SYSTEMATIC REVIEW

Association between gout and atrial fibrillation: A meta-analysis of observational studies [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Gout is a systemic inflammatory arthritis characterized by the deposition of monosodium urate crystals due to hyperuricemia. Previous studies have explored the link between gout and atrial fibrillation (AF). Given the increasing prevalence and incidence of gout, there is a need to quantify the relationship between gout and the risk of AF. Therefore, we conducted a systematic review and meta-analysis on this topic.

Methods: PubMed and Embase were searched for studies that reported the association between gout and AF using the following search term: ('Gout' and 'Arrhythmia'). The search period was from the start of the database to 3rd August 2018 with no language restrictions.

Results: A total of 75 and 22 articles were retrieved from PubMed and Embase, respectively. Of these, four observational studies (three cohort studies, one case-control study) including 659,094 patients were included. Our meta-analysis demonstrated that gout was significantly associated with increased risk of AF (adjusted hazard ratio: 1.31; 95% confidence interval: 1.00-1.70; P = 0.05; I² = 99%) after adjusting for significant comorbidities and confounders.

Conclusions: Our meta-analysis confirms the significant relationship between gout and AF. More data are needed to determine whether

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Approval Status ? ?

	1	2
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2. **Per Wändell** , Karolinska Institutet, Huddinge, Sweden

Any reports and responses or comments on the article can be found at the end of the article.

this risk can be adequately reduced by urate-lowering therapy.

Keywords

gout, atrial fibrillation, meta-analysis

This article is included in the **University College London** collection.

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Competing interests: No competing interests were disclosed.

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Introduction

Gout is a systemic inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals due to hyperuricemia. This is defined as serum uric acid levels above 6.8mg/dL and is due to impaired excretion and/or overproduction of uric acid¹. Atrial fibrillation (AF) is a multifactorial condition whose prevalence increases with age²⁻⁴. Previous studies have suggested a correlation between pro-inflammatory conditions such as gout and cardiovascular diseases⁵⁻⁷, and have explored the link between gout and AF⁸⁻¹³. Given the increasing prevalence and incidence of gout¹⁴, there is a need to quantify the relationship between gout and the risk of AF.

Methods

The meta-analysis was conducted in accordance with the MOOSE checklist. PubMed and Embase were searched for studies reporting the association between gout and AF using the search terms: ('Gout' and 'Arrhythmia'). The search period was from the start of the database to 3rd August 2018 with no language restrictions. Two researchers (KSKL and MG) independently conducted the search. Any disagreement was resolved by adjudication from a third reviewer (GT). Study selection was carried out by screening titles of full publications to determine compliance with the following inclusion criteria: (1) retrospective or prospective cohort studies in human subjects with gout and non-gout control group; (2) AF occurrence was reported; (3) adjusted hazard ratio (aHR) with 95% confidence intervals (95% CI) was reported or could be calculated. As all of the included studies reported sufficient information, contact with the original study authors was not required.

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle-Ottawa Quality Assessment Scale (NOS). The point score system evaluated the categories of study participant selection, comparability of the results and quality of the outcomes. The following characteristics were assessed: (1) representativeness of the exposed cohort;

(2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts.

Data were entered in prespecified spreadsheet in Microsoft Excel. The extracted data elements consisted of (1) surname of first author and publication year; (2) sample size of gout and non-gout cohorts; (3) follow-up duration; (4) population characteristics (age, gender, diabetes mellitus, hypertension, ischemic heart disease or coronary artery disease, chronic heart failure, hyperlipidemia, chronic obstructive pulmonary disease, liver disease).

Statistical analysis was performed using Review Manager (Version 5.3). Heterogeneity was assessed by the I^2 statistic. $I^2 > 50\%$ reflects significant statistical heterogeneity. Therefore, a random-effects model with the inverse variance heterogeneity method was used. Subgroup analyses were not performed due to the fact that not all studies consistently reported the outcomes for the same subgroups.

Results

A total of 97 entries were retrieved from 75 and 22 from PubMed and Embase, respectively. Of these, four observational studies (three cohort studies, one case-control study) including 659,094 patients were included (Figure 1)⁴⁻⁷. The main characteristics of the studies are summarised in Table 1. The four different cohorts were recruited from the United Kingdom, United States and Taiwan. All included studies had NOS scores ≥ 7 , indicating that they were of high quality (Table 2 and Table 3). Our meta-analysis demonstrated that gout was significantly associated with increased risk of AF (adjusted HR = 1.31; 95%CI: 1.00- 1.70; P = 0.05; $I^2 = 99\%$) (Figure 2). This was observed after adjusting for comorbidities and confounders of AF.

Figure 1. Flow chart for the study screening and selection process.

Table 1. Characteristics for the four studies included in the meta-analysis of gout and atrial fibrillation (AF).

Studies	Subjects	Age (y/o)	Males (n)	Follow-up (years)	DM (%)	HTN (%)	IHD/CAD (%)	CHF (%)	Hyperlipidaemia (%)	COPD (%)	Liver disease (%)
Chang-Fu Kuo 2015	Gout: 45348 Non-Gout: 45348	62.4±15.1 62.39±14.55	33012 33012	9	- (-)	15992 (35.2) 8578 (18.9)	6508 (14.3) 3525 (7.8)	3976 (8.8) 1141 (2.5)	- (-)	- (-)	- (-)
Seouyoung C Kim 2015	Gout: 70015 Osteoarthritis (Non-Gout): 210045	56.8±9.0 56.8±9.0	56992 190976	2	16874 (24.1) 37388 (17.8)	48660 (69.5) 106913 (50.9)	- (-)	- (-)	44740 (63.9) 113844 (54.2)	7422 (10.6) 26466 (12.6)	3011 (4.3) 6721 (3.2)
Singh JA 2018	Gout with incident AF: 10604 Non-Gout with incident AF: 150486	- -	- -	-	-	-	-	-	-	-	-
Yu-Jui Kuo 2016	Gout: 63624 Non-Gout: 63624	51.29±16.25 51.29±16.25	47070 47070	6	8933 (14.1) 4867 (7.7)	23412 (37.0) 11153 (17.6)	8868 (14.0) 4779 (7.6)	2783 (4.4) 1265 (2.16)	17119 (27.1) 4719 (7.6)	2199 (3.48) 1583 (2.50)	- (-)

*Data for Singh JA 2018 could not be extracted as data of AF and non-AF group were not separately displayed in the original paper and calculations are not viable.

Table 2. NOS risk of bias scale for included case-control studies.

Studies	Adequate definition of cases	Selection		Definition of controls	Comparability	Ascertainment of exposure	Exposure		Total score (0–9)
		Representativeness of cases	Selection of controls				Same method of ascertainment for subjects	Non-response rate	
Chang-Fu Kuo 2016	1	1	1	1	1 (age)	1	1	1	8

Table 3. NOS risk of bias scale for included cohort studies.

Studies	Representativeness of the exposed cohort	Selection		Outcome of interest not present at start of study	Comparability	Assessment of outcome	Outcome		Total score (0–9)
		Selection of the non-exposed cohort	Ascertainment of exposure				Adequacy of duration of follow-up	Adequacy of completeness of follow-up	
Chang-Fu Kuo 2016	1	1	1	0	1 (age)	1	1	1	7
Seoyoung C. Kim 2016	1	1	1	1	1 (age)	1	1	1	8
Jasvinder A Singh 2018	1	1	1	0	1 (age)	1	1	1	7

Figure 2. Hazard ratio for the risk of atrial fibrillation in the gout population relative to the non-gout population.

Discussion

Atrial cardiomyopathy, in particularly AF, is a significant clinical problem because it predisposes to stroke, which can be debilitating and increase mortality^{15–17}. Numerous predictors of AF have been identified, including co-morbid conditions¹⁸, blood biomarkers^{19–26}, and electrocardiographic predictors^{27–29}. The main finding of this meta-analysis is that gout is associated with a 31% higher risk of AF after adjusting for significant comorbidities and confounders.

Several mechanisms have been proposed to explain this relationship with reactive oxygen species as a critical player in the pro-inflammatory process^{13,30}. High serum uric acid levels in gout

patients overwhelm the uric acid transporter (URAT1) and their influx causes intracellular accumulation of urate, which in turn stimulates NADPH oxidase and subsequent reactive oxygen species (ROS) production. ROS produced activates the downstream ERK1/2 pathway and upregulates Kv1.5 protein expression, resulting in the attenuation of atrial cellular action potential and electrical remodelling of the left atrium, as illustrated in mice models³¹. Furthermore, the renin-angiotensin-aldosterone system that becomes activated by high urate acid levels in gout patients. Subsequent studies into gout treatment can prevent AF and lower its recurrence rate after pulmonary vein isolation (PVI) ablation^{32,33}. In preclinical studies, urate-lowering therapy can reduce oxidative stress and prevent adverse remod-

elling of the cardiac chambers^{33,34}. The NLRP3-inflammasome also contributes to the pathogenesis underlying AF in gout and can be activated by MSU crystals in gout³⁵. Its activation triggers the maturation and production of the pro-inflammatory cytokine interleukin-1 β (IL-1 β), which upregulates the expression of TGF- β 1, a key mediator for atrial fibrosis³⁶, which can lead to atrial conduction abnormalities^{37,38}, promoting AF by re-entry^{39,40}.

The main strength is that it included the largest cohort of ~660000 patients. However, the following limitations remain. Firstly, as the included studies were retrospective, they are susceptible to bias as in all studies of this study design. Secondly, only four studies were included and future studies are needed to confirm the relationship between gout and AF. Thirdly, definitions of AF also differed between studies. It was based on physician diagnosis or ICD-9 criteria from data obtained using administrative databases. Finally, the type of AF, such as

paroxysmal, sustained or permanent, was not reported. These limitations could explain the high heterogeneity observed in this meta-analysis.

In conclusion, our meta-analysis confirms the significant relationship between gout and AF. More data are needed to determine whether this risk can be adequately reduced by urate-lowering therapy.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Version 1

Reviewer Report 04 April 2019

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Per Wändell

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The review article is certainly of interest, but needs improvement on several points. As a complement to the earlier Reviewer (who certainly has given many good suggestions to improve the article) I add:

Remarks:

1. The authors performed searches in PubMed and Embase. One way to extend the search is a backwards and forwards search, i.e. to look at the articles in the reference lists of included articles (and on earlier reviews), and to search in Google Scholar which articles have cited the included articles. If not performed, this ought to be done.
2. As pointed out by Reviewer 1, the Introduction is too brief, and could certainly be extended. There are many connections between gout and atrial fibrillation that should be mentioned. For instance, hypertension is common in both conditions, with the use of many antihypertensive agents among certain medications may increase urate levels.
3. As regards diagnosis of gout, there are different definitions of gout, e.g. the ARA criteria. The mentioned definition of gout in the article is too simplified, and needs to be extended. In epidemiologic research the definition of gout differ. The authors should mention how gout has been defined in the included studies.
4. The authors could mention the known prevalence of gout and atrial fibrillation, respectively, in the world, and mention possible differences in different regions of the world, and different populations. This is important for the possibility to generalize their findings.
5. In the Discussion, the connections between gout and atrial fibrillation should also be mentioned.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardio-metabolic research (cardio-vascular and metabolic diseases), including systematic reviews.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 26 March 2019

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Wisit Cheungpasitporn

Division of Nephrology, Department of Medicine, University of Mississippi Medical Center (UMMC), Jackson, MS, USA

My points below are for potential improvement of this manuscript, and I have no conflicts of interest.

This systematic review needs several points to be significantly addressed as listed below:

- There are very limited number of included studies (three cohort studies, one case-control study).
- This systematic reviews and meta-analysis has not been registered. Lack of transparency. Please add this point in the limitation.
- The reason why only 4 studies are included because literature search was too superficial. Hyperuricemia should also be included in search term.
- Figure 1, suggest to use PRISMA 2009 Flow Diagram platform

Detailed comments as below:

1. Introduction is too brief and not adequate enough. Need to describe in detail about the impact of atrial fibrillation and gout and how one can affect another
2. This systematic review and meta-analysis has not been registered. Lack of transparency. Please add this point in the limitation.
3. Search terms in PubMed and Embase are different. 4. Please attach search terms that were used in each database as supplement for Data source and search strategies in the manuscript. Please provide details search terms in supplementary documents.
4. Please attach syntax used in each database as supplementary.

5. When Pubmed is used for the search, MESH terms are always recommended to be included.
6. Figure 1, suggest to use PRISMA 2009 Flow Diagram platform
7. The reason why only 4 studies are included because literature search was too superficial. Hyperuricemia should also be included in search term.
8. There are high heterogeneity observed in this meta-analysis.
9. Minor corrections are needed in English writing as below:
 - United States should be "the United States"
 - "Characteristics for the four studies" should be "Characteristics of the four studies"

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic reviews and meta-analysis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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