis 1, we similarly showed the dose–response relationship between ULT doses and the T2DM risk. In sensitivity analysis 2, the HR for T2DM increased from 0.92 to 1.45 with allopurinol exposure doses and from 1.06 to 1.47 with benzbromarone exposure doses.

### Developing risk of T2DM stratified by sex

Table 4 shows the association between allopurinol or benzbromarone use and the T2DM risk stratified by sex. The HR for the association of T2DM in women, were 1.19 (95% CI 1.02–1.40) for allopurinol use and 1.25 (95% CI 1.13–1.38) for benzbromarone use, respectively. However, only men with allopurinol use had a higher T2DM risk (HR = 1.16, 95% CI 1.05–1.29), and no significantly higher T2DM risk was found among men with benzbromarone use (HR = 1.02, 95% CI 0.95–1.10). Similarly, the higher T2DM risk was observed in patients taking high doses of allopurinol or benzbromarone compared those with nonuser among men and women.
Developing risk of T2DM stratified by age

Table 5 shows the association between the allopurinol or benzbromarone use and the type 2 diabetes risk stratified by age ≤ 50 years and age > 50 years. The HR for the association of T2DM with allopurinol or benzbromarone use was 2.28 (95% CI 1.84–2.81) or 1.90 (95% CI 1.64–2.20) in patients aged ≤ 50 years, respectively. A consistent result was found in those taking high doses. Patients with allopurinol or benzbromarone use by annual exposure day had higher risk for developing T2DM (S2 Table), whereas the HR for patients in aged > 50 years group with cumulative dose ≤ 1.3 mg/day of allopurinol or benzbromarone had lower risk of T2DM (HR = 0.74, 95% CI 0.58–0.94 for allopurinol; HR = 0.79, 95% CI 0.69–0.90 for benzbromarone).

Discussion

The results of this nested case-control study indicated that allopurinol or benzbromarone use is associated with the risk of developing T2DM, particularly in patients receiving high doses of allopurinol or benzbromarone and those with prolonged use. Such consistent result was also found in sex-specific and age-specific subgroup analysis. Compared with gout patients older...
than 50 years, we found that gout patients younger than 50 years were at a higher risk of T2DM. Uric acid-lowering therapy in gout patients may not be beneficial in lowering T2DM risk, particularly in gout patients younger than 50 years. Although gout patients with age greater than 50 years and a low dose of ULT may be beneficial in lowering T2DM risk, further clinical studies need to be confirmed these associations.

Gout and hyperuricemia have been linked with an increased occurrence of several comorbidities, such as coronary artery disease and hypertension [21], chronic kidney disease [22] or T2DM [23]. However, it is unknown whether the high serum uric acid is a causal factor in the development of these conditions or is a consequence of the manifestation of these disorders. In this study, gout patients older than 50 years with two ULT treatments had a protective effect on T2DM risk (HR = 0.89, 95% CI 0.84–0.95, P = 0.0002). The protective effect was also observed in the low dose of allopurinol or benzbromarone treatment in the older patients group (age >50 years old). The effects of ULT on developing T2DM risk were controversial in the different age groups. Because individuals with gout generally have an increased prevalence of hypertension, a decline in renal function [24] and obesity [25], these co-morbidities are well-known risk factors of T2DM and may modify the effects of ULT on developing T2DM risk. Further large studies need to be conducted to examine the interaction between co-morbidities and reduction of serum uric acid levels in developing T2DM risk.

### Table 5. Association between allopurinol or benzbromarone use and risk of developing type 2 diabetes stratified by age group.

|                   | Age≤50 years | Age≥50 years |
|-------------------|-------------|-------------|
|                   | Type 2 diabetes events, n (%) | Total people, n | Adjusted HR (95% CI) | P value | Type 2 diabetes events, n (%) | Total people, n | Adjusted HR (95% CI) | P value |
| Allopurinol (M04AA01) Cumulative exposure dose |          |                  |                  |          |                  |                  |          |                  |          |
| Non use           | 593 (2.58)  | 22994       | 1.00             |          | 5741 (15.71)    | 36536       | 1.00             |          |
| Use, mg/day       |            |                  |                  |          |                  |                  |          |                  |          |
| >0 to 1.3         | 22 (4.88)   | 451          | 1.82 (1.19–2.79) | 0.0058   | 67 (11.80)      | 568          | 0.74 (0.58–0.94) | 0.0126   |
| >1.3 to 4.2       | 27 (6.08)   | 444          | 2.31 (1.57–3.40) | <0.0001  | 92 (15.75)      | 584          | 0.98 (0.80–1.20) | 0.8460   |
| >4.2 to 15.2      | 25 (6.25)   | 400          | 2.17 (1.45–3.25) | 0.0002   | 131 (21.06)     | 622          | 1.20 (1.01–1.43) | 0.0375   |
| >15.2             | 28 (9.24)   | 303          | 2.93 (2.00–4.30) | <0.0001  | 159 (22.05)     | 721          | 1.17 (1.00–1.37) | 0.0494   |
| Increasing uric acid excretion | 267 (5.19) | 5146        | 1.90 (1.64–2.20) | <0.0001  | 1234 (16.63)    | 7420         | 0.99 (0.93–1.05) | 0.7127   |
| Both use’         | 326 (6.86)  | 4753         | 2.31 (2.01–2.65) | <0.0001  | 1321 (15.81)    | 8353         | 0.89 (0.84–0.95) | 0.0002   |
| Benzbromarone (M04AB03) Cumulative exposure dose |           |                  |                  |          |                  |                  |          |                  |          |
| Non use           | 593 (2.58)  | 22994       | 1.00             |          | 5741 (15.71)    | 36536       | 1.00             |          |
| Use, mg/day       |            |                  |                  |          |                  |                  |          |                  |          |
| >0 to 1.3         | 56 (3.72)   | 1506         | 1.45 (1.10–1.90) | 0.0083   | 214 (12.83)     | 1668         | 0.79 (0.69–0.90) | 0.0006   |
| >1.3 to 3.4       | 61 (4.59)   | 1328         | 1.77 (1.36–2.31) | <0.0001  | 236 (13.96)     | 1690         | 0.86 (0.75–0.97) | 0.0191   |
| >3.4 to 9.4       | 71 (5.96)   | 1191         | 2.13 (1.66–2.72) | <0.0001  | 303 (16.30)     | 1859         | 0.96 (0.85–1.07) | 0.4415   |
| >9.4              | 74 (7.38)   | 1003         | 2.40 (1.88–3.06) | <0.0001  | 467 (22.47)     | 2078         | 1.29 (1.17–1.42) | <0.0001  |
| Allopurinol       | 102 (6.38)  | 1598         | 2.28 (1.84–2.81) | <0.0001  | 449 (18.00)     | 2495         | 1.05 (0.95–1.15) | 0.3684   |
| Probenecid or Sulfinpyrazone | 5 (4.24)  | 118          | 1.56 (0.65–3.77) | 0.3194   | 14 (11.20)      | 125          | 0.66 (0.39–1.22) | 0.1257   |
| Both use’         | 326 (6.86)  | 4753         | 2.31 (2.01–2.65) | <0.0001  | 1321 (15.81)    | 8353         | 0.89 (0.84–0.95) | 0.0003   |

*Drugs used for increasing uric acid excretion were probenecid (M04AB01), sulfinpyrazone (M04AB02), and benzbromarone (M04AB03)

*Combination therapy involved allopurinol and drugs used for increasing uric acid excretion

Adjusted HR was calculated and adjusted for age group, sex, region, and comorbidities by using a Cox proportional hazards regression model.

Cumulative exposure allopurinol or benzbromarone dose: the accumulated allopurinol or benzbromarone dose divided by the total follow-up days (by the first treat gout date until the index date of type 2 diabetes or to the study end).

https://doi.org/10.1371/journal.pone.0210085.t005
We found a significant effect of ULT modification by sex, with the higher magnitude of the association among women than men. The mechanisms underlying the association of UA with the development of T2DM are not completely understood. Several potential pathophysiological mechanisms have been proposed, including inflammation, sex hormones, medication modification, and genetic effects. Ongoing low-grade inflammation in gout patients may promote the diabetogenic process. The differences in the baseline serum level between men and women and the difference in uric acid metabolism may explain the higher risk of diabetes in female gout patients compared with in male gout patients [12]. Sex hormones play a role in this regard. It is proposed that increased renal clearance of urate related to estrogen in premenopausal women may account for the lower SUA levels observed in women than in men [26]. A conceivable mechanism underlying the association between hyperuricemia and the risk of T2DM may occur at the renal level [11]. For example, urate transporter genes ABCG2, SLC2A9, and SLC22A12 modulate the relationship of renal urate homeostasis and gout [27] with T2DM. Although Mendelian randomization studies have shown that uric acid-associated loci are causally associated with gout incidence [28], no evidence of a causal association between uric acid-associated loci and T2DM is available for European and South Asian populations [23, 28, 29]. In addition, we found that only benzbromarone use and combination therapy were associated with a higher T2DM risk in women compared to men (Table 4). These findings support the evidence that impact of gout on T2DM risk was higher among women [12]. However, no such difference was found for allopurinol use. Uricosuric drugs may enhance the renal excretion of oxyipurinol, the active metabolite of allopurinol, thus reducing the efficacy of allopurinol [30, 31].

According to a 15-year follow-up study, hyperuricemia often precedes the development of hyperinsulinemia, impaired fasting glucose, and diabetes, particularly in young adults [32]. The American College of Rheumatology guidelines recommends that plasma urate should be maintained at a concentration less than 360 μmol/L (6 mg/dL) for all patients on ULT [33]. ULT is indicated for patients with recurrent gout attacks, chronic arthropathy, tophi, and gout with uric acid stones [15]. Although effective treatments exist that eliminate sodium urate crystals and “cure” the disease, the management of gout is often suboptimal [16]. Allopurinol and benzbromarone improve insulin resistance [8–10], and they may be beneficial in lowering the risk of type 2 diabetes. However, most doctors focus solely on managing acute attacks rather than long-term therapy, and only one-third to one-half of gout patients ever receive ULT [16, 34]; furthermore, adherence to ULT is often poor (10%–46%) [35, 36]. Studies have shown that only 30%–60% of patients are prescribed allopurinol 1 year after the initiation of therapy, and that the management of gout is frequently inappropriate [15, 37]. Studies have demonstrated that treatment provided to reach the serum urate target with dose escalation of ULT is effective for achieving the therapeutic target in most (82%–92%) gout patients [38–40]. The management of gout is poor in Taiwan, with only one in five affected people being treated with ULT [18], suggesting that uric acid-lowering therapies in gout patients may not be beneficial in lowering T2DM risk in Taiwan.

This study has some strengths and limitations. This study was performed using data from a large population-based database in Taiwan. Therefore, the findings are likely applicable to the general population. Because the definition of gout and T2DM is based on ICD-9-CM diagnoses, a certain level of misclassification of exposure is inevitable. The identification of gout patients was based on ICD codes without the examination of synovial fluid or tophus aspirate for monosodium urate crystals, which may have led to some misclassification bias. We used a strict definition of gout requiring three clinic visits with ULT, which was found to have a high positive predictive value for fulfilling the various classification criteria for gout in primary care [41]. Several important covariates that are also associated with the risk of type 2 diabetes and
gout (e.g., blood pressure, body mass index, use of diuretics, diet, consumption of alcohol, glucose levels, cholesterol, triglycerides, creatinine), could not be taken into account because of a lack of data. There is, thus, a possible risk for underestimation of some comorbidities, in particular hypertension, hyperlipidemia, obesity renal disease, and alcohol-related diseases, when ICD codes are used for definitions. In addition, we could not ascertain whether the patients had continued exposure to ULT beyond the index prescription date; thus, an immortal time bias may occur [42]. Nevertheless, we excluded immortal time by defining the start of follow-up for the treated group as the start of treatment for all subjects who received the urate-lowering drugs under investigation. Thus, patients were enrolled in the cohort at the time of their first prescription. Because of the lack of uric acid level at baseline, a detection bias may have occurred because persons with gout having higher uric acid values may more often visit doctors compared with those who are well-controlled. This could increase the likelihood of being diagnosed with T2DM. Individuals with T2DM have lower numbers of missing values for possible confounders such as hypertension, hyperlipidemia, obesity and renal disease. This may have led to residual confounding. Finally, although all included studies adjusted for a wide range of potential confounders for risk of developing T2DM, we cannot definitively exclude possible residual confounding effects because serum biochemistry, lifestyle, nutrition, and physical activity, are not routinely recorded in the NHIRD.

In conclusion, this study used data from a population-based database to determine a substantial association between ULT and a higher T2DM risk, particularly in gout patients younger than 50 years and those with prolonged ULT and a high dose of ULT. Despite the availability of effective ULT, only 22.93% of gout patients are prescribed urate-lowering treatment in Taiwan, which remained unchanged between 2005 and 2010 [18], possibly contributing to elevated urate doses and increased gout flares with major adverse consequences such as T2DM. These findings support appropriate recognition and management of the risk factor of T2DM by using ULT for hyperuricemia in gout patients.

**Supporting information**

S1 Table. Allopurinol and benzbromarone use in gout patients. (DOCX)

S2 Table. Association between allopurinol or benzbromarone use by annual exposure day and developing T2DM risk. (DOCX)

**Author Contributions**

Data curation: Ya-Wen Lin.

Formal analysis: Hsin-Wen Chang.

Investigation: Ming-Hung Lin, Ruey-Yun Wang.

Methodology: Hsin-Wen Chang, Ya-Wen Lin, Ming-Hung Lin, Yu-Ching Lan, Ruey-Yun Wang.

Supervision: Yu-Ching Lan.

Writing – original draft: Hsin-Wen Chang.

Writing – review & editing: Yu-Ching Lan, Ruey-Yun Wang.
References

1. Ogurtsov a K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128:40–60. https://doi.org/10.1016/j.diabres.2017.03.024 PMID: 28437734.

2. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol. 2011; 23(2):192–202. https://doi.org/10.1097/BOR.0b013e3283438e13 PMID: 21285714; PubMed Central PMCID: PMCPMC4104583.

3. Rho YH, Choi SJ, Lee YH, Ji JD, Choi KM, Baik SH, et al. The prevalence of metabolic syndrome in patients with gout: a multicenter study. J Korean Med Sci. 2005; 20(6):1029–33. https://doi.org/10.3346/jkms.2005.20.6.1029 PMID: 16361817; PubMed Central PMCID: PMCPMCC2779304.

4. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007; 116(8):894–900. https://doi.org/10.1161/CIRCULATIONAHA.107.703939 PMID: 17698728.

5. Johnson RJ, Merriman T, Lanaspa MA. Causal or Noncausal Relationship of Uric Acid With Diabetes. Diabetes. 2015; 64(8):2720–2. https://doi.org/10.2337/db15-0532 PMID: 26207039; PubMed Central PMCID: PMCPMC5860186.

6. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008; 31(2):361–2. https://doi.org/10.2337/dc07-1276 PMID: 17977935.

7. Bhole V, Choi JW, Kim SW, de Vera M, Choi H. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. Am J Med. 2010; 123(10):957–61. https://doi.org/10.1016/j.amjmed.2010.03.027 PMID: 20920699; PubMed Central PMCID: PMCPMC2779304.

8. Neogi T. Clinical practice. Gout. N Engl J Med. 2011; 364(5):443–52. https://doi.org/10.1056/NEJMcp1001124 PMID: 21288096.

9. Chin GL. Taiwan's 1995 health care reform. Health Policy. 1997; 39(3):225–39. PMID: 10165463.

10. Quan H, Sundararajan V, Halfon P, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–9. PMID: 16224307.
21. Richette P, Perez-Ruiz F, Doherty M, Jansen TL, Nuki G, Pascual E, et al. Improving cardiovascular and renal outcomes in gout: what should we target? Nat Rev Rheumatol. 2014; 10(11):654–61. https://doi.org/10.1038/nrrheum.2014.124 PMID: 25136785.

22. Kuwabara M, Bjornstad P, Hisatome I, Niwa K, Roncal-Jimenez CA, Andres-Hernando A, et al. Elevated Serum Uric Acid Level Predicts Rapid Decline in Kidney Function. Am J Nephrol. 2017; 45(4):330–7. https://doi.org/10.1159/000464260 PMID: 28285309; PubMed Central PMCID: PMC5894505.

23. Sluijs I, Holmes MV, van der Schouw YT, Beulens JW, Asselbergs FW, Huerta JM, et al. A Mendelian Randomization Study of Circulating Uric Acid and Type 2 Diabetes. Diabetes. 2015; 64(30):3028–36. https://doi.org/10.2337/db14-0742 PMID: 25918230.

24. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009–10. PLoS One. 2012; 7(11):e50046. https://doi.org/10.1371/journal.pone.0050046 PMID: 23209642; PubMed Central PMCID: PMCPMC3507834.

25. Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, et al. Asymptomatic Hyperuricemia Without Comorbidities Predicts Cardiometabolic Diseases: Five-Year Japanese Cohort Study. Hypertension. 2017; 69(6):1036–44. https://doi.org/10.1161/HYPERTENSIONAHA.116.08998 PMID: 28089980.

26. Kang E, Hwang SS, Kim DK, Oh KH, Joo KW, Kim YS, et al. Sex-specific Relationship of Serum Uric Acid with All-cause Mortality in Adults with Normal Kidney Function: An Observational Study. J Rheumatol. 2017; 44(3):380–7. https://doi.org/10.3899/jrheum.160792 PMID: 28396536; PubMed Central PMCID: PMCPMC5426964.

27. Dehghan A, Kottgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet. 2008; 372(9654):1953–61. https://doi.org/10.1016/S0140-6736(08)61343-4 PMID: 18834626; PubMed Central PMCID: PMC2803340.

28. Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, et al. Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. J Am Coll Cardiol. 2016; 67(4):407–16. https://doi.org/10.1016/j.jacc.2015.10.086 PMID: 26821629; PubMed Central PMCID: PMC5503188.

29. Krishnan E, Pandya BJ, Chung L, Hariri A, Dabous O. Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. Am J Epidemiol. 2016; 174(3):407–16. https://doi.org/10.1093/aje/kws002 PMID: 21711115.

30. Yamamoto T, Moriwaki Y, Takahashi S, Suda M, Higashino K. Effects of pyrazinamide, probenecid, and benzbrozamore on renal excretion of oxypurinol. Ann Rheum Dis. 1981; 50(9):631–3. PMID: 1929586; PubMed Central PMCID: PMCPMC1004507.

31. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrerio-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum. 2002; 47(4):356–60. https://doi.org/10.1002/art.10511 PMID: 12209479.

32. Neogi T, Hunter DJ, Chaisson CE, Allensworth-Davies D, Zhang Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. J Rheumatol. 2006; 33(1):104–9. PMID: 16267879.

33. Dalbeth N, Stamp LK. Gout: Why compare the effectiveness of suboptimal gout management? Nat Rev Rheumatol. 2015; 11(9):506–7. https://doi.org/10.1038/nrrheum.2015.94 PMID: 26150126.
39. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis. 2013; 72(6):826–30. https://doi.org/10.1136/annrheumdis-2012-201676 PMID: 22679303.

40. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011; 63(2):412–21. https://doi.org/10.1002/art.30119 PMID: 21279998.

41. Dehlin M, Stasinopoulos K, Jacobsson L. Validity of gout diagnosis in Swedish primary and secondary care—a validation study. BMC Musculoskelet Disord. 2015; 16:149. https://doi.org/10.1186/s12891-015-0614-2 PMID: 26077041; PubMed Central PMCID: PMCPMC4466844.

42. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010; 340:b5087. https://doi.org/10.1136/bmj.b5087 PMID: 20228141.