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The association between gout and cardiovascular disease in patients with atrial fibrillation

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Abstract

Objective: Gout is a sign of a disturbed metabolism and associated with atrial fibrillation (AF) and other cardio-vascular diseases. Our aim was to study associations between gout and cardiovascular co-morbidities in patients with AF.

Methods: The study population included all adults (n=12,283) ≥45 years diagnosed with AF visiting 75 primary care centers in Sweden 2001–2007. Logistic regression was used to calculate odds ratios with 95% confidence intervals (CIs) for the associations between prevalent gout and cardiovascular co-morbidities. In subsamples we studied incident congestive heart failure (CHF) and ischemic stroke (IS), excluding patients with earlier registered specific diagnosis, using Cox regression (to estimate hazard ratios (HR) with 95% CIs).

Results: Gout was significantly and positively associated with CHF, obesity and diabetes among men and women, and among men also with hypertension and coronary heart disease. Prevalent gout was negatively associated with incident IS (HR and 95% CI: 0.64, 0.49–0.82; 0.50, 0.39–0.64) in both full model (adjusted for sex, age, socio-economic factors and comorbidities) and CHA_2DS_2-VASc model (adjusted for CHA_2DS_2-VASc, sex and age). Adding gout to full model increased Harrell's C by 1% in CHA_2DS_2-VASc model.

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Conflict of interest

The authors have no conflict of interest to disclose.

Conclusions: In this clinical setting we found gout to be associated with most cardiometabolic diseases except cerebrovascular diseases, and with decreased risk of IS, with gout adding significantly to the predictive value compared to CHA_2DS_2-VASc without gout included.

Keywords

Atrial fibrillation; Gout; Congestive heart failure; Ischemic stroke; Gender; Hypertension

1. Introduction

Gout is the most common inflammatory arthritis, with deposition of monosodium urate crystals in both joints and soft tissues. Gout leads not only to acute attacks of excruciating pain, but could also lead to debilitating complications, including chronic joint damage and renal insufficiency,[1] without proper treatment. The prevalence of gout in Sweden is estimated at between 1.4%, and 1.8%.[2, 3] Worldwide, the prevalent number of patients with gout is estimated at 34 million, compared to 21 million with rheumatoid arthritis.[4] However, in terms of years lived with disability, gout only contributes to less than one per cent of all musculo-skeletal diseases.[4]

However, gout is also associated with or caused by different cardio-metabolic conditions, including not only insulin resistance,[5] the metabolic syndrome and diabetes mellitus,[6] but also different cardiovascular diseases, i.e. hypertension and antihypertensive treatment,[7, 8] coronary heart disease,[9] chronic heart failure,[7] and chronic kidney disease;[10] and may thus be used as a sign of a more aggressive disease development.

As one important cardiovascular disease atrial fibrillation (AF) is also of interest in relation to gout. AF is the most common arrhythmia in the population, with a prevalence of 2% in Sweden.[11] Worldwide, 46 million individuals are living with prevalent AF or atrial flutter, i.e. around 10% of all with prevalent cardiovascular diseases and 11% of years lived with disability due to cardiovascular diseases.[4] High serum acid levels are found to be associated with an increased risk of incident AF.[12] AF is also in itself is related to other cardiovascular diseases,[13] out of which ischemic stroke is the most important complication.[14] As regards gout in relation to ischemic stroke, hyperuricemia is shown to increase the risk of ischemic stroke,[15] and add to predictive value to the most common clinical risk predictor of ischemic stroke in AF, i.e. the CHA_2DS_2-VASc.[16] However, there are also other risks with AF, with congestive heart failure (CHF) being more common among patients with AF compared to individuals without AF,[17] and CHF is the most common cause of death among patients with AF.[18] AF is also associated to development of dementia.[19]

We have earlier studied AF patients in primary care regarding the effect of co-morbid conditions or cardiovascular medications in relation to incident heart failure,[20] incident dementia.[21, 22] and mortality.[23, 24] We have also studied anticoagulant treatment in AF in relation to ischemic stroke,[25] haemorrhagic stroke,[26] and myocardial infarction.[27] As patients with AF not only have different cardiovascular comorbidities but are also treated with many cardiovascular drugs which may increase the risk of gout,[28] it is also important to examine gout in patients with AF. We have also studied the effect of socio-economic status on mortality in AF patients.[29]

The aims herein were therefore to study the association between gout and cardiovascular co-morbidities among men and women with AF in Swedish primary care, and to study the association between prevalent gout and incident CHF, ischemic stroke and dementia among patients with AF. We believe that a patient population with AF is of particular interest as the cardiovascular comorbidities that are common in patients with gout are also common in patients with AF.

2. Methods

2.1 Design

The study used individual-level patient data from 75 primary health care centers (PHCCs), 48 of which were located in Stockholm County. Individuals attending any of the participating PHCCs between 2001 and 2008 were included in the study. We used *Extractor* software (http://www.slso.sll.se/SLPOtemplates/SLPOPage1____10400.aspx; accessed September 19, 2010) to extract individual electronic patient records (EPRs). National identification numbers were replaced with new unique serial numbers to ensure anonymity. The files were linked to a dataset including data from the Total Population Register, the National Patient Register (NPR), and the Swedish Cause of Death Register, which contains individual-level data on age, sex, education, cause of death, and hospital diagnosis for all residents registered in Sweden. Thus, a new research dataset containing clinical data and information on socioeconomic status on the individuals (n=1,098,420) registered at the 75 PHCCs was created. Data from the Cause of Death Register were used for the follow-up.

The investigation conforms with the principles outlined in the Declaration of Helsinki. Ethical approvals were obtained from regional boards at Karolinska Institutet (Dnr 12/2000) and the University of Lund (Dnr 409/2008 with completion from 19/1 2010).

2.2 Study population

The study included all patients with diagnosed AF, identified by the presence of the ICD-10 code (10th version of the World Health Organization's International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records at the PHCCs. The following cardiovascular-related disorders were used as covariates: hypertension, CHD, cerebrovascular diseases (CVD), and diabetes mellitus (for specific codes, see below). Patients with CHF during the study period were identified in two ways, either through a diagnosis in the EPR in the PHCC or through a hospital diagnosis. In total, 12,283 individuals (6,646 men and 5,637 women), aged 45 years or older at the time of AF diagnosis and who visited any of the 75 participating PHCCs from January 1, 2001, until December 31, 2007, with data on neighborhood socioeconomic status available, were included in the study.

2.3 Outcome variable

For logistic regression: prevalent gout. For Cox regression: time from first AF diagnosis to first diagnosis of CHF, IS or dementia (until December 31, 2010).

2.4 Demographic and socio-economic variables

Sex was stratified into men and women.

We classified individuals into the following age groups 45–54, 55–64, 65–74, 75–84, and ≥85 years, and also excluded individuals younger than 45 years of age.

Educational level was categorized as ≤9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling), and >12 years (college and/or university studies).

Marital status was classified as married, unmarried, divorced, or widowed.

Neighborhood socioeconomic status (SES) was categorized into three groups according to the neighborhood index: more than one standard deviation (SD) below the mean (high SES or low deprivation), more than one SD above the mean (low SES or high deprivation), and within one SD of the mean (middle SES or deprivation). The neighborhood index was based derived from the following four variables: low educational status (<10 years of formal education), low income (<50% of the median individual income from all sources), unemployment, and receipt of social welfare. The neighborhood deprivation index was categorized into three groups: more than one standard deviation (SD) below the mean (high SES or low deprivation level), more than one SD above the mean (low SES or high deprivation level), and within one SD of the mean (moderate SES or moderate deprivation level).

2.5 Co-morbidities

We identified the following cardiovascular co-morbidities from the EPRs among the individuals in the study population: hypertension (I10–15); CHD (I20–25), also including registered hospitalizations for myocardial infarction from the NPR; CHF (I50 or I110), also including hospitalizations for CHF from the NPR; CVD (I60-I69), also including registered hospitalizations for ischemic or hemorrhagic stroke from the NPR; obesity (E65-E68); diabetes mellitus (E10-E14); COPD (J40-J47); depression (F32-F34, F38-F39); anxiety disorders (F40-F41); and dementia (F00-F03, F10.7A, G30).

Results were also estimated by CHA_2DS_2-VASc scores, however after omitting the CHF item in the CHF analysis, with scores between 0 and 7 for men, and 1 and 8 for women, otherwise 0–8 for men and 1–9 for women.

2.7 Statistical analyses

Analyses were performed stratified by sex, with results presented as means with standard deviation, or rates in per cent.

Multivariate logistic regression was performed to explore the association of gout with the background factors, i.e. socio-economic factors and comorbidities, categorized into sex, with results of interaction with sex for the different factors.

Cox regression analyses were performed, with hazard ratios (HRs) with 95% confidence intervals (CIs), to analyze the estimate of gout using time to diagnosis of mortality, incident CHF, ischemic stroke and dementia. In these analyses we excluded with an earlier registered diagnosis of CHF, ischemic stroke and dementia, respectively, before first diagnosis of AF, for CHF (n=2,859), ischemic stroke (n=766), and dementia (n=187). We also used C-statistics (Harrell's C) to study the predictive value of adding gout to the Cox regression analyses and considered a 1% increment in prediction as clinically relevant. Full Cox regression models were adjusted for the following variables in separate models: age, socio-demographic factors (educational level, marital status, and neighborhood socio-economic status), co-morbidities (hypertension, CHD, CHF, cerebrovascular diseases, obesity, diabetes, COPD, depression, anxiety, dementia) with the exclusion of some comorbidities in the specific models, but including anticoagulant treatment. Results for mortality or newly diagnosed CHF, ischemic stroke and dementia were also calculated using Cox regression models adjusted for CHA_2DS_2-VASc scores, age and sex.

A two-sided *p*-value of <0.05 was considered statistically significant for variables in the logistic regression and Cox regression models. All analyses were performed in STATA 15.2 (StataCorp, College Station, TX, USA).

3. Results

Characteristics of the entire study population consisting of patients with AF (n=12,283), stratified by sex (6,646 men and 5,637 women), and into those with a diagnosis of gout (yes/no) are shown in Table 1.

Results from the logistic regression are shown in Table 2, also stratified by sex. Statistically significant factors more commonly prevalent in patients with gout were for both men and women age, CHF, obesity and diabetes; and for men only also prevalent hypertension and coronary heart disease. Gout was statistically less common in divorced and widowed women. Educational status and neighborhood socioeconomic status were not associated with prevalent gout.

Table 3 shows the follow-up analysis of mortality (n=12,283), incident CHF (n=9,424) incident ischemic stroke (n=11,527) or incident dementia (n=12,096), with HRs for gout being significantly higher for incident CHF in the model adjusted for CHA_2DS_2-VASc and with borderline significance for full model (p=0.053). A significantly lower risk was seen in both models for ischemic stroke, and also significantly lower risk of dementia in patients with gout in a model adjusted for CHA_2DS_2-VASc, age and sex. Improvement in Harrell's C were below 1% for all models but the CHA_2DS_2-VASc model for ischemic stroke. We also tested the risk of incident MI, finding a HR of 1.00.

4. Discussion

The main finding of this study was that gout was associated with a decreased risk for ischemic stroke in patients with AF. Adding information about prevalent gout lead to an improved prediction of ischemic stroke than CHA_2DS_2-VASc alone.

We found gout to be statistically significantly associated with a lower risk of incident ischemic stroke. In contrast, an earlier study from Taiwan using the “National Health Insurance Research Database” in Taiwan found hyperuricemia, actually defined as at least one attack of gout and on long-term anti-gout treatment, to be a significant risk factor of ischemic stroke in patients with AF.[15] Earlier reviews have found a modestly increased risk of stroke in general by hyperuricemia.[30, 31] We have no good explanation to this discrepancy.

We also found some gender differences in comorbidities to gout, however, with only obesity showing a significant difference between men and women. In an earlier Swedish study, both diabetes and insulin resistance were associated with gout in both women and men.[13] However, we also found different patterns in men and women, although not statistically significant: with gout being associated with hypertension and CHD in men with AF, but surprisingly not among women with AF. The frequency of hypertension is remarkably low in the present cohort compared to another Swedish study using data from all caregivers with a hypertension rate of 65%,[11] and possibly this diagnosis could have been dropped earlier in favour of other cardiovascular diagnoses such as CHD, CHF or cerebrovascular diseases. Antihypertensive agents such as diuretics are associated with higher levels of uric acid and gout,[32] why a higher rate of hypertension could be expected in patients with AF. One explanation could be that thiazides are prescribed in lower doses in clinical practice in Sweden now compared to how these drugs were used previously. The association between gout and prevalent CHF, as well as an association with incident CHF showing a trend value, could partly be explained by the use of loop diuretics. In an earlier study we found loop diuretics to be associated with incident CHF, and an explanation for this could be that loop diuretic treatment is used owing to signs of CHF without a formally registered diagnosis.

We found no improvement in the Cox regression models when adding gout to models with established risk factors to study mortality and myocardial infarction. Earlier systematic reviews have only found a marginally increased CHD risk,[33–35] however with an increased risk among women,[33] including both CHD and all-cause mortality.[34, 35] With this marginally increased risk, the present study have no statistical power to detect these differences.

There are several limitations of this study. As the study sample is a subgroup of the AF population, i.e. patients registered in primary health care, the results could not directly be extrapolated to all AF patients. It has previously been estimated, that 36% of all patients registered with a diagnosis of AF in Stockholm County were not known with this diagnosis in primary health care.[11] The medical co-morbidities were based on registered diagnoses, with risk of both over- and under-estimation. Severity of AF, gout, CHF or CHD could not be classified, and the indications for the specific pharmacotherapies were not registered. Drugs to treat gout were not assessed. Thus, the results may partly have been biased due to these limitations. Furthermore, AF could not be classified as paroxysmal, persistent, or permanent, and heart rhythm could not be classified as sinus rhythm or fibrillation rhythm. Some diagnoses such as obesity are less often registered the electronic patient records, and an obesity diagnosis probably reflects a more severe condition. All these mentioned factors could have affected the results, and yielded discrepant findings. A major strength of this

study was that we were able to link clinical data from individual EPRs to data from national demographic and socioeconomic registers with less than 1% of information missing.

In conclusion, in this clinical setting with patients with AF treated in primary care, we found gout associated with a decreased risk of incident ischemic stroke.

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Significance and relevance:

1. In this clinical setting we found gout to be associated with most cardiometabolic diseases
2. A diagnosis of gout was be associated with a decreased risk of ischemic stroke in patients with atrial fibrillation
3. Identifying a gout diagnosis in patients with atrial fibrillation improves to the predictive value to the risk for ischemic stroke compared to CHA_2DS_2-VASc without gout included

Table 1

Baseline characteristics for patients aged ≥45 years with diagnoses of AF (*N*=12,283), and with or without gout in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007, divided by sex

	All	Men (N=6,646)		Women (N=5,637)	
		No gout	Gout	No gout	Gout
	N=12,283	N=5,959	N=687	N=5,275	N=362
	Numbers (%)	Numbers (%)	Numbers (%)	Numbers (%)	Numbers (%)
Number of deaths	3,954 (32.1)	1,739 (29.2)	244 (35.5)	1,817 (34.5)	154 (42.5)
Age (years), mean (SD)	74.4 (10.1)	72.0 (10.2)	73.5 (9.3)	77.0 (9.3)	78.4 (8.1)
Age groups (years)					
45–54	475 (3.9)	348 (5.8)	22 (3.2)	104 (2.0)	1 (0.3)
55–64	1,743 (14.2)	1,110 (18.6)	112 (16.3)	499 (9.5)	22 (6.1)
65–74	3,308 (26.9)	1,852 (31.1)	190 (27.7)	1,191 (22.6)	75 (20.7)
75–79	2,427 (19.8)	1,092 (18.3)	165 (24.0)	1,090 (20.7)	80 (22.1)
80–84	2,447 (19.9)	962 (16.1)	121 (17.6)	1,261 (23.9)	103 (28.5)
≥85	1,883 (15.3)	595 (10.0)	77 (11.2)	1,130 (21.4)	81 (22.4)
Educational level					
Compulsory schooling	5,085 (45.2)	2,219 (39.4)	267 (41.1)	2,427 (52.1)	172 (58.1)
Secondary schooling	3,995 (35.5)	2,110 (37.4)	257 (39.5)	1,535 (33.0)	93 (31.4)
College and/or university studies	2,161 (19.2)	1,310 (23.2)	127 (19.5)	693 (14.9)	31 (10.5)
Marital status					
Married	5,613 (45.9)	3,567 (60.1)	383 (55.9)	1,554 (29.6)	109 (30.3)
Unmarried	1,029 (8.4)	566 (9.5)	64 (9.3)	384 (7.3)	15 (4.2)
Divorced	1,813 (14.8)	908 (15.3)	113 (16.5)	744 (14.2)	48 (13.3)
Widowed	3,777 (30.9)	895 (15.1)	125 (18.3)	2,659 (48.9)	188 (52.2)
Neighborhood SES					
High	4,604 (37.5)	2,385 (40.0)	271 (39.5)	1,834 (34.8)	114 (31.5)
Middle	5,807 (47.3)	2,712 (45.5)	318 (46.3)	2,600 (49.3)	177 (48.9)
Low	1,872 (15.2)	862 (14.5)	98 (14.3)	841 (15.9)	71 (19.6)
Diagnosis					
Hypertension	5,449 (44.4)	2,396 (40.2)	330 (48.0)	2,532 (48.0)	191 (52.8)

	All	Men (N=6,646)		Women (N=5,637)	
		No gout	Gout	No gout	Gout
	N=12,283	N=5,959	N=687	N=5,275	N=362
	Numbers (%)	Numbers (%)	Numbers (%)	Numbers (%)	Numbers (%)
Coronary heart disease	3,234 (26.3)	1,472 (24.7)	250 (36.4)	1,395 (26.5)	117 (32.3)
Congestive heart failure	5,684 (46.3)	2,432 (40.8)	424 (61.7)	2,560 (48.5)	268 (74.0)
Cerebrovascular diseases	2,566 (20.9)	1,139 (19.1)	138 (20.1)	1,208 (22.9)	81 (22.4)
Obesity	614 (4.6)	297 (5.0)	55 (8.0)	222 (4.2)	40 (11.1)
Diabetes mellitus	2,366 (19.3)	1,109 (18.6)	185 (26.9)	958 (18.2)	114 (31.5)
COPD	1,416 (11.5)	618 (10.4)	92 (13.4)	648 (12.3)	58 (16.0)
Depression	1,039 (8.5)	372 (6.2)	40 (5.8)	586 (11.1)	41 (11.3)
Anxiety	496 (4.0)	168 (2.8)	15 (2.2)	285 (5.4)	28 (7.7)
Dementia	937 (7.6)	343 (5.8)	45 (6.6)	512 (9.7)	37 (10.2)

Information on educational level (men 356, women 686) and marital status (men 25, women 26) is missing for some individuals.

Table 2

Multivariate logistic regression for the association between baseline characteristics and prevalent gout, with odds ratios (ORs) and 95% confidence interval (CI), for patients aged ≥45 years with diagnoses of AF (n=11,209 patients) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007

	All N=11,209	Men N=6,273	Women N=4,936	Interaction between men and women
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**p-value**
Age (years), mean (SD)	**1.01 (1.00–1.02)**	**1.01 (1.00–1.02)**	**1.02 (1.00–1.04)**	0.86
Educational level				
Compulsory schooling	1 (ref)	1 (ref)	1 (ref)	
Secondary schooling	1.04 (0.89–1.22)	1.08 (0.89–1.31)	0.97 (0.74–1.28)	0.33
College and/or university studies	0.89 (0.73–1.10)	0.92 (0.73–1.17)	0.85 (0.56–1.29)	0.34
Marital status				
Married	1 (ref)	1 (ref)	1 (ref)	
Unmarried	0.92 (0.71–1.19)	1.12 (0.84–1.51)	**0.55 (0.32–0.98)**	0.070
Divorced	1.02 (0.84–1.25)	1.15 (0.91–1.46)	0.73 (0.50–1.07)	0.15
Widowed	0.89 (0.74–1.07)	1.03 (0.81–1.31)	**0.67 (0.50–0.90)**	0.065
Neighborhood SES				
High	1.05 (0.89–1.23)	1.13 (0.93–1.38)	0.87 (0.65–1.16)	0.53
Middle	1 (ref)	1 (ref)	1 (ref)	-
Low	0.98 (0.78–1.23)	0.85 (0.64–1.13)	1.27 (0.88–1.84)	0.35
Diagnosis				
Hypertension	**1.24 (1.07–1.42)**	**1.32 (1.11–1.56)**	1.09 (0.85–1.40)	0.45
Coronary heart disease	**1.21 (1.04–1.40)**	**1.38 (1.15–1.65)**	0.94 (0.72–1.23)	0.067
Congestive heart failure	**2.32 (2.00–2.69)**	**2.12 (1.77–2.53)**	**2.80 (2.12–3.70)**	0.097
Cerebrovascular diseases	0.99 (0.83–1.17)	0.98 (0.79–1.21)	1.03 (0.77–1.37)	0.84
Obesity	**1.94 (1.51–2.49)**	**1.57 (1.14–2.17)**	**2.73 (1.82–4.09)**	**0.020**
Diabetes mellitus	**1.44 (1.23–1.69)**	**1.31 (1.08–1.59)**	**1.70 (1.30–2.23)**	0.054
COPD	1.07 (0.87–1.30)	1.06 (0.82–1.36)	1.12 (0.80–1.56)	0.59
Depression	0.97 (0.75–1.25)	1.00 (0.71–1.42)	0.95 (0.65–1.40)	0.98
Anxiety	0.94 (0.65–1.36)	0.75 (0.43–1.33)	1.13 (0.69–1.85)	0.28

	All N=11,209	Men N=6,273	Women N=4,936	Interaction between men and women
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**p-value**
Dementia	0.97 (0.74–1.26)	0.92 (0.64–1.31)	1.02 (0.69–1.52)	0.63

Information on educational level (1,042) and marital status (n=51) is missing for some individuals, giving lower numbers than in Table 1. Statistically significant values shown in bold.

Table 3.

Cox regression models with hazard ratios (HRs) and 95% confidence interval (95% CI) for the association between gout and mortality, as well as incident congestive heart failure (CHF), ischemic stroke (IS) and dementia.

	Mortality		Incident CHF		Incident IS		Incident Dementia	
	Full Model	**CHA2DS2-VASc model**	**Full Model**	**CHA2DS2-VASc model**	**Full Model**	**CHA2DS2-VASc model**	**Full Model**	**CHA2DS2-VASc model**
Gout	0.92 (0.82–1.03)	0.98 (0.88–1.09)	1.21 (1.00–1.47)	**1.25 (1.04–1.51)**	**0.64 (0.49–0.82)**	**0.50 (0.39–0.64)**	0.79 (0.58–1.08)	**0.64 (0.48–0.86)**
Harrell's C without gout	0.7488	0.7541	0.6926	0.6679	0.6650	0.6172	0.7556	0.7387
Harrell's C with gout included	0.7490	0.7541	0.6940	0.6690	0.6679	0.6279	0.7563	0.7414
Model improvement with gout	0.0002	0.0000	0.0014	0.0011	0.0029	**0.0107**	0.0007	0.0027

Fully adjusted models (age, sex, socio-economic variables, co-morbidity, anticoagulant treatment) and models adjusted for CHA2DS2-VASc (with age and sex included) are shown. Bold values are statistically significant for HRs, or exceeding 0.01 in model improvement for Harrell's