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Sex Differences in the Clinical Profile Among Patients With Gout: Cross-sectional Analyses of an Observational Study

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ABSTRACT. ***Objective***. Research findings in gout result predominantly from studies about men and might not be generalizable to women. To improve insight into sex differences in gout, our study compared clinical characteristics and comorbidities of female and male patients with gout, and explored the influence of menopause on these differences.

Methods. Data from patients referred to 2 rheumatology clinics and diagnosed with gout were used. Clinical characteristics and comorbidities of each sex were compared univariately. Sex difference in comorbidities were further explored in multivariate logistic regression analyses adjusting for age, BMI, smoking, and alcohol consumption in both the total group and in those with gout onset ≥ 55 years (as a surrogate for menopausal state).

Results. There were 954 patients, including 793 (83%) men, included. Women were on average older (65 vs 62 yrs), were more often obese (54% vs 36%), had a higher serum uric acid (sUA) level (0.53 vs 0.49 mmol/L), used diuretics more often (60% vs 30%), and consumed alcohol less frequently (47% vs 72%). Additionally, women more frequently had reduced renal function (64% vs 31%), hypertension (78% vs 56%), heart failure (23% vs 12%), and type 2 diabetes (39% vs 17%; all $P < 0.05$). In those with gout onset ≥ 55 years, differences in comorbidities were less pronounced and disappeared after adjusting for lifestyle.

Conclusion. Our study confirmed sex differences in clinical characteristics and comorbidities among newly diagnosed patients with gout, and revealed that sex differences in comorbidities among those with gout onset beyond the age of female menopause were strongly attenuated and fully explained by lifestyle.

Key Indexing Terms: age of onset, comorbidity, gout, sex, uric acid

Gout, the most common type of inflammatory arthritis, is a predominantly male disease[1]. Among patients with gout ≤ 65 years, the prevalence in men is 4-times higher than in women[2]. Above this age, the prevalence of gout narrows to a more equal sex distribution, especially due to the sharp increase in the incidence of gout among older women[3,4]. Despite the increasing prevalence of gout, particularly in the aging female population, most studies are performed on predominantly male populations and few studies examine the differences between sexes[4,5,6,7].

There are a number of potential biological pathways explaining sex differences in the occurrence of gout, and most evidence points to the role of the uricosuric effect of estrogen[8,9,10,11]. The uricosuric effect of estrogen was initially emphasized by epidemiological research, showing an increase in serum uric acid (sUA) levels among postmenopausal women[12,13,14]. Previously, a study of patients undergoing male-to-female gender reassignment demonstrated that estrogen therapy reduced sUA concentrations and increased urinary uric acid (UA) excretion[8,10]. Apart from estrogen, other sex-specific differences on the effect of genetic variants on sUA levels have been found. In a study on gout risk with a large population of European ancestry, a gene-sex interaction was identified for *ABCG2*, a unidirectional secretory urate transporter in the proximal renal tubule[15], and PDZK1, a key regulatory protein for several secretory urate transporters[16,17], with a greater influence on sUA in men than in women. In addition, *SLC2A9*, encoding the GLUT9 protein and facilitating reabsorption of urate, explains approximately 3% of the effect of variance in urate levels. Although *SLC2A9* has a stronger effect on sUA in women, it would not explain differences in the occurrence of gout between men and women[16,17,18,19]. Overall, gene-sex interactions suggest a greater influence of secretory urate transporters on sUA and gout risk in men, yet the overall effect size on sUA levels and on the occurrence of gout remains unclear.

In addition to the biological pathways explaining sex differences in hyperuricemia and the onset of gout, differences in risk factors and clinical manifestations also require attention[20,21].

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A systematic literature review of 9 (mainly small) studies on differences between male and female patients with gout[3], completed by 2 previous gout cohort studies[22,23], consistently showed that female patients with gout tend to be older, have lower levels of alcohol consumption, have a higher BMI, and are prescribed diuretics more often. Compared to male patients with gout, women also more commonly presented with a polyarticular pattern, and suffered more frequently from common gout-related comorbidities, such as hypertension (HTN), type 2 diabetes mellitus (T2DM), osteoarthritis, and renal insufficiency[13,22,23,24,25,26]. However, none of these studies explored sex-specific differences in excretion of urate, which is especially important considering the existing evidence on the uricosuric effect of estrogen. Further, none of these studies investigated the effect of onset of gout ≥ 55 years (when the protective effect of estrogen disappears, since by age 55 almost all women have gone through menopause) on sex differences in clinical manifestations[27]. It would be expected that the clinical profile of gout with regard to risk factors and comorbidities would become more comparable between sexes in this age group[28].

The objectives of this study were therefore first, to add data on the clinical differences between female and male patients with newly diagnosed gout, and second, to explore the role of gout onset ≥ 55 years to represent the disappearance of the protective effect of estrogen. We expected to confirm previously reported sex differences and hypothesized that (1) the differences in clinical characteristics and comorbidities between sexes would be strongly reduced in those with a first gout flare ≥ 55 years, and (2) that no difference in urinary UA excretion would be present between male and female patients with gout ≥ 55 years.

MATERIALS AND METHODS

Study sample. New patients referred to 1 of 2 regional nonacademic rheumatology outpatient clinics in the Netherlands and diagnosed with gout were considered for this cross-sectional study. Sample A included patients at Clinic A between January 2015 and October 2017 and Sample B included patients at Clinic B between July 2011 and May 2016. All patients were diagnosed using the American College of Rheumatology/European League Against Rheumatism gout classification criteria, and most patients had monosodium urate (MSU) crystal-proven gout[29]. Patients could have been referred by either the primary care physician or other specialists within the hospital. Our study was approved by the ethical committee at the hospital of Sample A (METC 16-4-032.1). Ethical approval for this type of study was not required according the policy of the hospital of Sample B. All patients provided written informed consent.

Data collection. Data collected at the first visit comprised demographics (age, sex); lifestyle factors [BMI (with BMI ≥ 30 kg/m^2 being obese), current smoking status (yes/no; Sample B only), and current alcohol consumption (yes/no; Sample B only)]; date of first gout flare (Sample B only); the presence of tophi in clinical examination (yes/no); use of specific medication types (diuretics, colchicine prophylaxis for gout, and sUA-lowering drugs); laboratory tests [UA and creatinine concentration in serum and spot urine (Sample A only)]; and comorbidities confirmed by rheumatologists [HTN, peripheral arterial disease, cerebrovascular accident, myocardial infarction, heart failure, heart arrhythmia, dyslipidemia, T2DM, nephrolithiasis, and hepatic steatosis (all yes/no answers)]. Laboratory tests were used to calculate renal function and fractional excretion of uric acid (FEUa). Renal function is presented as the estimated glomerular filtration rate (eGFR) and was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[30]. The FEUa was only available for Sample A and was calculated using the following equation: (urinary UA × serum creatinine) ÷ (sUA x urinary creatinine). The FEUa represents the percentage of sUA filtered in the kidneys and distinguishes underexcretors (FEUa < 4.0%) from overproducers[31]. Among healthy subjects, average FEUa ranges from 6% to 8%, whereas patients with gout have generally an average FEUa of 3–5%[31,32]. Since the UA urine-plasma ratio will increase significantly with the use of a uricosuric (e.g., benzbromarone) and is independent of the use of a xanthine oxidase inhibitor (e.g., allopurinol or febuxostat), FEUa was not calculated for the patients treated with uricosurics[31].

Statistical analyses. Univariable comparisons of clinical characteristics and comorbidities between women and men were performed using independent *t*-tests for continuous and normally distributed variables and chi-square test for categorical variables. In the sample comprising data on age of gout onset (Sample B), logistic regression was performed to explore the adjusted role of sex (female compared to male) on the presence of comorbidities and clinical characteristics, first in the total sample and then in those with gout onset ≥ 55 years (representing postmenopausal women). Multivariate regression analyses were limited to comorbidities and clinical characteristics that were significantly ($P < 0.05$) associated with sex in univariate analyses. Potential confounders were defined *a priori* based on plausibility, and comprised age (Model 1) and lifestyle factors [i.e., smoking, alcohol consumption and BMI (if obesity was not the outcome); Model 2]. In the sample comprising laboratory data of spot urine (Sample A), the FEUa was compared between sexes among patients ≥ 55 years. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp). A P value < 0.05 (2-tailed) was considered to be statistically significant.

RESULTS

Sex differences in clinical characteristics in the total sample. In the total sample, 954 patients with gout were included, of which 161 (17%) were female and 793 (83%) were male (Figure 1). Clinical characteristics of female and male patients for the total sample are shown in Table 1, and for Samples A (n = 255) and B (n = 699) in Supplementary Table 1 (available with the online version of this article). In the total sample, some relevant and significant differences between sexes were found: women were 2.6 years older than men, had a 2.2 kg/m^2 higher BMI with a 2.09-times higher prevalence of obesity (95% CI 1.47–2.98), and used diuretics 3.51-times more frequently (95% CI 2.48–4.99; Table 1 and Supplementary Table 2). sUA level was 0.04 mmol/L higher in women ($P < 0.001$), and no differences in the presence of tophi were seen (95% CI 0.76–1.68) between sexes. Women also had a significantly higher prevalence of comorbidities, including a 2.76-times higher prevalence of HTN (95% CI 1.86–4.10), a 2.30-times higher prevalence of heart failure (95% CI 1.50–3.53), a 3.11-times higher prevalence of T2DM (95% CI 2.15–4.48), and an eGFR 14.9 mL/min/1.73 m^2 lower than men (all $P < 0.05$; Supplementary Table 2). Additional logistic regression (Model 1) revealed that the differences between sexes on (significantly different) comorbidities and clinical characteristics could not be explained by age (Supplementary Table 2).

Sex differences in comorbidities and clinical characteristics in patients with gout onset ≥ 55 years (Sample B). When exploring the effect of postmenopausal status on clinical characteristics in Sample B, the age of the first gout flare was available for 484 (69%) patients, with 259 having had their first gout flare ≥ 55

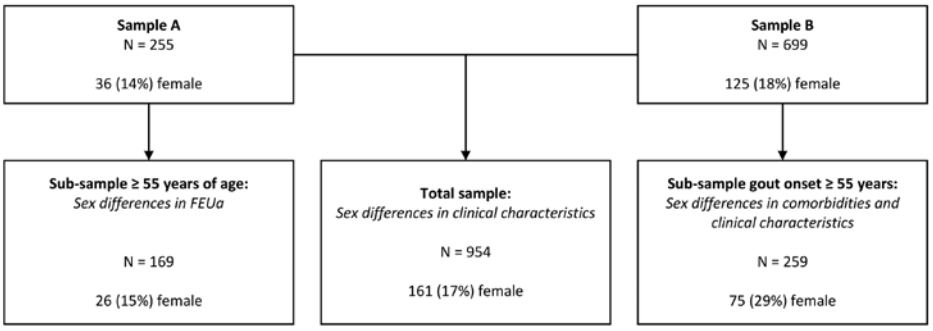

Figure 1. Flowchart of the study and data analyses. FEUa: fractional excretion of uric acid.

Table 1. Baseline characteristics of female and male patients with gout (total sample).

Variable	Females, n = 161	Males, n = 793	*P*
Age, yrs, mean (SD)	64.9 (14.9)	62.3 (13.0)	0.04
BMI, kg/m^2, mean (SD)	31.1 (7.4)	28.9 (4.9)	0.001
< 25 kg/m^2	29 (19.2)	125 (16.6)	
25–29.9 kg/m^2	40 (26.5)	357 (47.3)	
≥ 30 kg/m^2	82 (54.3)	273 (36.2)	
Tophi	40 (25.0)	180 (22.7)	0.53
MSU crystal-proven	142 (93.4)	688 (90.8)	0.29
sUA, mmol/L mean (SD)	0.53 (0.13)	0.49 (0.11)	< 0.001
Current smoking[a]	17 (13.9)	100 (18.1)	0.23
Alcohol consumption[a]	57 (47.1)	400 (71.9)	< 0.001
Comorbidities			
Hypertension	125 (77.6)	442 (55.7)	< 0.001
Peripheral arterial disease	9 (5.6)	61 (7.7)	0.35
CVA	16 (9.9)	50 (6.3)	0.10
MI	20 (12.4)	118 (14.9)	0.42
Heart failure	37 (23.0)	91 (11.5)	< 0.001
Heart arrhythmia	36 (22.4)	141 (17.8)	0.17
Dyslipidaemia	41 (25.5)	168 (21.2)	0.23
T2DM	63 (39.1)	136 (17.2)	< 0.001
Nephrolithiasis	15 (9.3)	65 (8.2)	0.64
Hepatic steatosis	24 (14.9)	85 (10.7)	0.13
eGFR, mL/min per 1.73 m^2, mean (SD)	58.3 (66.3)	73.2 (30.7)	< 0.001
eGFR < 60 mL/min per 1.73 m^2	100 (64.1)	237 (30.6)	< 0.001
Diuretic use	97 (60.2)	239 (30.1)	< 0.001

Values are presented as n (%) unless otherwise stated. [a] Data only available in Sample B. CVA: cerebrovascular accident; T2DM: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; MSU: monosodium urate; sUA: serum uric acid.

years [75 (29%) women and 184 (71%) men; Table 2]. The sex differences in the group of patients without age of onset available (n = 215) were comparable to the sex differences in those with age of onset available (n = 484), except for a lower prevalence of tophi among men with missing date of gout onset. In patients with gout onset ≥ 55 years, women were 3.0 years older and their sUA levels were almost comparable to men with gout onset ≥ 55 years. Further, 0.61-times fewer women with gout onset ≥ 55 were smokers (95% CI 0.24–1.56). Women were 0.38-times less likely to consume alcohol (95% CI 0.22–0.67) and had a 2.4 kg/m^2 higher BMI compared to men with gout onset ≥ 55 years (Supplementary Table 3, available with the online version of this article). Multivariate regression analysis of sex on comorbidities and clinical characteristics (Table 2) revealed that the age-adjusted association between sex and outcomes (Model 1) was clearly lower among patients with gout onset ≥ 55 years when compared to the total group, and only significant for T2DM, diuretic use, and obesity (Table 2). When adjusting additionally for lifestyle factors (Model 2), the strength of association decreased in both groups (decrease of coefficient between 8–22% in the total group and between 15–28% in the subsample with gout onset ≥ 55 years) and became insignificant for all outcomes in those with gout onset ≥ 55 years, except for the association between female sex and obesity (Table 2).

Sex differences in FEUa in patients ≥ 55 years (Sample A). When exploring FEUa among male and female patients ≥ 55 years in Sample A, data were available for 169 (66%) patients, including 26 (15%) female and 143 (85%) male subjects (Table 3). Two female patients and 1 male patient with extremely high FEUa (≥ 10%) were excluded, as this was likely due to unusual contextual effects on UA excretion. Average FEUa in Sample A was similar between women and men [4.6% (1.9) vs 4.4% (1.5); *P* = 0.51]. Notwithstanding, women ≥ 55 years [n = 9 (35%)] were somewhat less frequently underexcretors compared to males ≥ 55 years [n = 64 (45%); *P* = 0.34). When including the 3 outliers, results were comparable.

DISCUSSION

Our study confirms that female patients referred to a rheumatologist and diagnosed with gout differ significantly from male patients. On a homogeneous group level, the female patient is older, has a higher BMI with increased prevalence of obesity, is prescribed diuretics more often, less frequently consumes alcohol, has a higher sUA level at presentation, and has more frequent comorbidities, such as HTN, heart failure, T2DM, and advanced renal insufficiency. In those with gout onset ≥ 55 years, sex differences in comorbidities were strongly attenuated, while lifestyle factors continued to play a relevant role in explaining sex differences.

When comparing our results with those of 11 previously published studies on sex differences in patients with

Table 2. Uni- and multivariate logistic regressions presenting the influence of sex (female vs male) on comorbidities and clinical characteristics in the subsample with date of gout onset and lifestyle factors available (Sample B).

	Descriptive Data		Univariable Association		Multivariable Model 1[a]		Multivariable Model 2[b]	
	Females, n (%)	Males, n (%)	OR	95% CI	OR	95% CI	OR	95% CI
Total group	n = 87	n = 397	n = 484		n = 484		n = 484	
Comorbidities, n (%)								
Hypertension	70 (80.5)	248 (62.5)	2.47	1.40–4.36	2.46	1.39–4.34	2.10	1.15–3.83
Heart failure	24 (27.6)	50 (12.6)	2.64	1.52–4.61	2.67	1.53–4.66	2.14	1.17–3.92
T2DM	30 (34.5)	61 (15.4)	2.90	1.72–4.87	2.99	1.78–5.04	2.33	1.34–4.08
eGFR < 60 mL/ min per 1.73 m^2	50 (60.2)	107 (27.6)	3.98	2.43–6.51	4.10	2.49–6.75	3.77	2.21–6.43
Clinical characteristics, n (%)								
Diuretic use	57 (65.5)	144 (36.3)	3.34	2.05–5.43	3.46	2.11–5.68	2.79	1.67–4.68
Obesity	48 (55.2)	154 (39.4)	1.89	1.19–3.03	1.95	1.21–3.12	1.94	1.19–3.18
Gout onset ≥ 55 yrs	n = 75	n = 184	n = 259		n = 259		n = 259	
Comorbidities, n (%)								
Hypertension	61 (81.3)	137 (74.5)	1.50	0.77–2.92	1.48	0.75–2.92	1.12	0.54–2.35
Heart failure	22 (29.3)	35 (19.0)	1.77	0.95–3.28	1.62	0.86–3.04	1.30	0.65–2.60
T2DM	29 (38.7)	34 (18.5)	2.78	1.53–5.05	2.69	1.47–4.91	2.05	1.06–3.97
eGFR < 60 mL/ min per 1.73 m^2	46 (64.8)	86 (47.8)	2.01	1.14–3.55	1.63	0.89–3.00	1.39	0.72–2.66
Clinical characteristics, n (%)								
Diuretic use	53 (70.7)	98 (53.5)	2.11	1.19–3.76	1.99	1.11–3.56	1.43	0.77–2.67
Obesity	43 (57.3)	67 (36.6)	2.33	1.35–4.02	2.83	1.59–5.04	2.77	1.53–5.03

[a] Multivariable Model 1 includes age. [b] Multivariable Model 2 includes age, BMI (where appropriate), smoking, and alcohol consumption. eGFR: estimated glomerular filtrate rate; T2DM: type 2 diabetes mellitus.

Table 3. Biochemical gout characteristics of the female and male patients with gout older than 55 years (Sample A).

	Females, n = 26	Males, n = 143	*P*
sUA, mmol/L	0.46 (0.13)	0.45 (0.12)	0.73
Urinary UA	1.5 (1.1)	1.8 (1.2)	0.29
Serum creatinine	108.6 (38.9)	121.7 (51.1)	0.21
Urinary creatinine	71.1 (45.4)	97.8 (66.6)	0.05
eGFR, mL/min per 1.73 m^2	49.8 (20.1)	59.2 (20.7)	0.04
FEUa, %	4.6 (1.9)	4.4 (1.5)	0.51
< 4.0, n (%)	9 (34.6)	64 (44.8)	0.34
≥ 4.0, n (%)	17 (65.4)	79 (55.2)	

Values are presented as mean (SD) unless otherwise stated. eGFR: estimated glomerular filtrate rate; FEUa: fractional excretion of uric acid; sUA: serum uric acid; UA: uric acid.

gout[1,5,12,13,22,23,33–37] (Table 4), our findings support evidence that women with gout are on average older (7/10 studies)[1,12,13,22,23,33–37]; more often suffer from renal insufficiency (6/9 studies)[1,12,13,22,23,33-36], obesity (3/4 studies)[5,13,22,23], and HTN (6/10 studies)[1,12,13,22,23,33–37]; used diuretics more frequently (8/9 studies)[1,5,12,13,22,23,33,34,37]; and were less likely to heavily consume alcohol (7/8 studies)[5,12,13,22,23,33,34,37]. Further, no sex differences were noted in the presence of tophi (5/6 studies)[12,13,22,33,34,35], while findings on articular manifestations were conflicting. In our study, we used age of onset ≥ 55 years to represent postmenopausal women in order to explore the role of estrogen on gout characteristics. The mean age of menopause in western European women is 51 years of age, and therefore almost all women above 55 years are postmenopausal[27]. We demonstrated first that age of onset ≥ 55 years attenuated the sex differences in comorbidities. Our results therefore suggest that < 55 years, women are protected by estrogen against the effect of classic gout risk factors, such as decreased renal function, HTN, heart failure, and frequency of alcohol consumption. Notably, independent of age of onset, lifestyle factors always played a role in sex differences, since sex differences were attenuated when adjusting for BMI, smoking, and alcohol consumption. Lifestyle factors consistently attenuated the association between sex and comorbidities, but the effect was somewhat stronger among those with gout onset ≥ 55 years. Interestingly, obesity played a more important role in sex differences in patients ≥ 55 years.

In gout, the relationship between sUA and comorbidities is a complex interaction, whereby comorbidities can be both the cause and effect of elevated sUA levels. Moreover, comorbidities are interrelated, complicating the exploration of their independent roles. Finally, lifestyle factors and medication (especially diuretics) play a key role in the complex interplay of sUA and comorbidities in patients with gout[38]. Nonetheless, we cannot ignore the role of sex in the presentation of gout characteristics. It was a remarkable finding that women referred to gout clinics used diuretics 3.51-times more frequently. Starting diuretics has previously been associated with hyperuricemia, and thus an increased risk of gout in women[39,40]. Although diuretic use has been shown to be a safe and effective first-line treatment for HTN, our population of females with gout was characterized by more frequent diuretic use compared to the male gout population, which was partly related to the higher prevalence of HTN.

Table 4. Literature review of sex differences in patients with gout according to 11 articles.

First Author (Yr)	Country	Study Design	Population	Diagnosis	Sample Size, n (%)	Age, Yrs (SD)	Females After Menopause, n (%)	Differences in Outcomes in Females vs Males [a] Clinical and Lifestyle Factors	Comorbidities	Nonsignificant Outcomes
Lally (1986)[12]	USA	Cross-sectional	Rheumatology clinic	MSU	M: 75 (77) F: 23 (23)	M: 50 (–) F: 58 (–)[a]	21 (91%)	· Alcohol intake (10 vs 45%) · Diuretics (78 vs 25%)	Renal insufficiency (30 vs 12%)	Podagra, tophi, HTN
Meyers (1986)[33]	South Africa	Retrospective cohort	Rheumatology clinic	ACR	M: 178 (66) F: 92 (34)	M: 58 (–) F: 67 (–)	–	· Diuretics (78 vs 48%) · Monoarticular gout (27 vs 61%) · Alcoholism (2 vs 11%)	Renal insufficiency (25 vs 15%)	Tophi, HTN, dyslipidemia, T2DM
Deesomchok (1989)[36]	Thailand	Cross-sectional	Rheumatology clinic	ACR	M: 172 (89) F: 22 (11)	M: 52 (14) F: 59 (11)[a]	18 (82%)	Podagra (32 vs 69%)	Hematologic malignancy (23 vs 3%)	Articular features, HTN, T2DM, renal insufficiency
Puig (1991)[13]	Spain	Cross-sectional	Rheumatology clinic	MSU/ ACR	M: 220 (86) F: 37 (14)	M: 51 (13) F: 61 (14)[a]	32 (86%)	· Alcohol intake (14 vs 55%) · sUA (0.55 vs 0.50 mmol/L) · FEUa (7.0 vs 4.7%) · Tophi (27 vs 10%) · Diuretics (57 vs 14%)	· Renal insufficiency (54 vs 12%) · HTN (78 vs 33%) · OA (81 vs 40%)	Articular features, obesity, T2DM
Tickly (1998)[37]	South Africa	Case-control	Rheumatology clinic	ACR	M: 69 (77) F: 21 (23)	M: 54 (–) F: 55 (–)	20 (95%)	· Alcohol intake (57 vs 82%) · Diuretics (50 vs 33%)	HTN (65 vs 59%)	T2DM
Chang (2004)[35]	Taiwan	Population-based cohort	GP	ACR	M: 101 (79) F: 27 (21)	M: 49 (15) F: 63 (11)[a]	22 (81%)	CCr (5.6 vs 8.6 mmol/L)	Renal dysfunction (85 vs 65%)	Tophi
De Souza (2005)[34]	Brazil	Observational cohort	Rheumatology clinic	MSU/ ACR	M: 31 (53) F: 27 (47)	M: 61 (9) F: 64 (11)	19 (70%)	· Less podagra[a] · More upper limb manifestation[a]	OA (56 vs 26%)	Diuretics, alcohol intake, tophi, HTN, T2DM, renal insufficiency, dyslipidemia
Harrold (2006)[1]	USA	Population-based cohort	GP	ACR	M: 4975 (81) F: 1158 (19)	M: 58 (14) F: 70 (12)[a]	–	Diuretics (77 vs 40%)	· Renal insufficiency (18 vs 10%) · HTN (81 vs 57%) · Dyslipidemia (42 vs 38%) · T2DM (30 vs 17%) · Peripheral arterial disease (7 vs 4%) · Renal failure (12 vs 6%)	Nephrolithiasis
Bhole (2010)[5]	USA	Longitudinal cohort	Rheumatology clinic	ACR	M: 200 (66) F: 104 (34)	–	–	· Obesity (36 vs 26%) · Diuretics (47 vs 29%) · Heavy alcohol intake (13 vs 43%)	HTN (82 vs 69%)	–
Harrold (2017)[22]	USA	Observational cohort	Rheumatology clinic	ACR	M: 1011 (79) F: 262 (21)	M: 61 (14) F: 71 (11)[a]	–	· BMI (33.5 vs 31.9 kg/m^2) · Alcohol intake (OR: 0.13) · Diuretics (51 vs 22%)	· HTN (77 vs 57%) · T2DM (28 vs 17%) · Renal disease (24 vs 13%) · OA (46 vs 25%)	Tophi, heart disease
Drivelegka (2018)[23]	Sweden	Case-control	GP	ICD	M: 9513 (67) F: 4600 (33)	M: 65 (15) F: 71 (15)[a]	–	· Obesity (12 vs 10%) · Diuretics (53 vs 39%) · Alcoholism (2 vs 5%)	· T2DM (18 vs 15%) · HTN (72 vs 65%) · CHF (21 vs 16%) · COPD (7 vs 5%) · Thromboembolism (14 vs 10%)	Coronary heart disease, renal disease

[a] $P < 0.05$ in univariate analyses. ACR: American College of Rheumatology; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CCr: creatinine clearance; HTN: hypertension; ICD: International Classification of Diseases; F: female; FEUa: fraction excretion of uric acid; GP: general practice; M: male; MSU: monosodium urate crystals; OA: osteoarthritis; sUA: serum uric acid; T2DM: type 2 diabetes mellitus.

Yet the differences in diuretic use disappeared in the group with gout onset ≥ 55 years after adjustments had been made for age and lifestyle factors (Model 2). When including HTN in multivariate analyses, no influence on the observed association was found, although confounding between obesity and HTN was found (data not shown). Possibly, obese women are prescribed diuretics more frequently. Also, striking differences in the prevalence of T2DM were revealed even after adjustments for lifestyle factors (including BMI) were made. While the reduced renal function of the female patients might mediate the relation between T2DM and sUA, and therefore gout, sUA has also been identified as an independent risk factor for T2DM, and it has been suggested that female patients with gout are at a higher risk of developing T2DM than male patients with gout[41,42]. This could be a possible explanation for the striking differences in T2DM, seen also when limiting the analyses to those with gout onset above the age of menopause. Moreover, T2DM, together with HTN, independently increases the risk of heart failure in women[43], and this relationship is 3-fold stronger in women compared to men[44].

Further, we compared the FEUa between sexes for patients ≥ 55 years, when the presumed protective uricosuric effect of estrogen disappears. The average FEUa was similar in women ≥ 55 years as it was in men in the same age group, yet the classic male gout profile of underexcretor was still less frequently encountered in the population of females with gout ≥ 55 years. Adjusting the relationship between sex and FEUa with potential confounders (age, diuretics use, and BMI) had no relevant effect on the results (data not shown). While we hypothesized that women ≥ 55 years would be underexcretors as frequently as men, we could not confirm this hypothesis. Whether this is due to residual confounding, the small sample size or a gene-sex interaction of the urate transporter genes cannot be further analyzed/studied in our sample, but warrants exploration since this may have therapeutic implications.

Studies on clinical differences between men and women have received much attention in the last decade. In this research area, it is recommended to distinguish gender difference from sex differences[20]. In gout, a limited number of studies have explored the potential role of biological differences (i.e., sex-related research), but fewer studies have explored the role of gender in areas such as behavior, lifestyle, life experience, and healthcare access (i.e., gender-associated research)[20,21]. In our study, it seems contradictory to make a strong distinction between gender and sex since both aspects seem to play a role in the observed sex differences in gout. For example, women are more often obese compared to men, both in our study population and in the general population[45]. Differences in obesity can partly be explained by the influence of chromosomal, hormonal, and neuroendocrine influences on energy balance and fat distribution (sex differences); however, they can also be explained by behavioral and sociocultural factors (gender-specific). Moreover, HTN is more prevalent among obese gout patients and may be treated more frequently with diuretics in women compared to men, partly based on biological grounds but partly also on the behavioral choices of the prescribing physician.

Results from this study should be interpreted in consideration of several limitations. Strong conclusions on pathways explaining sex differences and the role of menopause on sUA metabolism and clinical characteristics were impeded by the cross-sectional nature of this study; incomplete information on the dates of onset for comorbidities, gout onset, age of menopause, and urinary UA excretion; actual data on menopause and the effect of estrogen on plasma levels; and residual confounding. For example, the number of females with a first gout flare < 55 years or with data on FEUa ≥ 55 years was too small (n = 12 and n = 26, respectively) to perform a meaningful comparison on sex differences in these subgroups. Despite these limitations, the current study, is the first, to our knowledge, to provide a better understanding of sex differences in gout patient profiles, and highlights the need for awareness and the potential effect of sex-specific pathophysiology and management of gout.

Analyses of our currently identified population confirmed the existence of sex differences in clinical characteristics and comorbidities, but revealed that differences were attenuated in patients with an onset of gout ≥ 55 years. Further studies are needed to understand whether prevention and management of gout should be different between sexes before and after the age of menopause.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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