Sex differences in gout epidemiology: evaluation and treatment

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Sex differences in gout epidemiology: evaluation and treatment

L R Harrold, R A Yoo, T R Mikuls, S E Andrade, J Davis, J Fuller, K A Chan, D Roblin, M A Raebel, A Von Worley, R Platt, K G Saag

Background: Little is known about the characteristics, evaluation and treatment of women with gout.

Objective: To examine the epidemiological differences and differences in treatment between men and women in a large patient population.

Methods: The data from approximately 1.4 million people who were members of seven managed care plans in the USA for at least 1 year between 1 January 1999 and 31 December 2003 were examined. Adult members who had pharmacy benefits and at least two ambulatory claims specifying a diagnosis of gout were identified. In addition, men and women who were new users of urate-lowering drugs (ULDs) were identified to assess adherence with recommended surveillance of serum urate levels within 6 months of initiating urate-lowering treatment.

Results: A total of 6133 people (4975 men and 1158 women) with two or more International Classification of Disease-9 codes for gout were identified. As compared with men with gout, women were older (mean age 70 (SD 13) v 58 (SD 14), p < 0.001) and had comorbidities and received diuretics more often (77 v 40%; p < 0.001). Only 37% of new users of urate-lowering treatment had appropriate surveillance of serum urate levels post-initiation of urate-lowering treatment. After controlling for age, comorbidities, gout treatments, number of ULD dispensings and health plan, women were more likely (odds ratio 1.36, 95% confidence interval 1.11 to 1.67) to receive the recommended serum urate level testing.

Conclusions: Women with gout were older, had greater comorbidities and more often used diuretics and received appropriate surveillance of serum urate levels, suggesting that the factors leading to gout as well as monitoring of treatment are very different in women and men.

Methods

Setting
The study population included members from seven health plans that are part of the HMO Research Network Center for Education and Research on Therapeutics. The HMO Research Network Center for Education and Research on Therapeutics member organisations include staff, group, network, independent practice association and mixed model HMOs that provided healthcare for approximately 7 million people in more than 1000 practice sites in the year 2000. We chose a representative sample of roughly 200 000 members, from each of the seven HMOs that participated, for inclusion into the dataset. The sampling scheme and demographic distribution of this population have been described elsewhere. The dataset had computerised information on use of clinical characteristics of adults with gout suggests that women with gout tend to be older and have a higher prevalence of comorbid disease. To the best of our knowledge, no population-based studies have examined how the risk factors of gout differ between women and men and whether such differences influence the evaluation and treatment of gout. We hypothesised that although the drug and disease factors contributing to the development of gout differ between women and men, the evaluation and treatment of the condition would be similar.

Abbreviations: CPT, current procedural terminology; HMO, health maintenance organisation; ICD, International Classification of Disease; NSAIDs, non-steroidal anti-inflammatory drugs; ULD, urate-lowering drug
diuretics (thiazide, potassium-sparing, loop and others), using national drug codes for the following drug classes: them. Drug usage was identified by determining dispensings the same CPT code; we were thus unable to differentiate between Aspirations and injections of joints and bursae have the current procedural terminology (CPT) codes (table AII). aspirations and therapeutic injections were ascertained using and synovial fluid analyses, and joint or bursal diagnostic of serum urate levels, 24-h urine tests for uric acid secretion failure (table AI). Laboratory testing, including measurement was used for the subsequent analyses.

Study population and design
We identified members from the dataset who met the criteria for enrolment into the “gout cohort”. Criteria for inclusion in the gout cohort were as follows: >=19 years of age at the time of the first gout diagnosis, two or more ambulatory visits at least 30 days apart associated with an International Classification of Disease-9 (ICD-9) code for a gout diagnosis (ICD-9 codes 274.0, 274.1, 274.8, 274.9) and continuous enrolment in the health plan with drug coverage during the period 6 months before and 12 months after the first gout diagnosis. Risk factors for gout (comorbidities and diuretic use) and relevant laboratory testing and treatments were identified during this period using the claims data. Age, as of first gout diagnosis, and sex were ascertained from the demographic data. From the gout cohort, we identified new users of ULDs. A new user was defined as a cohort member who received no dispensing of a ULD (allopurinol, probenecid or sulfinpyrazone) during the 6 months before the gout diagnosis but was subsequently dispensed a ULD. In this subset of gout patients, the same demographic and healthcare usage information was gathered as described above during the period 6 months before and 6 months after the first dispensing of a ULD. Age at the time of the first dispensing of ULD was used for the subsequent analyses. We ascertained the presence of comorbidities from the ICD-9 diagnosis codes associated with ambulatory care. Comorbidities of interest included coronary heart disease, diabetes mellitus, dyslipidaemia, hypertension, nephrolithiasis, peripheral arterial disease, renal insufficiency and renal failure (table AI). Laboratory testing, including measurement of serum urate levels, 24-h urine tests for uric acid secretion and synovial fluid analyses, and joint or bursal diagnostic aspirations and therapeutic injections were ascertained using current procedural terminology (CPT) codes (table AII). Aspirations and injections of joints and bursae have the same CPT code; we were thus unable to differentiate between them. Drug usage was identified by determining dispensings using national drug codes for the following drug classes: diuretics (thiazide, potassium-sparing, loop and others), non-acetylated salicylates, both cyclooxygenase selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, colchicine, uricosuric drugs, allopurinol and glucocorticoids. Analyses Differences between men and women were evaluated using t test or the Wilcoxon rank sum test for continuous variables and \( \chi^2 \) test or Fisher’s exact test for categorical variables. Differences between women and men in the evaluation and treatment of gout were assessed using multivariable logistic regression, adjusting for age, total number of encounters with a gout diagnosis, comorbidities, use of diuretics and health plan. Odds ratio (OR) and 95% confidence intervals (CI) were estimated. We also compared new users of ULDs who received serum urate monitoring within 6 months after initiating treatment with those who did not, for demographic characteristics (including age and sex), comorbidities, use of diuretics and treatment practices. The 6-month time frame for serum urate monitoring after initiation of a ULD was chosen based on the gout quality-of-care indicators developed by Mikuls et al.\textsuperscript{20} Multivariable logistic regression was used to assess the strength of association between sex and receipt of the recommended surveillance of serum urate levels. We controlled for number of encounters associated with a gout diagnosis, as women may be more likely to receive laboratory monitoring because they had more healthcare encounters for gout than men. OR and 95% CI were estimated. Analyses were conducted using SAS V.9.1. Results Table 1 shows the characteristics of the study population. As compared with men with gout, women with gout were older and more often had hypertension, dyslipidaemia, coronary heart disease, diabetes mellitus, peripheral arterial disease, renal insufficiency and renal failure. Use of diuretics was almost twofold greater in women than in men (thiazide diuretics 35% vs 30%; p < 0.001 and any diuretic 77% vs 40%, p < 0.001). The proportion of women with gout who had serum urate levels tested during the period under study was similar to that observed in men (table 2); however, after controlling for age, number of encounters with a gout diagnosis, comorbidities, use of diuretics and health plan, women were more likely to have this test carried out. Although 24-h urine tests for uric acid excretion were carried out in a minority of patients, after multivariable adjustment

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of the study population*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Total</td>
</tr>
<tr>
<td>Age (mean years)</td>
</tr>
<tr>
<td>Mean and median number of</td>
</tr>
<tr>
<td>encounters for gout</td>
</tr>
<tr>
<td>Gout-associated comorbidities</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Drugs that can trigger or</td>
</tr>
<tr>
<td>exacerbate gout (receipt of &gt;1</td>
</tr>
<tr>
<td>prescription)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>All diuretics</td>
</tr>
</tbody>
</table>

* p Values represent comparisons between men and women for the variables listed.
women were more likely to undergo this test. In adjusted analyses, women were less likely to have synovial fluid cell counts and synovial crystal analysis carried out, but no less likely to receive diagnostic aspirations and therapeutic injections. Women were considerably more likely than men to receive cyclo-oxygenase selective NSAIDs, non-acylated salicylates, narcotics and glucocorticoids (table 3). Interestingly, the proportion of men and women who received allopurinol was identical (56%). However, after accounting for confounding variables, women were considerably less likely to receive this drug.

Only 37% of new users of ULDs had serum urate levels assessed within 6 months of starting a ULD. Even among people who received six or more dispensings of a ULD in the 6-month period under study, only 45% received the recommended surveillance. After controlling for age, comorbidities, treatments for gout, number of visits associated with a diagnosis of gout, number of ULD dispensings and health plan, women were more likely (OR 1.36, 95% CI 1.11 to 1.67) to receive surveillance of serum urate levels (table 4).

DISCUSSION
Our study is the first to examine, from a population-based perspective, sex differences in the population characteristics, evaluation and treatment of gout. The differences between women and men with gout are striking, as the women are about a decade older, have more associated comorbidities and are more likely to be taking diuretics. Over the past 20 years there have been only four small studies specifically examining sex differences in clinical characteristics of gout, none of which were population based.1721 Lally et al in 1991 compared the clinical features of 37 women with gout with 2002 men with gout. Here again, the women developed gout at a later age, had more associated comorbidities and received diuretics more often. Both Meyers and Monteagudo21 and DeSouza et al examined the medical records of women and men with gout and found that women were more likely to have tophi or polyarticular disease at presentation and upper extremity joint involvement, suggesting potentially that in women the diagnosis of gout may be delayed or the condition may be confused with other forms of arthritis.

Our findings as well as those of others31721 indicate that the risk factors for gout in women are different from those in men. For example, renal disease and receipt of diuretics, both of which predispose to gout, were more common in women. Current recommendations calling for the use of thiazide diuretics as the preferred treatment for hypertension15 may have important implications in terms of gout frequency, particularly among older women. Hypertension, also an independent risk factor for hyperuricaemia and gout, is more common in women >50 years than in men of the same age.16

It was surprising that after adjustment for age, comorbidities and use of diuretics, women were less likely to receive allopurinol than men. In addition, it was interesting that women in our study received glucocorticoids and narcotics more often than men, possibly suggesting they had more severe episodes, greater chronicity to their gout or intolerance to other gout treatments; however, these drugs are not specific for gout and could have been used for other conditions. Further investigation into the management of gout in women and men is needed to assess whether treatment differences reflect appropriate care based on differences in the clinical spectrum of gout.

As shown in our study, substantial proportions of people who initiate treatment with ULDs do not receive surveillance of serum urate levels after initiation of the drug.

### Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Men</th>
<th>Women</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urate</td>
<td>3327 (67%)</td>
<td>795 (69%)</td>
<td>1.09 (0.95 to 1.25)</td>
<td>1.20 (1.02 to 1.40)</td>
</tr>
<tr>
<td>24-h urine for uric acid excretion</td>
<td>245 (5)</td>
<td>67 (6)</td>
<td>1.19 (0.90 to 1.57)</td>
<td>1.40 (1.04 to 1.90)</td>
</tr>
<tr>
<td>Synovial fluid cell count</td>
<td>226 (5)</td>
<td>34 (3)</td>
<td>0.64 (0.44 to 0.92)</td>
<td>0.56 (0.38 to 0.83)</td>
</tr>
<tr>
<td>Synovial crystal analysis</td>
<td>245 (5)</td>
<td>32 (2)</td>
<td>0.56 (0.38 to 0.80)</td>
<td>0.49 (0.34 to 0.72)</td>
</tr>
<tr>
<td>Diagnostic aspirations or therapeutic joint or bursal injections</td>
<td>771 (15)</td>
<td>217 (19)</td>
<td>1.26 (1.07 to 1.49)</td>
<td>1.10 (0.91 to 1.32)</td>
</tr>
</tbody>
</table>

*Adjusted for age, number of encounters with a gout diagnosis, gout-associated comorbidities (including hypertension, dyslipidaemia, coronary heart disease, peripheral arterial disease, diabetes mellitus, nephrolithiasis, renal insufficiency and renal failure), use of diuretics and health plan.

### Table 3

<table>
<thead>
<tr>
<th>Treatments for gout (receipt of ≥1 prescription of the following)</th>
<th>Men</th>
<th>Women</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective NSAID</td>
<td>3791 (76%)</td>
<td>798 (69%)</td>
<td>0.69 (0.60 to 0.80)</td>
<td>0.95 (0.80 to 1.11)</td>
</tr>
<tr>
<td>Selective NSAID</td>
<td>249 (5)</td>
<td>111 (10)</td>
<td>2.01 (1.59 to 2.54)</td>
<td>1.68 (1.29 to 2.18)</td>
</tr>
<tr>
<td>Non-acylated salicylates</td>
<td>191 (4)</td>
<td>114 (10)</td>
<td>2.74 (2.15 to 3.48)</td>
<td>1.99 (1.54 to 2.58)</td>
</tr>
<tr>
<td>Narcotics</td>
<td>2336 (47)</td>
<td>698 (60)</td>
<td>1.71 (1.50 to 1.95)</td>
<td>1.44 (1.24 to 1.67)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>2203 (44)</td>
<td>567 (49)</td>
<td>1.21 (1.06 to 1.37)</td>
<td>1.07 (0.93 to 1.24)</td>
</tr>
<tr>
<td>Uricosuric drug</td>
<td>201 (4)</td>
<td>57 (5)</td>
<td>1.23 (0.91 to 1.66)</td>
<td>1.16 (0.84 to 1.61)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>2792 (56)</td>
<td>647 (56)</td>
<td>0.99 (0.87 to 1.13)</td>
<td>0.78 (0.67 to 0.90)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>1631 (33)</td>
<td>488 (42)</td>
<td>1.49 (1.31 to 1.70)</td>
<td>1.30 (1.12 to 1.50)</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug.

*Adjusted for age, number of encounters with a gout diagnosis, gout-associated comorbidities (including hypertension, dyslipidaemia, coronary heart disease, peripheral arterial disease, diabetes mellitus, nephrolithiasis, renal insufficiency and renal failure), use of diuretics and health plan.
Interestingly, women were more likely than men to receive appropriate monitoring after controlling for age, comorbidities, gout treatments, number of ULD dispensings and health plan. Although beyond the scope of this study, potential reasons for these differences could include greater vigilance by doctors when treating women with gout owing to a greater number of associated comorbidities and associated drugs, more overall healthcare encounters by women resulting in greater opportunities for monitoring, or better adherence by women with physician recommendations. Because we cannot account for serum urate tests ordered but not carried out, it is not possible to separate physician non-adherence with ordering a recommended laboratory test from patient non-adherence with obtaining the test.

An important strength of this study is that it includes a large population of patients with two or more diagnoses of gout at least 30 days apart, thus increasing the likelihood that these people were truly considered to have gout by the treating doctor. In addition, the patient sample is derived from seven health plans across the USA and thus includes a diversity of people. Limitations include lack of validation of diagnostic and procedure claims data, although any bias that occurred would be non-differential between women and men. In addition, we cannot verify that the drugs examined were prescribed for gout. We were unable to assess the clinical implications of adherence and non-adherence with the recommended surveillance of serum urate levels in terms of provider response to serum urate levels, efficacy of urate-lowering treatment and clinical outcomes. Lastly, our results may not be generalisable to other health plans or other systems of healthcare delivery. At a minimum, these results are probably generalisable to at least 1 in 4 (24.6%) residents in the USA who are enrolled in HMOs.

In summary, this is the first population-based study examining sex differences in gout epidemiology, evaluation and treatment. The characteristics of women and men with gout are strikingly different, suggesting different risk factors for the condition. Nonetheless, women were less likely to receive allopurinol after controlling for confounders using multivariable logistic regression. Lastly, women with gout were also more likely to receive the recommended surveillance of serum urate levels within the first 6 months after ULD initiation. This work suggests further investigation into quality of care for gout to ensure that both women and men with gout receive the recommended evaluation and treatment.

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