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Impact of gout on the risk of atrial fibrillation

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Abstract

Objectives. To examine the risk of atrial fibrillation (AF) at the time of first diagnosis of gout compared to matched controls and to follow incident gout patients and their matched controls after diagnosis to compare their subsequent risk of AF.

Methods. 45,378 incident gout patients and 45,378 age-, sex-, practice-, registration year- and index year-matched controls were identified from the UK Clinical Practice Research Data-link. Index dates were initial diagnosis date for gout patients and their matched controls. The risk of AF at diagnosis (odds ratios [ORs], using conditional logistic regression) and after the diagnosis of gout (hazard ratios [HRs], using Cox proportional models) were estimated, adjusted for body mass index, smoking, alcohol consumption, ischaemic heart disease, heart failure, heart valve disease, hyperthyroidism and other comorbidities and medications.

Results. The prevalence of AF at index date in gout patients (male, 72.3%; mean age, 62.4 ± 15.1 years) was 7.42% (95% confidence interval [CI], 7.18%–7.66%) and in matched controls 2.83% (95% CI, 2.67%–2.98%). The adjusted OR (95% CI) was 1.45 (1.29–1.62). The cumulative probability of AF at 1, 2, 5 and 10 years after index date was 1.08%, 2.03%, 4.77% and 9.68% in gout patients and 0.43%, 1.08%, 2.95% and 6.33% in controls (log-rank test, $p < 0.001$). The adjusted HRs (95% CIs) was 1.09 (1.03–1.16).

Conclusions. This population-based study indicates that gout is independently associated with a higher risk of AF at diagnosis and the risk is also higher after the diagnosis.

Keywords: gout, atrial fibrillation, relative risks, population study, CPRD

Key messages:

1. Gout patients often have multiple comorbidities.

2. Gout is independently associated with a higher risk of atrial fibrillation.

3. Electrocardiogram is warranted for gout patients at diagnosis.

Introduction

Gout is the most common inflammatory arthritis worldwide and affects one in 40 individuals in the UK [1]. In addition to episodic acute arthritis, gout also results in chronic joint damage, subcutaneous tophi and peri-articular inflammation [2]. It is generally accepted that gout is highly associated with the features of metabolic syndrome[3] and chronic renal impairment [4]. In addition, gout patients are also at higher risk for developing many different conditions, such as cardiovascular [5-12], metabolic [3, 11, 13], renal [4, 11], and many other comorbidities [14-16], which collectively lead to an increased mortality [17, 18]. A recent study of co-morbidities that associate with gout also provided evidence for an association with cardiac arrhythmias [11], an observation not reported previously.

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia present in clinical practice [19]. In the UK, the incidence of chronic AF was reported in 2002 as 1.7 per 1,000 person-years, and this increased markedly with age [20]. Affected patients are at increased risk of heart failure, thromboembolic events such as stroke, and increased mortality [21, 22]. The Framingham study reported a 4 to 5-fold risk for stroke in patients with AF [23]. In addition, AF is also associated with a 2-fold risk of silent stroke [24]. The major risk factors recognised for AF include heart failure, ischaemic heart disease, hypertension, thyroid disease, heavy drinking and obesity [25]. Interestingly, stroke and many predictors for AF are also common comorbidities in gout patients [11], suggesting that there may be a potential link

between gout and AF. For example, a recent study has indicated that hyperuricaemia is associated with a larger left atrial dimension [26, 27] and a greater risk of AF [26-28]. However, despite some evidence that hyperuricaemia, the prerequisite for gout, may be a risk factor for AF, the association between gout and AF has not been formally studied.

Therefore, using data representative of the general population of UK from the Clinical Practice Research Data-link (CPRD), this study aimed to examine the risk of AF at the time of first diagnosis of gout compared to matched controls. We further followed incident gout patients and their matched controls after diagnosis to compare their subsequent risk of AF.

Methods

We hypothesised that gout patients have a higher risk of AF at the time of first diagnosis and that the risk would continue to be higher after the diagnosis of the disease. We addressed this hypothesis using both retrospective (prior to diagnosis) and prospective case control study (after diagnosis) within the CPRD. The study complies with the Declaration of Helsinki and the protocol was approved by the Independent Scientific Advisory Committee for MHRA Database Research (protocol 11-021R). All data in this study were totally anonymised therefore patient consents are exempted.

Data source

In the UK, general practitioners are the ‘gatekeepers’ for all resources of the health care system. CPRD is a database containing primary care data prospectively collected by general practitioners in 684 practices who were trained to record medical information to ensure the accuracy of the data but were unware of the information of research based on the database.

Currently the database contains data on more than 15 million people across the UK and is broadly representative of the UK general population in age and sex structure [29]. The database has been described previously[29] and has been validated for many diagnoses, including gout[30] and many other medical conditions [30-34]. A recent systematic review reported that the median percentage of cases confirmed by validation was 89% (33-100%) [33]. Importantly, 87% of diagnoses from secondary care specialists were captured and recorded [33]. The database contains comprehensive information on patient demographics, lifestyle factors, medical diagnoses, results of investigations and examinations and prescribed medications. The CPRD is also linked to additional data sources including secondary care, the Office for National Statistics cause of death data and information from specific disease registries.

Study design

In this study, our source population was based on the August 2014 version of CPRD. The study population consisted of all incident gout patients diagnosed between 1997 and 2005 who had at least 3 years of continuous registration. Each incident gout patient was matched at random to one control patient who was registered in the same practice and did not have gout and any prescription of urate-lowering treatment. Control patients were frequency-matched in a 1:1 ratio to incident gout patients by year of birth (±2 years), gender, general practice and year of first continuous registration (±2 years) at this CPRD practice. The same index date was assigned to each of the matched controls. As with incident gout patients the matched controls had at least three years of registration prior to the index date. For prospective analysis, follow-up time started from index date and ended when they had AF, died, transferred out of the practice, or the last data collection date of the practice they registered, whichever came first.

Study groups

We classified patients according to Read codes, which are diagnostic codes used by general practitioners to define diseases, procedure and other patient characteristics in UK primary care. Patients with gout were identified using a code list for gout, which our group has been using consistently[1, 11, 35] and which was validated previously with an overall ascertainment rate of 90% [30]. The case definition was based on physician-diagnosis using 18 READ codes indicative of incident gout [1]. The gout diagnosis in the CPRD has been validated previously by a review of medical records of 10 confirmed and 28 probable gout patients showing that 10 out of 10 confirmed cases and 24 out of 28 probable cases were true gout patients (overall ascertainment rate 90%) [30]. In the UK, ULT is indicated only for gout or uric acid nephrolithiasis. However, some patients did receive ULT prior to their first recording of gout diagnosis or without any diagnosis. These patients were excluded from this study.

Atrial fibrillation outcome assessment

Our primary outcome of interest was AF based physician diagnosis. This case definition has been validated previously [20, 36]. These validation studies contacted practitioners for a questionnaire asking them to classify 1714 AF patients according to a set of criteria. Among 1606 valid questionnaires, only 66 patients were confirmed not to have AF [20, 36].

Assessment of covariates

We collected life style characteristics (alcohol use, smoking and body mass index [BMI]), comorbidities (hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, heart valve disease, hyperthyroidism, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease,

liver disease, diabetes mellitus, renal diseases, cancer and anaemia), medication use (antihypertensive, glucocorticoid, statin, lipid-lowering agents, hypoglycaemic agents, insulin, aspirin, anticoagulants and hormone replacement treatment) and number of consultations in the one year prior to the index date. Life style characteristics were ascertained using the nearest possible measurement prior to the index date. Comorbidities were ascertained within 10 years and medications and the number of visits to practitioners was ascertained within one year prior to the index date.

Statistical analysis

Patient characteristics at index date were compared between gout patients and matched controls. The prevalence of AF was calculated using the number of people ever diagnosed with AF during the past three-year period before the index date as the numerator and the number of incident gout patients or matched controls as denominators. Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate the association between gout and AF at diagnosis. Conditional logistic regression was used to adjust for the aforementioned covariates. Missing data for BMI, smoking and alcohol status were coded as 'unknown'. Both gout patients and matched controls were followed up from the index date to the earliest date of occurrence of AF, death, transfer out or end of study (31 December 2013), whichever came first. Kaplan–Meier product-limit analysis were used to estimate the cumulative probability of AF in people with incident gout and matched controls. HRs with 95% CIs were calculated for AF using a Cox proportional hazards model. Only people without AF at index date were considered in the Cox model. We checked the proportional hazards assumptions by examining the log-log survival curves in our models. The HRs were adjusted by the aforementioned covariates. Data were missing for alcohol use, smoking and BMI in 24.76%, 17.62% and 17.62% patients, respectively. These lifestyle characteristics were generally

obtained when patients visit GPs. Therefore we assumed that data were missing at random (the missing pattern does not depend on the unobserved data). We used multiple imputation to handle these missing data using SAS MI procedure. The imputation model used logistic regression for alcohol and smoking and regression for BMI. We include all lifestyle, comorbidity and consultation frequency variables in the imputation model. The procedure generated 5 imputed datasets. The datasets were pooled for logistic regression and Cox proportional hazards models using Rubin's strategy [37]. We performed a sensitivity analysis using different method handling missing values (multiple imputation and setting a new category for missing value). All statistical analyses were performed using SAS statistical software, version 9.3.

Results

Study population

We identified 45,378 incident gout patients during the period 1997 to 2005 (mean age 62.4 ± 15.1 years; 72.3% being men). Female patients were older than male patients and had more comorbidities and medications use. They were 1:1 matched to 45,378 controls with the same age and sex structure (Table 1). The median observation periods (interquartile range) before and after index date were 15 (9–27) and 9 (5–12) years with no statistical difference between gout patients and controls. Gout patients consumed more cigarettes and alcohol and had a higher BMI, Charlson score and more general practice than controls. The prevalence of hypertension, ischaemic heart disease, cerebrovascular disease, heart failure and heart valve disease was significantly higher in gout patients than controls in both genders. More gout patients were prescribed medications (Table 1).

Retrospective observation

At time of index date, the proportion of people having AF was significantly higher in incident gout patients (7.42%; 95% CI, 7.18%–7.66%) than in controls (2.83%; 95% CI, 2.67%–2.98%; $p<0.001$). The prevalence of AF at index date was higher in both men and women with gout than in their respective controls (Table 2). Using a conditional logistic regression models, the unadjusted OR was estimated to be 2.89 (95% CI, 2.70–3.09) for AF. After consideration of all covariates including traditional risk factors for AF such as cardiovascular diseases and hyperthyroidism, gout was still associated with an increased odds for AF, with an adjusted OR of 1.45 (95% CI, 1.29–1.62). Separate estimates for men and women were shown in table 2. Both men and women with gout had a higher AF prevalence than that in the controls.

Follow-up data after index date

As shown in Figure 1, the cumulative probability for incident AF was significantly higher in gout patients than in matched controls at all time since index date (log-rank test $p<0.001$). The cumulative probability of AF in gout patients who were free of AF at first presentation was 1.08% at one year, 2.03% at 2 years, 4.77% at 5 years and 9.68% at 10 years after index date. In comparison, the cumulative probability of AF in controls was 0.43%, 1.08%, 2.95% and 6.33% at 1, 2, 5, and 10 years after index date (log-rank test $p < 0.001$). After a median follow-up of 9 years, 3,534 gout patients and 2,322 matched controls who were free of AF at index date developed AF. The matched HR was 1.66 (1.59–1.74) and adjusted HR was 1.09 (95% CI, 1.03–1.16) respectively. Separate estimates for men and women were shown in Table 3. The unadjusted and adjusted HR estimates were similar in magnitude for both men and women.

Sensitivity analysis

Next, we undertook a sensitivity analysis by replacing missing values (alcohol consumption, smoking and BMI categories) by a new category and performing logistic regression and Cox proportional models again. As shown in Table 4, all estimates were very similar to estimates in the primary analysis.

Discussion

This study used a large primary care database in the UK to compare the risk of AF in gout patients with matched controls at diagnosis (index date) and also to estimate the risk of future AF diagnosis. The prevalence of AF was two-fold higher in gout patients than controls at diagnosis. Furthermore, approximately 12% of gout patients developed AF within 5 years from the diagnosis whereas only 6% of matched controls developed AF. The incidence of AF was 60% higher in AF-free gout patients than matched controls. After controlling for known predictors for AF (such as ischaemic heart disease, heart failure, valvular heart disease and hyperthyroidism) [25], other comorbidities and medication use, gout was still independently associated with AF although the magnitude of association was diminished. Gout is probably an independent risk factor for AF, despite it also being associated with many comorbidities that also contribute to development of AF. Overall, the burden of AF is very high at diagnosis of gout and the risk of developing new comorbidity is also elevated in incident gout patients compared to the general population.

Currently, there is no explicit explanation for the link between gout and AF. The potential mechanism underlying the increased risk of AF in gout patients is hyperuricaemia. Increasing evidence suggests that uric acid participates in the atrial remodelling process which enhances the risk of AF [38]. Previous studies suggesting a higher risk of AF in individuals with hyperuricaemia are scarce. Cross-sectional studies generally found a higher prevalence of AF in hyperuricaemic patients with or without heart diseases [39-43]. However, these studies were retrospective in nature and many were based on hospital records, which may introduce selection bias. The prospective studies supporting the link between hyperuricaemia and AF include the Atherosclerosis Risk in Communities study which observed 15,382 AF-free patients aged 45 to 64 years for a median of 16.8 years [44]. The study found that one

standard deviation (SD) increase in serum uric acid (SUA) levels is associated with a HR of 1.56 for AF in black Americans but no significant association was identified for white Americans. A recent study following 400 patients with type 2 diabetes found that a 1-SD increment SUA level was associated with approximately 2.5-fold increase in the risk of incident AF [45]. Our finding with a higher risk of AF in gout patients at diagnosis supports the assumption that hyperuricaemia is associated with an increased risk of AF because invariably gout patients are exposed to long-term hyperuricaemia.

After diagnosis, the incidence of AF in gout patients is still 60% higher than their matched controls. However, the adjusted HRs for AF diminished, despite it still being statistically significant. There are two potential explanations. Firstly, some patients may be treated by urate-lowering treatment which may then reduce their risk of developing AF. However, against this is the finding in our recent studies that the majority of gout patients did not receive urate-lowering treatment [1] even long after the initial diagnosis [35]. Secondly, hyperuricaemia not only increase the risk of AF but also increased the risk of other cardiovascular diseases that hasten the development of AF. For example, gout is consistently associated with heart failure [11, 12] and ischaemic heart disease [5-9], both of which are established risk factors for AF [25]. Since many gout patients already had such risk factors for AF at or shortly after diagnosis [11], the effect of gout on AF may be diluted. Nevertheless, the absolute risk of AF in gout patients is approximately 60% more than age- and sex- matched controls. Therefore, vigilance for AF should be entertained for all gout patients at diagnosis or thereafter.

AF is one of the most important risk factor for stroke [46]. Our findings linking gout and AF support previous studies documenting that gout patients have a higher risk of stroke [10, 11]. We previously compared the risks of comorbidities in 39,111 patients with incident gout and

39,111 matched controls using the CPRD and found that gout was associated with an OR of 1.50 for stroke at diagnosis and with a HR for 1.29 for stroke after diagnosis [11]. This finding was supported by another study linking CPRD and data from secondary care [10]. Collectively these findings indicate that gout patients are at risk for both AF and stroke. Our study cannot differentiate the impact of gout and AF on stroke but gout is known to have a high burden of cardiovascular comorbidities in addition to AF [11], so cardiovascular vigilance seems warranted and current guidelines and recommendations [47, 48] support this practice. However, none of these practice recommendations and guidelines specifically advise undertaking an electrocardiogram on gout patients, which is an inexpensive screening for AF. Therefore, this study supports the case for a clinical cardiovascular assessment and inclusion of an electrocardiogram as a part of the initial assessment of gout patients at diagnosis and close observation, for example by annual assessment, for the occurrence of incident AF, especially for the elderly and those having other AF risk factors.

There are several limitations to this study. Firstly, misclassification bias could exist since the identification of gout patients was based on physician diagnosis, rather than according to classification criteria [49, 50] or to the 'gold standard' of urate crystal identification. However, the validity of gout diagnosis in the CPRD has been investigated and found to be high [30]. Similarly there may have been some misclassification of AF, though again this diagnosis has been validated previously and the recordings of a diagnosis of AF are generally reliable [20, 36]. In addition, there is no reason to suspect a differential misclassification of AF between gout and non-gout patients. Secondly, differential ascertainment bias between incident gout patients and controls cannot be excluded entirely. However, we have adjusted for consultation frequency in our models and the observation periods before and after the index date were comparable between cases and controls. Thirdly, potential confounders may exist and biased our results toward null. For example, the Framingham Heart Study incorporate age, sex,

systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, body mass index, and heart failure into a risk prediction model for AF [51]. Among these factors, the PR interval on an electrocardiogram and clinically significant cardiac murmurs are not available in the CPRD.

In conclusion, gout patients have a higher risk of AF at diagnosis and the risk is also higher afterwards. This study suggests an electrocardiogram as a part of the initial assessment of gout patients at diagnosis and close observation for the occurrence of incident AF after initial diagnosis of gout.

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the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. WZ, MJG and MD supervised the study. MD is the guarantor.

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