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Relative and attributable diabetes risk associated with hyperuricemia in US veterans with gout

E. KRISHNAN[1], K.S. AKHRAS[2], H. SHARMA[3], M. MARYNCHENKO[3], E.Q. WU[3], R. TAWK[2], J. LIU[4] and L. SHI[4]

From the [1]Department of Medicine, Stanford University, 300 Pasteur Drive, Stanford, CA 94305, USA, [2]Takeda Pharmaceuticals International Inc. One Takeda Parkway, Deerfield, IL 60015, USA, [3]Analysis Group, Inc. 111 Huntington Ave., Boston, MA 02199, USA and [4]Tulane University, 1440 Canal Street, New Orleans, LA 70112, USA

Address correspondence to M Marynchenko, Analysis Group Inc., 111 Huntington Avenue, Tenth Floor, Boston, MA 02199, USA. email: mmarynchenko@analysisgroup.com

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Summary

Background: Hyperuricemia is known to be a risk factor for incident type 2 diabetes mellitus, but the absolute magnitude of the association is not known. We aimed to evaluate the strength of association between hyperuricemia and the risk of developing diabetes among the US veterans with gout.
Methods: Patients (age $\geqslant$ 18 years) with $\geqslant$2 clinical encounters with gout diagnoses, no history of inflammatory diseases or diabetes and two serum urate (sUA) measurements between 1 January 2002 and 1 January 2011 were selected. Diabetes was identified using International Classification of Disease-9-Clinical Modification codes, use of anti-diabetic medications or HbA1c $\geqslant$6.5%. sUA levels were assessed at 6-month cycles (hyperuricemia: sUA >7 mg/dl). Accumulated hazard curves for time to first diabetes diagnosis were derived from Kaplan–Meier (KM) analysis. Risk of diabetes associated with hyperuricemia was estimated using a Cox proportional hazards model. Population attributable fraction (AF) of new-onset diabetes within 1 year was estimated using logistic regression.
Results: Among 1923 patients, average age was 62.9 years, body mass index was 30.6 kg/m^2, and follow-up time was 80 months. Diabetes rates from KM were 19% for sUA $\leqslant$ 7 mg/dl, 23% for 7 mg/dl < sUA $\leqslant$ 9 mg/dl and 27% for sUA > 9 mg/dl at the end of follow-up period (P < 0.001). Hyperuricemia was associated with a significantly higher risk of developing diabetes, after adjusting for confounding factors (hazard ratio: 1.19, 95% confidence interval: [1.01–1.41]). Approximately, 8.7% of all new cases of diabetes were statistically attributed to hyperuricemia.
Conclusions: Among veterans, hyperuricemia was associated with excess risk for developing diabetes. Approximately, 1 in 11 new cases of diabetes were statistically attributed to hyperuricemia.

Introduction

Gout is a common inflammatory condition caused by the formation of monosodium urate crystals in joints and other tissues. Such crystal formation is associated with elevated serum uric acid levels or hyperuricemia. Gout prevalence has increased in recent decades, making it the most common inflammatory joint disease in males and the most common inflammatory arthritis in older females.[1] A recent study based on the US National Health and Nutrition Examination Survey 2007–08 estimated the prevalence of gout to be 3.9%.[2] In addition, hyperuricemia, defined as serum urate (sUA) levels of more than 7.0 mg/dl in men and more than

5.7 mg/dl in women, was present in 21.2% of men and 21.6% of women. A range of comorbidities is often exhibited by patients with gout, including but not limited to hypertension, chronic kidney disease, obesity and type 2 diabetes.[3] Men with gout were found to have a 34–66% higher risk of developing type 2 diabetes compared with men without gout after adjustment for various factors.[4] Between 1996 and 2008, 15.1% of more than 177 000 US gout patients were diagnosed with diabetes.[5]

Hyperuricemia is a recognized risk factor for gout, and higher sUA is associated with a greater risk of the disease.[1] Elevated sUA on its own has been linked to other gout-related conditions such as metabolic syndrome, insulin resistance, renal disease and hypertension.[6,7] Hyperuricemia has also been linked to atherosclerosis and diabetes.[8]

Several studies from around the world have observed a positive association between sUA levels and diabetes.[9–15] However, not all studies have found a strong association between the two. In a prospective cohort study in Japan, sUA was not associated with an increased risk of type 2 diabetes.[16] Furthermore, some studies have found a differential impact of sUA on the risk of diabetes across gender, with some observing a positive correlation only among women,[17] and others observing a positive correlation only among men.[18]

The association between hyperuricemia and diabetes is not fully established and has not been studied extensively in gout-specific populations. As gout patients are at higher risk for diabetes and hyperuricemia, understanding the relationship between these conditions is important for clinicians. While previous studies using different patient populations have observed different attributable fractions (AFs) of diabetes due to risk factors such as high sUA, smoking and being overweight/obese,[11,19–23] it is unclear how many new diabetes cases can be attributed to hyperuricemia as opposed to other risk factors. This retrospective study assessed the effect of hyperuricemia on the risk of new-onset diabetes in male US veteran patients with gout.

Methods

Data source

Electronic medical records from the South Central Veterans' Affairs Health Care Network (VISN 16) data warehouse were used for the study. The VISN 16 data warehouse is an integrated, de-identified, individual-level database that covers a geographic region of ~170 000 square miles, including records for more than 445 000 veterans located in Arkansas, Louisiana, Mississippi, Oklahoma and parts of Alabama, Florida, Missouri and Texas. Records from 10 medical centers and 40 community-based outpatient clinics are included in the database. Elements of the database include demographic data, inpatient and outpatient records, pharmacy prescriptions, lab results, vital-sign data (height and body weight) and mortality information (date of death) for each patient treated within the network. The data are updated monthly and maintained by the VISN 16 Information Technology Development Group. Data covering the period from 1 January 2002 to 1 January 2011 were used for this study. Appropriate institutional review board approval was obtained prior to the study initiation.

Patients

Selected patients were required to have at least two recorded sUA measurements between 30 June 2002 and 1 January 2011 and were continuously enrolled in the database for a minimum of 6 months prior to and 12 months following their first sUA measurement. The date of the first sUA reading for each patient was defined as the index date. Patients without at least two sUA values recorded during their continuous eligibility period were excluded from the analysis.

Only patients above the age of 18 were included in the analysis. Patients were required to have a diagnosis of gout [International Classification of Disease-9-Clinical Modification (ICD-9-CM): 274.xx] on at least two different dates. Since a very small proportion of veterans enrolled in VISN 16 are female, the study was restricted to male patients. Patients receiving any diagnoses for other inflammatory diseases including rheumatoid arthritis (ICD-9-CM: 714), diffuse diseases of connective tissue such as lupus, scleroderma and others (ICD-9-CM: 710), vasculitis (ICD-9-CM: 446), psoriatic arthritis (ICD-9-CM: 696.0), autoimmune disease (ICD-9-CM: 283.0, 580–583, 242.0, 340, 358.0, 130.3, 422.0, 422.9, 429.0, 390–398), pseudogout (ICD-9-CM: 712.2, 727.82, 275.4) and other inflammatory arthritis (ICD-9-CM: 711.1, 711.3, 712, 713.1, 720) at any time were excluded from the analysis. The study was limited to patients with no diabetes prior to the index date, as identified by recorded diagnosis codes (ICD-9-CM: 250) and/or claims for anti-diabetic medications or HbA1c $\geqslant$ 6.5%.

Given that the use of diuretics can be associated with the development of diabetes, a subgroup analysis was performed among patients who did not use diuretics during their entire available history.[24] As hyperuricemia is frequently

found in the patients with renal insufficiency, a subgroup analysis was conducted among patients with no history of kidney disease during the entire available history.

Outcomes

The primary outcome of interest in this study was time to the first diabetes diagnosis starting from the index date. As described in the sample selection process, diabetes was identified by recorded diagnosis codes (ICD-9-CM: 250) and/or claims for antidiabetic medications or HbA1c 6.5%.

The sUA levels and other relevant covariates of interest, such as demographic variables and baseline comorbidities, were included in the analysis. For each patient, mean sUA level was estimated for each 6-month cycle starting from the index date until the end of continuous eligibility. Since not every cycle had sUA readings, a linear extrapolation using adjacent sUA readings was applied to obtain sUA levels for all cycles. Using these sUA levels, patients were classified as having hyperuricemia (>7 mg/dl) or not ($\leqslant$7 mg/dl) for each 6-month time interval. Several studies have used sUA > 7 mg/dl[25,26] or sUA $\geqslant$ 7 mg/dl to define hyperuricemia for men.[4,27,28] Accordingly, for this study, sUA > 7 mg/dl was used to define hyperuricemia. In addition, for the descriptive analysis, one cohort with no hyperuricemia (sUA $\leqslant$ 7 mg/dl) and two cohorts with hyperuricemia (7 mg/dl < sUA $\leqslant$ 9 mg/dl and sUA > 9 mg/dl) were created based on the average sUA level estimated using the average area under the curve (AUC) method over the entire study period.

Other predictors of diabetes were measured during the 6-month pre-index baseline period, while demographic variables were assessed as of the index date. These characteristics included age at the index date, year of index date, race (white or non-white), state of residence (Arkansas, Louisiana, Mississippi, Oklahoma or Texas), body mass index (BMI) and baseline tobacco use, hyperlipidemia and hypertension. These factors were selected *a priori* based on the existing literature and data availability.[4,9–11,29,30]

This study also estimated the average AFs for different diabetes risk factors, including hyperuricemia during the first year. All risk factors except for hyperuricemia were measured during the 6-month pre-index baseline period. Average sUA levels were measured within the first year, and patients were classified into hyperuricemia (sUA > 7 mg/dl) vs. no hyperuricemia (sUA $\leqslant$ 7 mg/dl) cohorts.

Statistical analysis

Patient characteristics were assessed for the overall study sample during the 6-month period prior to the index date and summarized in terms of mean $\pm$ standard deviation (SD) for continuous variables or proportions for categorical variables.

Time to first diabetes diagnosis was compared between the three sUA categories using Kaplan–Meier (KM) analysis. KM analyses were used to derive accumulated hazard curves for the three sUA categories and were compared using a log-rank test. In addition to the unadjusted KM analysis, a multivariate adjusted analysis was performed using a Cox proportional hazards model to estimate the hazard of developing diabetes associated with hyperuricemia in all three patient cohorts: (i) all patients, (ii) patients who did not use diuretics during their entire available history and (iii) patients with no kidney disease during their entire available history. Hyperuricemia was assessed during each 6-month cycle and used as a time-varying covariate. Correlation between different cycles for the same patient was addressed using a model-based, robust sandwich estimate for the covariance matrix.[31] The model adjusted for age at the index date, year of index date, race (white or non-white), state of residence (Arkansas, Louisiana, Mississippi, Oklahoma or Texas), BMI and baseline tobacco use, hyperlipidemia and hypertension. The estimated impact of sUA level on developing new-onset diabetes was presented in the form of a hazard ratio (HR) and 95% confidence interval (CI).

AFs were estimated using the average AFs method, which has been discussed extensively in the literature.[32,33] A logistic regression model was used to identify the proportion of diabetes cases attributable to all available risk factors in the population. This method assumed dichotomous risk factors and estimated AFs by removing the factors from the population, i.e. classifying everyone as unexposed irrespective of actual status. Predicted probabilities of having diabetes for each patient using dichotomous risk factors: age $\geqslant$65 years, BMI $\geqslant$ 30 kg/m^2, hyperuricemia and presence of hyperlipidemia, hypertension and smoking were estimated and summed up to get the expected number of cases of the disease. Average fraction was then estimated as follows:

$$\text{AF} = (\text{observed cases} - \text{expected cases})/\text{observed cases}.$$

The results were presented in the form of average AFs for different risk factors.

Results were considered statistically significant at the 5% level. SAS version 9.2 was used to conduct the analyses.

Results

A total of 1923 patients met the study inclusion criteria. Figure 1 provides the detailed sample counts. Mean follow-up time was 12.9 (± 4.42) 6-month cycles (~6.5 years). On average, each patient had 4.0 (± 2.65) recorded sUA values during follow-up, including the sUA measurement on the index date. Using the AUC method to estimate average sUA levels for the study period, 1138 (59.2%) patients were categorized into overall hyperuricemia group (>7 mg/dl) and the remaining 785 (40.8%) patients into overall no hyperuricemia group (⩽7 mg/dl).

Table 1 summarizes the patient characteristics. The average age among the patients was 62.9 (± 12.2) years. The majority of patients in the study were white (52%) and resided in Mississippi (55%). A substantial number of patients had hypertension (93%) and hyperlipidemia (64%) during the 6-month baseline period. Average BMI for the selected patients was 30.6 (± 6.7) kg/m^2. The patients in the overall no hyperuricemia cohort were mostly white (60 vs. 47%; $P<0.001$) and older (65.2 vs. 61.3 years; $P<0.001$) and had lower BMI (30.1 vs. 30.9 kg/m^2; $P<0.001$) compared with the overall hyperuricemia cohort. Baseline hyperlipidemia rates were higher for the overall no hyperuricemia cohort (68 vs. 61%; $P=0.002$) compared with the overall hyperuricemia cohort, but hypertension (92 vs. 93%; $P=0.74$) and smoking (7 vs. 9%; $P=0.05$) rates were similar between the overall no hyperuricemia and hyperuricemia cohorts, respectively.

Based on the accumulated hazard curve derived from KM analysis, there was a significant difference in the rates of new-onset diabetes between patients in the three cohorts: 7 mg/dl < sUA ⩽ 9 mg/dl, sUA > 9 mg/dl and sUA ⩽ 7 mg/dl ($P<0.001$) over time (Figure 2). The estimated diabetes rates in the three cohorts were 2, 4, 6, 19% for sUA ⩽ 7 mg/dl, 3, 5, 9, 23% for 7 mg/dl < sUA ⩽ 9 mg/dl and 3, 6, 10, 27% for sUA > 9 mg/dl at year 1, year 2, year 3, and end of follow-up period, respectively.

The multivariate analysis using the Cox proportional hazards model corroborated the findings from the descriptive analysis. Multivariate regression-adjusted results revealed that hyperuricemia was associated with a significantly higher risk of new-onset diabetes compared with no hyperuricemia (HR: 1.19; 95% CI: 1.01–1.41) after controlling for the independent effects of age, race, index year, state of residence, BMI and the presence of other

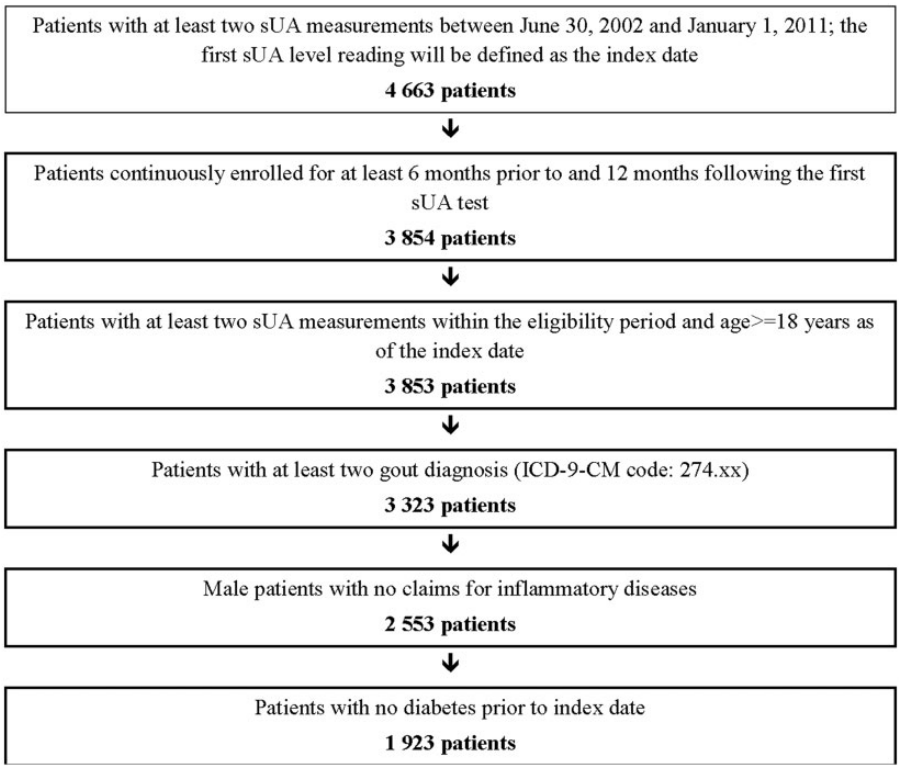

Figure 1. Sample selection.

Table 1 Patient characteristics

Characteristics	Patients with no diabetes prior to index date			
	All patients ($n=1923$)	Hyperuricemia ($n=1138$)	No hyperuricemia ($n=785$)	*P*-value
Age at first sUA level test date (years; mean [SD])	62.9 [12.1]	61.3 [12.3]	65.2 [11.5]	<0.001
Race, *n* (%)				<0.001
White	1003 (52)	532 (47)	471 (60)	
Region, *n* (%)				0.001
Arkansas	327 (17)	163 (14)	164 (21)	
Louisiana	333 (17)	207 (18)	126 (16)	
Mississippi	1052 (55)	652 (57)	400 (51)	
Oklahoma	186 (10)	102 (9)	84 (11)	
Texas	25 (1)	14 (1)	11 (1)	
BMI kg/m^2(mean [SD])	30.6 [6.7]	30.9 [5.9]	30.1 [7.7]	<0.001
Average number of 6-month cycles during the study period (mean [SD])	12.9 [4.4]	12.6 [4.5]	13.3 [4.2]	0.002
Average number of sUA values (mean [SD])	4.0 [2.7]	4.2 [2.9]	3.7 [2.2]	0.001
Index year, *n* (%)				0.08
2002	583 (30)	330 (29)	253 (32)	
2003	526 (27)	301 (26)	225 (29)	
2004	233 (12)	138 (12)	95 (12)	
2005	178 (9)	105 (9)	73 (9)	
2006	115 (6)	68 (6)	47 (6)	
2007	102 (5)	69 (6)	33 (4)	
2008	111 (6)	79 (7)	32 (4)	
2009	75 (4)	48 (4)	27 (3)	
Comorbidities, *n* (%)				
Hyperlipidemia	1232 (64)	697 (61)	535 (68)	0.002
Hypertension	1783 (93)	1057 (93)	726 (92)	0.74
Smoking	161 (8)	107 (9)	54 (7)	0.05

A patient is considered to have hyperuricemia if the average AUC for sUA levels is >7 mg/dl during the study period. Otherwise, the patient is considered to have no hyperuricemia. This sample is used for survival analysis.

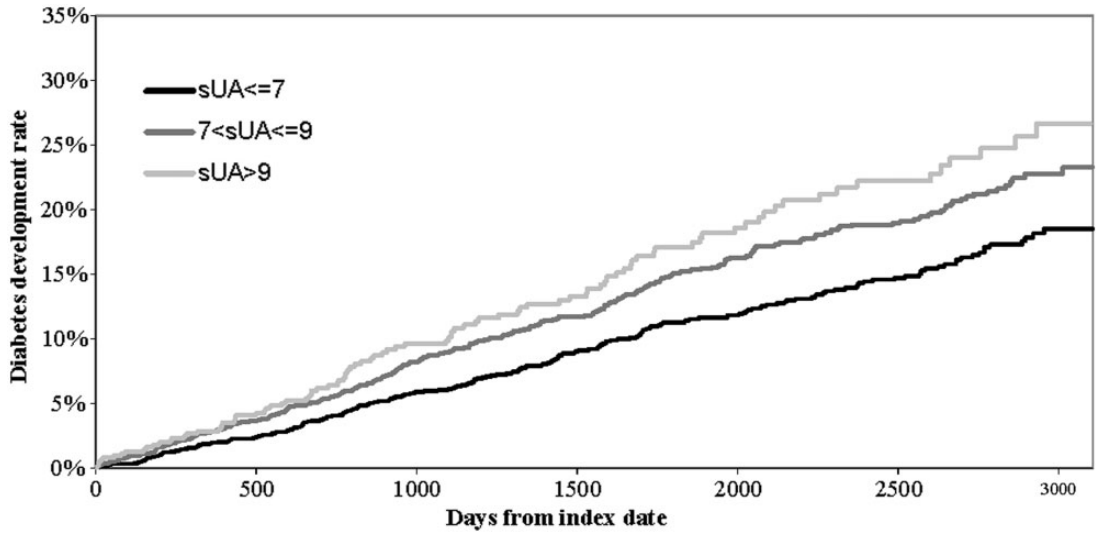

Figure 2. Accumulated hazard curve for time to the first diabetes diagnosis by sUA categories. $7 \leqslant$ sUA (black line), $7 <$ sUA $\leqslant 9$ (dark gray line) and sUA > 9 (light gray line); *P*-value < 0.001.

Table 2 Univariate HRs for development of diabetes for patients with no diabetes prior to index date

Variables	Unadjusted HR (95% CI)
Age at first sUA level test date	0.996 (0.990–1.003)
Race	
White	0.892 (0.759–1.048)
Region	
Arkansas	0.686 (0.516–0.911)
Louisiana	0.720 (0.544–0.951)
Mississippi	0.630 (0.496–0.800)
Texas	1.315 (0.710–2.436)
BMI	1.021 (1.010–1.032)
Index year	
2002	0.498 (0.268–0.927)
2003	0.483 (0.259–0.900)
2004	0.546 (0.287–1.039)
2005	0.482 (0.247–0.939)
2006	0.471 (0.230–0.967)
2007	0.376 (0.170–0.830)
2008	0.615 (0.289–1.307)
Comorbidities	
Hyperlipidemia	1.132 (0.954–1.342)
Hypertension	1.445 (1.042–2.004)
Smoking	1.421 (1.088–1.857)

Variables are treated as independent in the Cox model. Control group for race, region and index year is 'other', 'Oklahoma' and '2009', respectively.

comorbidities. Other significant predictors of new-onset diabetes from the univariate Cox proportional hazards model included BMI (HR: 1.02; 95% CI: 1.01–1.03), hypertension (HR: 1.45; 95% CI: 1.04–2.00) and smoking (HR: 1.42; 95% CI: 1.09–1.86) (Table 2).

Population AFs analysis confirmed that a substantial number of new diabetes cases can be statistically attributed to hyperuricemia (~8.7%) during the first year. Hypertension had the highest AF with 22.1%, while only 2.9% of new-onset diabetes cases were statistically attributable to hyperlipidemia. Statistically, high BMI, older age and smoking had 17.7, 10.0 and 4.1% of the new-onset diabetes cases attributable to them (Table 3).

Sensitivity analysis

Among the 1923 patients who met the study inclusion criteria, only 490 patients did not use diuretics during the entire available history and were available for sensitivity analysis. Multivariate regression-adjusted results revealed that hyperuricemia was associated with a significantly higher risk of new-onset diabetes compared with no hyperuricemia (HR: 1.51; 95% CI: 1.01–2.24) after controlling for the independent effects of age, race, index year, state of residence, BMI and the presence of other comorbidities among gout patients who did not use diuretics. On the other hand, among patients with no history of kidney disease ($N = 1231$), the regression-adjusted risk of new-onset diabetes was higher among patients with hyperuricemia compared with no hyperuricemia, but the results were not statistically significant (HR: 1.03; 95% CI: 0.82–1.31).

Among patients with no history of diuretics use, a substantial number of new diabetes cases (~20.5%) can be statistically attributed to hyperuricemia during the first year. In this population, BMI greater than or equal to 30 was associated with the highest AF with 26.5%, while only 2.2% of new-onset diabetes cases were statistically attributable to smoking. Similarly, among patients with no kidney disease, 5.1% of new-onset diabetes can be statistically attributed to hyperuricemia. In this population, hypertension was associated with the highest AF with 33.1%, while only 1.3% of new-onset diabetes cases were statistically attributable to smoking (Table 3).

Discussion

This retrospective cohort study examined the association between hyperuricemia and risk of new-onset diabetes among male US veterans with gout and no prior evidence of diabetes. A high proportion of the sample suffered from hyperuricemia: almost 60% of patients had an average sUA level >7 mg/dl during the follow-up period. Hyperuricemia categories among gout patients were associated with a significantly higher risk of developing diabetes compared with the no hyperuricemia group, in the descriptive analysis. Even after adjustment for demographics and baseline health factors, hyperuricemia predicted a significantly higher risk of new-onset diabetes as observed from the results of the multivariate Cox proportional hazards analysis. Furthermore, population AF analysis showed that a large number of new diabetes cases can be statistically attributed to hyperuricemia.

The results of this study confirm previous findings that linked sUA levels with the risk of new-onset diabetes. Several studies of disease-specific populations supported the impact of hyperuricemia in development of diabetes. For example, in a prospective cohort of middle-aged and elderly Chinese patients, elevated sUA was associated with a significantly increased risk of diabetes.[30] Moreover, a large meta-analysis of 11 cohort studies

Table 3 Population AFs (AF) for diabetes among patients with no diabetes prior to index date

Risk factor	Average AF (%) (all patients, $N=1923$)	Average AF (%) (patients with no diuretics use, $N=490$)	Average AF (%) (patients with no kidney disease, $N=1231$)
Hyperuricemia	8.7	20.5	5.1
Age $\geqslant 65$ years	10.0	5.4	11.5
BMI $\geqslant 30\,kg/m^2$	17.7	26.5	19.3
Hyperlipidemia	2.9	12.9	13.2
Hypertension	22.1	4.1	33.1
Smoking	4.1	2.2	1.3

All variables except for sUA levels were measured during the baseline period. Patients were classified into hyperuricemia vs. no hyperuricemia based on average sUA measured during the first year.

found that sUA levels were associated with a higher risk of developing type 2 diabetes regardless of study-specific characteristics.[29] Studies have found sUA to be a predictor of diabetes in other comorbid conditions, such as primary hypertension.[34] The present analysis of male veterans diagnosed with gout adds to the body of evidence that elevated uric acid is an independent risk factor for new-onset diabetes. The sensitivity analysis among patients who did not use diuretics confirmed the main findings of our study. However, among patients with no kidney disease, the risk of new-onset diabetes was not significantly higher in patients with hyperuricemia vs. no hyperuricemia. These results in general suggest that managing sUA levels may play an important role in the treatment of gout and its related comorbidities.

Several studies have estimated the population AF for different risk factors for diabetes, but population and methodological differences make it difficult to compare results from different studies. In our study, ~8.7% of new-onset diabetes cases were statistically attributable to hyperuricemia, a fraction smaller than in another study where one quarter of diabetes cases were attributed to high sUA.[11] However, in our sensitivity analysis among patients who did not use diuretics, we observed that ~20.5% of new-onset diabetes cases were statistically attributable to hyperuricemia. In patients with no kidney disease, only 5.1% of the new-onset diabetes was statistically attributable to hyperuricemia. These results signal a variation in the number of diabetes cases attributable to hyperuricemia in different populations. Similarly, the AF of diabetes to obesity in our main analysis was lower than other published estimates (17.7 vs. 25.5%)[23] but the sensitivity analysis among patients who did not use diuretics showed that ~26.5% of new diabetes cases can be attributed to obesity. It is important to note that AF of hypertension decreased from 22.1% in our main analysis to only 4.1% in our sensitivity analysis, which excluded patients who used diuretics at some point during the available history.

While most of the studies in the literature observed a positive association between hyperuricemia and diabetes risk, there are some studies that have found insignificant impact of sUA on diabetes risk. A cohort study of Japanese patients did not find a significant positive effect of elevated sUA on diabetes risk.[16] It is possible that the differences in the findings between the two studies can be explained by differences in the studied population and statistical methodology. Unlike some of the earlier studies, this study observed sUA levels over time during the study period and did not simply rely on a baseline sUA measure as a predictor of new-onset diabetes. Utilizing more recent sUA information in assessing the risk of diabetes provides a richer and more accurate picture of the association between sUA levels and diabetes.

The results of this study identify hyperuricemia as a significant risk factor for diabetes in gout patients. Treatments for long-term control of sUA level are available, and medical interventions aimed at managing hyperuricemia have the potential to reduce the risk of diabetes among patients at risk. Further research on the efficacy of medical interventions in controlling urate levels and, in turn, reducing the risk of diabetes would be necessary to evaluate the potential benefits to gout patients.

Limitations

Our findings should be treated with caution, as this study is subject to several limitations including the general limitations of observational and retrospective analyses. First, unobserved confounding factors may have led to bias that was not fully adjustable

between patients with high- and low-uric acid levels, although this study attempted to control for any potential confounding factors. Second, even though many studies, including ours, used sUA > 7 mg/dl to identify hyperuricemia in men, there is no consensus on the sUA level cut-off point for identifying hyperuricemia. Third, the VISN 16 database is subject to the same limitations as other health record databases and may not be a complete representation of all clinical activity of the patients in question. Finally, all the study patients were enrolled in the Veterans Affairs network, which may reduce the representativeness of the study sample. However, the fact that the veteran patient sample was rather homogeneous limited the likelihood of confounding factors influencing the outcomes.

Conclusions

In summary, hyperuricemia (sUA > 7 mg/dl) was a significant risk factor for new-onset diabetes in male US veterans with gout. Approximately, 1 in 11 cases of new diabetes were statistically attributed to hyperuricemia. Further studies should consider the impact of sUA reduction in the prevention of diabetes as a part of the overall management of gout patients with hyperuricemia.

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