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Original article

The risk of Sjogren's syndrome in the older adults with gout: A medicare claims study

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ABSTRACT

Objectives: In the absence of previous studies, our objective was to assess whether gout was associated with an increase or decrease in the risk of Sjogren's Syndrome (SS) in older adults, 65 years or older.
Methods: We used the 5% Medicare claims from 2006–2012. A multivariable Cox regression model assessed the association of gout with incident SS adjusting for age, sex, race, Charlson–Romano comorbidity index, and the use of medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and gout (allopurinol, febuxostat). Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.
Results: There were 3,186 new cases of SS in the study cohort with crude incidence rates of SS of 30/100,000 person-years in patients without gout and 49/100,000 person-years in patients with gout. Multivariable-adjusted analyses showed that gout was independently associated with a higher hazard ratio of SS of 1.73 (95% CI, 1.45, 2.06). Sensitivity analyses that substituted continuous Charlson–Romano comorbidity index score with categorized score (model 2) or individual comorbidities plus three common cardiovascular diseases (hypertension, hyperlipidemia, and coronary artery disease; model 3), confirmed the main study findings with minimal attenuation of hazard ratio, 1.70 (95% CI, 1.43, 2.02) and 1.48 (95% CI, 1.25, 1.77), respectively. Younger age, female sex, White race and higher comorbidity score were associated with a higher hazard of SS.
Conclusions: Gout was associated with more than 1.7-fold higher risk of incident SS in adults 65 years or older. This finding needs to be reproduced and the underlying mechanisms for this association need further study.

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1. Introduction

Sjogren's Syndrome (SS) is a chronic autoimmune condition affecting the elderly, caused by infiltration of salivary and lacrimal glands with mononuclear cells and characterized by dry eyes and dry mouth and systemic inflammation [1]. The incidence rate of SS ranges 7-20/100,000 people in the general population and increases with age [2].

Gout is the most common inflammatory arthritis in adults, characterized by the formation of monosodium urate (MSU) crystals in synovial structures including the joints. The MSU crystals lead to the activation of the nucleotide-binding domain and leucine-rich repeat containing (NLR) protein 3 (NLRP3) inflammasome, resulting in the formation of interleukin-1 beta (IL-1β), IL-6 and other pro-inflammatory cytokines that manifests as acute gout flares [3] and chronic joint and systemic inflammation.

SS often coexists with and shares disease mechanisms with other autoimmune diseases such as lupus, scleroderma, rheumatoid arthritis, etc. [1], which have not been reported to commonly occur concomitantly with gout. Particularly, RA does not co-exist with gout [4]. These observations would suggest that gout might be associated with a lower risk of SS.

On the other hand, gout and SS have some biomarkers in common, which raises the question whether the risk of SS may be increased in patients with gout. Studies in SS reported an activation of NLRP3 inflammasome [5,6], an increase in IL-1β levels [7,8] and a reduction in dry eye symptoms, corneal epitheliopathy and fatigue with anakinra (an inhibitor of IL-1β) [9,10].

To our knowledge, no studies to date have assessed the association of gout with SS. Adults 65 years or older are a rapidly growing population in the U.S. that will increase from 34.4 million in 2000

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to more than 70 million in 2030 [11]. Therefore, we aimed to assess whether gout was associated with a higher or lower risk of SS in the elderly, and whether this association varied by age, sex or race/ethnicity in subgroup analyses.

2. Methods

2.1. Data sources and study cohort

We used the 5% Medicare claims sample from 2006–2012 to perform this study. We selected Medicare beneficiaries, if they were enrolled in Medicare fee-for-service (Parts A, B), and not enrolled in Medicare Advantage Plan (part C; since people with this coverage have incomplete claims data) and lived in the U.S. from 2006-2012. The study was approved by University of Alabama at Birmingham's Institutional Review Board that waived the requirement for informed consent.

2.2. Study outcome

The study outcome of interest was incident SS, defined as an absence of SS diagnosis in the baseline period of 365 days (1/12005-12/31/2005) and the presence of at least two claims for SS at least 4 weeks apart in 2006-2012, identified with International Classification of Diseases, ninth revision, common modification (ICD-9-CM) code of 710.2. This approach using the ICD-9-CM codes is valid for identifying patients with SS with sensitivity of 96% and specificity of 96% [12].

2.3. Predictor of interest, covariates and confounders

Our main predictor of interest was gout, identified by the presence of two claims at least 4 weeks apart with ICD-9-CM diagnostic code, 274.xx. The date of the second diagnostic code for gout was considered as date a patient met the diagnosis of gout. This algorithm for gout has high accuracy with sensitivity of 90% and specificity of 100% [13], confirmed in another study [14].

We adjusted for several variables that are potential confounders or important covariates. These included patient demographics (age, sex, and race/ethnicity), comorbidities, common cardiovascular medications and gout medications for the baseline period, obtained from the Medicare denominator file, beneficiary summary file, inpatient and outpatient claim files, and prescription claims from the Medicare part D file. We assessed medical comorbidity using the Charlson–Romano comorbidity index score, a validated weighted comorbidity index developed for claims data analysis [15]. We included common cardiovascular drugs (statins, beta-blockers, diuretics, and angiotensin converting enzyme (ACE)-inhibitors), and urate-lowering therapy (ULT) for gout (allopurinol, febuxostat), to reduce confounding bias by controlling for common conditions they are used to treat (as markers of active or severe disease), and/or their independent effects on inflammation and other related pathways.

2.4. Statistical analyses

We compared the baseline characteristics of patients with and without incident SS and calculated the crude incidence rates of SS in people with vs. without gout. We used a multivariable-adjusted Cox proportional hazard regression model to calculate the hazard ratio (HR) of incident SS with gout. Our main multivariable-adjusted model included age, sex, race, Charlson–Romano comorbidity index score, the cardiovascular and gout medications. Age and medication use were modeled as time-varying covariates. We used the sensitivity analyses to test the robustness of our findings by replacing the continuous Charlson–Romano Score with:

- categorical variable (score of 0, 1 or ≥ 2; model 2); and;
- by individual Charlson–Romano comorbidities (model 3; also included hypertension, hyperlipidemia, and coronary artery disease).

We performed subgroup analyses by race, sex and age to understand whether the association of gout with SS varied by these key patient characteristics. We performed a Cochran–Mantel–Haenszel test to assess whether the association of gout with SS was independent of the presence of connective tissue disease, a disease strongly associated with SS [1].

2.5. Role of the funding source

The funding source did not play any role in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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3. Results

3.1. Study cohort characteristics and Crude Incidence rate of SS

There were 3,186 cases of incident SS during the follow-up out of a total of 1,736,901 people that met the study inclusion criteria, 3,036 in people without gout and 150 in people with gout, with the respective crude incidence rates of SS at 30 versus 49 per 100,000 person-years. Compared to people who did not develop SS, people who developed SS were more likely to be female (58% vs. 86%), white (86% vs. 89%) and had a Charlson–Romano Comorbidity Score ≥ 2 (37% vs. 41%; Table 1). Higher prevalence of several comorbidities was noted in people with incident SS compared to those without, in particular chronic pulmonary disease and connective tissue disease (Table 1).

3.2. Multivariable-adjusted estimates for Hazards of Incident SS with gout

The main multivariate model showed an increased adjusted hazard ratio (HR) of incident SS among people with gout 1.73 (95% CI, 1.45, 2.06; Table 2). Women were 5-times more likely than men to have SS and oldest age and black race were each associated with a reduced risk of SS. Compared to people with no medical comorbidity, presence of a medical comorbidity was associated with an adjusted HR of 1.4 of incident SS and 2 or more comorbidities with a HR of 1.7 (model 2; sensitivity analysis). In sensitivity analyses that controlled for each of the 17 Charlson–Romano comorbidities including connective tissue disease, HR of gout with SS was minimally attenuated at 1.5 (model 3, sensitivity analysis; Table 2). Among comorbidities, chronic pulmonary disease and connective tissue disease were associated with adjusted HR of 1.24 (95% CI, 1.13, 1.36) and 7.71 (95% CI, 7.04, 8.43), respectively. Using a Cochran–Mantel–Haenszel test, the association of gout with SS was significant regardless of whether people had connective tissue disease or not ($P < 0.01$).

Subgroup analyses by age, race, and sex showed no statistically significant differences by age, race or sex, likely due to wide confidence intervals (Fig. 1). Specifically, the multivariable-adjusted HR of incident SS associated with gout was 1.75 (1.43, 2.14) for females and 1.67 (1.17, 2.38) for males.

Table 1
Demographic and clinical characteristics of people with and without Incident Sjogren's Syndrome (SS) and the entire study cohort.

	Entire cohort	Incident Sjogren's syndrome during the follow-up	
		No	Yes
Total, *n*	1,736,901[a]	1,733,715	3,186
Age, mean (SD)	75.3 (7.6)	75.3 (7.6)	73.3 (6.2)
Gender, *n* (%)			
Male	736,846 (42.4%)	736,409 (42.5%)	437 (13.7%)
Female	1,000,055 (57.6%)	997,306 (57.5%)	2749 (86.3%)
Race/Ethnicity, *n* (%)			
White	1,496,285 (86.1%)	1,493,439 (86.1%)	2846 (89.3%)
Black	142,616 (8.2%)	142,457 (8.2%)	159 (5.0%)
Other/unknown	98,000 (5.6%)	97,819 (5.6%)	181 (5.7%)
Charlson–Romano comorbidity score, mean (SD)	1.61 (2.39)	1.61 (2.39)	1.53 (2.07)
Charlson–Romano Score			
0	912,956 (52.6%)	911,437 (52.6%)	1519 (47.7%)
1	174,822 (10.1%)	174,448 (10.1%)	374 (11.7%)
≥ 2	649,123 (37.4%)	647,830 (37.4%)	1293 (40.6%)
Charlson–Romano comorbidities			
Myocardial Infarction	69,171 (4.0%)	69,078 (4.0%)	93 (2.9%)
Heart Failure	204,462 (11.8%)	204,149 (11.8%)	313 (9.8%)
Peripheral vascular disease	170,037 (9.8%)	169,715 (9.8%)	322 (10.1%)
Cerebrovascular disease	169,866 (9.8%)	169,529 (9.8%)	337 (10.6%)
Dementia	78,417 (4.5%)	78,371 (4.5%)	46 (1.4%)
Chronic pulmonary disease	271,864 (15.7%)	271,236 (15.6%)	628 (19.7%)
Connective tissue disease	47,976 (2.8%)	47,303 (2.7%)	673 (21.1%)
Peptic ulcer disease	32,971 (1.9%)	32,883 (1.9%)	88 (2.8%)
Mild liver disease	8549 (0.49%)	8505 (0.49%)	44 (1.4%)
Diabetes	321,696 (18.5%)	321,178 (18.5%)	518 (16.3%)
Diabetes with end organ damage	95,095 (5.5%)	94,929 (5.5%)	166 (5.2%)
Hemiplegia	14,426 (0.83%)	14,417 (0.83%)	9 (0.28%)
Renal failure/disease	59,890 (3.4%)	59,791 (3.4%)	99 (3.1%)
Any tumor leukemia lymphoma	175,193 (10.1%)	174,849 (10.1%)	344 (10.8%)
Moderate or severe liver disease	2009 (0.12%)	2005 (0.12%)	4 (0.13%)
Metastatic cancer	18,045 (1.0%)	18,018 (1.0%)	27 (0.85%)
AIDS	554 (0.03%)	553 (0.03%)	1 (0.03%)
Hypertension	840,038 (48.4%)	838,217 (48.3%)	1821 (57.2%)
Hyperlipidemia	605,238 (34.8%)	603,798 (34.8%)	1440 (45.2%)
Coronary artery disease	306,049 (17.6%)	305,491 (17.6%)	558 (17.5%)

SD: standard deviation.
[a] Met eligibility criteria and did not have SS in the baseline 365-day period.

Table 2
Multivariable-adjusted association of gout and select risk factors with Incident Sjogren's Syndrome (SS).

	Multivariable-adjusted[a] (Model 1) HR (95% CI)	Multivariable-adjusted[a] (Model 2) HR (95% CI)	Multivariable-adjusted[a] (Model 3) HR (95% CI)
Age (in years)			
65 – < 75	Ref	Ref	Ref
75 – < 85	0.77 (0.72, 0.83)[b]	0.76 (0.70, 0.82)[b]	0.74 (0.69, 0.80)[b]
≥ 85	0.41 (0.35, 0.48)[b]	0.40 (0.34, 0.47)[b]	0.43 (0.37, 0.51)[b]
Gender			
Male	Ref	Ref	Ref
Female	5.02 (4.53, 5.55)[b]	5.03 (4.54, 5.57)[b]	4.43 (4.00, 4.92)[b]
Race			
White	Ref	Ref	Ref
Black	0.55 (0.47, 0.64)[b]	0.55 (0.47, 0.64)[b]	0.58 (0.50, 0.68)[b]
Other	0.96 (0.83, 1.12)	0.97 (0.84, 1.13)	1.02 (0.88, 1.19)
Charlson–Romano Score, per unit change	1.09 (1.08, 1.11)[b]	N/A	N/A
Charlson–Romano Score	N/A		N/A
0		Ref	
1		1.44 (1.29, 1.62)[b]	
≥ 2		1.70 (1.58, 1.84)[b]	
Gout	1.73 (1.45, 2.06)	1.70 (1.43, 2.02)[b]	1.48 (1.25, 1.77)[b]

N/A: not applicable; HR: hazard ratio; CI: confidence interval; Ref: referent category.
[a] Model 1 included Charlson–Romano score as a continuous variable; model 2 replaced it with categorized Charlson–Romano score; and Model 3 replaced it with each of the 17 Charlson–Romano comorbidities (including connective tissue disease) plus hypertension, hyperlipidemia and coronary artery disease. All models were also adjusted for medications for cardiovascular diseases (statins, beta-blockers, diuretics, ACE-inhibitors) and for gout (allopurinol, febuxostat).
[b] $P < 0.0001$.

4. Discussion

In a study of elderly Americans who are Medicare recipients, gout was independently associated with a 1.7-fold higher risk of incident SS, after adjusting for demographics, comorbidity and the use of common medications, a novel finding to our knowledge. The multivariable-adjusted hazard ratios of SS associated with gout were independent of all other factors included in each multivariable

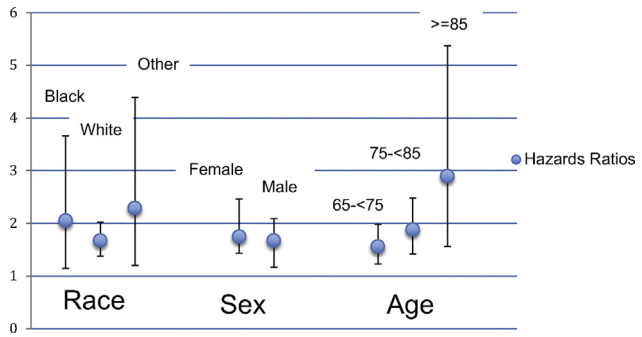

Fig. 1. Association of gout with incident SS in subgroups by race, gender, and age. Point estimate for hazard ratios of the association of gout with incident SS are indicated by filled circles for each variable category, and the whiskers represent the 95% confidence intervals. Hazards ratio are statistically non-significant when the 95% confidence interval includes the hazard ratio of 1.0 on the y-axis, i.e., no effect. P-values for interaction terms were all non-significant and were as follows: Gout*age *P*-value = 0.56; Gout*sex *P*-value = 0.97; Gout*race *P*-value = 0.77.

model. For example, model 3 that included each Charlson–Romano comorbidity (including connective tissue diseases). The relationship between baseline gout and incident SS makes a good case for, but does not imply cause and effect, since common underlying processes might be at work (see details below).

The hallmark of acute flare of gout is NLRP3 inflammasome activation that leads to higher levels of IL-1β and other cytokines [3]. Recent observations show an important role of NLRP3 inflammasome and IL-1β in SS. Experimental studies using the murine dry eye model and human corneal epithelial cells from patients with SS showed the NLRP3 inflammasome activation [5,6]. Clinical studies in SS showed increased IL-1β mRNA and IL-1β levels in patients with SS; organ damage and disease severity in SS was associated with higher IL-1β mRNA and systemic NLRP3 inflammasome activation [16,17]. Patients with SS had increased IL-1β levels in salivary glands and the peripheral blood [7,8]. A salivary gland IL-1/IL- receptor antagonist (IL-1ra) imbalance may promote inflammatory oral lesions in SS levels [18]. IL-1β may be involved in the destruction of salivary glands [19]. Inhibition of IL-1β by anakinra, a recombinant form of the human IL-1ra, was associated with a reduction of dry eye symptoms and corneal epitheliopathy [9] and fatigue [10] in SS, in randomized trials. Our study generates the hypothesis that NLRP3 inflammasome activation, with increased IL-1β activity as one of the key mediators, may underlie this association. It remains to be seen whether gout and SS share the common mechanism of inflammasome activation or other disease pathways related to inflammasome, i.e. IL-1β associated pathways.

The HR of 1.7 for SS associated with gout compares well to that observed for people having 2 or more Charlson index medical comorbidities compared to no comorbidity (also HR of 1.7), indicating that the strength of association with gout was similar to having 2 or more Charlson index medical comorbidities and stronger than that found for an additional Charlson index medical comorbidity. The 10-fold higher risk of SS with rheumatologic conditions (rheumatoid arthritis, lupus, scleroderma, polymyositis or PMR) and 5-fold risk in women vs. men noted in our study is consistent with clinical knowledge and experience and previously published data [2]. Our study provides a better understanding of these risk associations with SS: HR of 1.4 with single medical comorbidity, 1.7 with gout and 7.7 for connective tissue diseases (includes lupus, scleroderma, polymyositis, rheumatoid arthritis, polymyalgia rheumatica). Elderly blacks were half as likely as elderly whites to have SS, which is another novel finding to our knowledge.

Our study has several limitations. An observational study design puts our findings at the risk of confounding bias. We tried to reduce confounding by including several potential confounders in our study, performing sensitivity analyses and controlling for diuretic use, a common medication associated with dry mouth as an adverse event. We attempted to reduce misclassification bias by using validated algorithm of diagnostic codes to identify gout and SS [12–14], but some bias is still possible. Use of many other medications can be associated with dry mouth, which can be misdiagnosed as SS, another study limitation. The misclassification bias would most likely be non-differential, but we do not know the direction of the bias. Other gout algorithms have combined diagnostic codes with ULT prescription. The high rates of ULT discontinuation by patients with gout [20], and the potential confounding by ULT (associated adverse event) by its inclusion in definition (which now measures disease, treatment or both), made this algorithm undesirable. Our study included a large sample size, and a representative population of the U.S. elderly and study findings were robust, replicated in several multivariable-adjusted models. We considered limiting the cohort to those without other autoimmune diseases, but decided in favor of the current cohort-based approach to allow the generalization of our study findings to all older adults with gout.

5. Conclusion

In conclusion, we found that gout was associated with 1.7-fold higher risk of SS in the elderly, independent of other factors. Younger age, female sex, White race and higher medical comorbidity were associated with a higher risk of incident SS. Future studies should explore the common disease mechanisms that underlie this association, including a focus on the inflammasome and pro-inflammatory cytokines such as IL-1ß.

Author contributions

JAS designed the study, developed study protocol, reviewed analyses and wrote the first draft of the paper. JDC performed the data abstraction and data analyses. All authors made revisions to the manuscript, read, and approved the final manuscript.

Consent to publish

No individual person's data were presented in any form in this study and therefore no consent to publish is required.

The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study.

Disclosure of interest

JAS has received research grants from Takeda and Savient pharmaceuticals and consultant fees from Crealta/Horizon, Fidia, UBM LLC, Medscape, WebMD, the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in Amarin pharmaceuticals and Viking therapeutics. JAS is a member of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS served as a member of the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies.

JDC declares that he has no competing interest.

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