Sex differences in the clinical profile among patients with gout: cross-sectional analyses of an observational study

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Abstract

Background: Research findings in gout result predominantly from studies among men, and might not be generalizable to women. To improve insight into sex differences, this study compared clinical characteristics and comorbidities between female and male gout patients and explored the influence of menopausal state on these differences.

Methods: Data from patients referred to two rheumatology services and diagnosed with gout were used. Clinical characteristics and comorbidities between sexes were compared univariately. Sex difference in comorbidities were further explored in multivariable logistic regressions adjusting for age, body mass index, smoking and alcohol consumption in the total group and in those with gout onset ≥55-years (as surrogate for menopausal state).

Results: 954 patients of which 793 (83%) men were included. Women were on average older (65 vs 62 years), were more often obese (54 vs 36%), had a higher serum uric acid level (0.53 vs 0.49 mmol/L), used more often diuretics (60 vs 30%), and consumed less frequently alcohol (47 vs 72%). Additionally, women had more frequently a 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: This study confirms sex differences in clinical characteristics and comorbidities among newly diagnosed gout patients, 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.

Introduction

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 four times higher than in women (2). Above this age, the prevalence of gout narrows to a more equal sex distribution, especially due to the sharper increase of the incidence in gout among older women (3, 4). Despite the increasing prevalence of gout, particularly in the aging female population, most studies are performed in predominantly male populations and few studies examine the differences between sexes (4-7).

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 oestrogens (8-11). The uricosuric effect of oestrogens was initially emphasized by epidemological research, showing an increase in serum uric acid (sUA) level among postmenopausel women (12-14). More recently, a study of patients undergoing male-to-female gender reassignment demonstrated that oestrogen therapy reduced sUA concentrations and increased urinary uric acid (UA) excretion (8, 15). Apart from oestrogens, sex-specific differences in the effect of genetic variants on sUA levels have been revealed. In a large population of European ancestry, a gene-sex interaction was identified for ABCG2 - a unidirectional secretory urate transporter in the proximal renal tubule (16) - and PDZK1 - a key regulatory protein for several secretory urate transporters (17) - on gout risk, with a greater influence on sUA in men than in women (17, 18). In addition, SLC2A9 - encoding the GLUT9 protein and facilitating reabsorption of urate - explains approximately 3% effect of variance in urate levels. Although SLC2A9 has a stronger effect on sUA in women, it would not explain differences in gout occurrence between men and women (17-20). Overall, gene-sex interactions suggest a greater influence of secretory urate transporters on sUA and gout risk for men. Yet, the overall effect size on sUA levels and on occurrence of gout remains unclear.

In addition to the biological pathways explaining sex differences in hyperuricemia and onset of gout, differences in risk factors and clinical manifestations require attention (21, 22). A systematic literature review of nine (mainly small) studies on differences between male and female patients with gout (3), completed by two recent gout cohort studies (23) (24), showed consistently that female patients with gout are older, have a lower alcohol consumption, more frequently have an increased body mass index (BMI), and are prescribed more often diuretics. Also, women presented more commonly with a polyarticular pattern, and suffered more frequently from common gout related comorbidities, mainly hypertension, diabetes mellitus type 2 (DM2), osteoarthritis, and renal insufficiency compared to male patients with gout (13, 23-27). However, none of the studies so far explored sex-specific differences in excretion of urate, which is especially important in view of the existing evidence on the uricosuric effect of oestrogens. Further, none of the studies investigated the effect of onset of gout ≥ 55 years - when the protective effect of oestrogens disappears, because by age 55 almost all women have gone through menopause - on sex differences in clinical manifestations (28). It would be expected that the clinical profile of gout with regard to risk factors and comorbidities would become more comparable between sexes as the protective effect of oestrogens disappears above this age (29).

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 next to explore the role of gout onset ≥ 55 years, as a surrogate for the disappearance of the protective effect of oestrogens. We expected to confirm previously reported sex differences and hypothesized that (a) the differences in clinical characteristics and comorbidities between sexes would be strongly reduced in those with a first gout flare above the age of 55 years, and (b) no difference in urinary UA excretion would be present between male and female gout patients older than 55 years.

Methods

Study sample

New patients referred to one of two regional non-academic rheumatology outpatient clinics in the Netherlands and diagnosed with gout were considered for this cross-sectional study. Clinic A included patients from January 2015 until October 2017 (sample A) and clinic B included patients from July 2011 until May 2016 (sample B). All patients were diagnosed with the ACR/EULAR gout classification criteria, and most patients had monosodium urate (MSU) crystal-proven gout (30). Patients could have been referred by either the primary care physician, or other specialists within the hospital. The study was approved by the ethical committee of the hospital of sample A (METC 16-4-032.1) and ethical approval for this type of study was not required in accordance with 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 (BMI $\geq$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 the first gout flare (sample B only); the presence of clinical examination of tophi (yes/no); use of specific medication types (diuretics, colchicine prophylaxis of gout, and sUA lowering drugs); laboratory tests (UA and creatinine concentration in serum and spot-urine (sample A only)); and finally comorbidities confirmed by rheumatologists (hypertension, peripheral arterial disease, cerebrovascular accident, myocardial infarction, heart failure, heart arrhythmia, dyslipidaemia, DM2, nephrolithiasis, and hepatic steatosis (all yes/no answers)). Laboratory test were used to calculate renal function and fractional excretion of uric acid (FEUa). Renal function is presented as the estimated

Glomerular Filtrate Rate (eGFR) and was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (31). The FEUa was calculated as (urinary UA x serum creatinine) / (sUA x urinary creatinine) and available for sample A only. The FEUa represents the percentage of sUA filtered in the kidney and distinguishes underexcretors (FEUa <4.0%) from overproducers (32). Among healthy subjects average FEUa ranges between 6-8%, whereas patients with gout have generally an average FEUa between 3-5% (32, 33). As 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 (XOI) (e.g. allopurinol or febuxostat), FEUa was not calculated for the patients treated with uricosurics (32).

Statistical analyses

Univariable comparisons of clinical characteristics and comorbidities between women and men were performed using independent t-test for continuous and normally distributed variables and $\chi 2$ test for categorical variables. In the sample comprising data on age of onset of gout (sample B), logistic regressions were performed to explore the adjusted role of sex (female opposed to male) on presence of comorbidities and clinical characteristics first in the total sample and next in those with gout onset $\geq$ 55 years (as surrogate for menopausal state). Multivariable regressions were limited to comorbidities and clinical characteristics that were significantly ($p<0.05$) associated with sex in univariate analyses. Potential confounders were a priori defined based on plausibility, and comprised in a first step age (model 1), and in a second step additionally 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 older than 55 years. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp). A p-value of less than 0.05 (two-tailed) was considered as statistically significant.

Results

Sex differences in clinical characteristics in the total sample

In the total sample, 954 patients with gout were included, of which were 161/954 (17%) female and 793/954 (83%) male patients (figure 1). Clinical characteristics of female and male patients for the total sample are shown in table 1, and for the subsamples A (n=255) and B (n=699) in supplementary table S1. In the total sample some relevant and significant differences between sexes were found: women were 2.6 years older as compared to men, had a 2.2 kg/m^2 higher BMI with a 2.09 times increased prevalence of obesity (95% CI: 1.47-2.98), and used 3.51 times more frequently diuretics (95% CI: 2.48-4.99). The sUA-level was 0.04 mmol/L higher in women ($p<0.001$), and no differences in 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 increased prevalence of hypertension (95% CI: 1.86-4.10), a 2.30 times increased prevalence of heart failure (95% CI: 1.50-3.53), a 3.11 times increased prevalence of DM2 (95% CI: 2.15-4.48), and a 14.9 mL/min per 1.73m^2 lower eGFR (all $p<0.05$) (supplementary table S2). 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 S2).

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 484/699 (69%) patients of which 259 had a first gout flare ≥ 55 years (75/259 (29%) women and 184/259 (71%) men) (table 2). The sex differences in the group 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 at age 55 years or older, women were 3.0 years older and the sUA-level was almost comparable to men with gout onset ≥ 55 years. Further, women with gout onset ≥ 55 years were 0.61 times less frequently smokers (95% CI: 0.24-1.56), 0.38 times less likely alcohol consumers (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 S3). Multivariable regressions 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 persons with gout onset ≥ 55 years (subsample with gout onset ≥ 55 years of table 2) when compared to the total group (total group of table 2), and only significant for DM2, diuretic use and obesity. When adjusting additionally for lifestyle factors (model 2), the strength of association decreased in both groups (decrease of coefficient between 8% and 22% in the total group and between 15% and 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 of age (sample A)

When exploring FEUa among male and females patients ≥ 55 years from sample A, data were available for (n=169/255 (66%)) patients of which 26/169 (15%) female and 143/169 (85%) male subjects (table 3). Two female and one 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 older than 55 years (n=9/26 (35%)) were somewhat less frequently underexcretors compared to males older than 55 years (n=64/143 (45%)) (p=0.34). When including the three outliers results were comparable.

Discussion

This 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 more often diuretics, is less frequently an alcohol consumer, has a higher sUA level at presentation, and has more frequently comorbidities such as hypertension, heart failure, DM2, and advanced renal insufficiency. In those with gout onset ≥ 55 years, sex differences in comorbidities 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 gout (1, 5, 12, 13, 23, 24, 34-38) (table 4), our findings support evidence that women with gout are on average older (7/10 studies [1, 12, 13, 23, 24, 34-38]), have more often renal insufficiency (6/9 studies [1, 12, 13, 23, 24, 34-37]), obesity (3/4 studies [5, 13, 23, 24]), hypertension (6/10 studies [1, 5, 12, 13, 23, 24, 34, 35, 37, 38]), used more frequently diuretics (8/9 studies [1, 5, 12, 13, 23, 24, 34, 35, 38]), and were less likely (heavy) alcohol consumers (7/8 studies [5, 12, 13, 23, 24, 34, 35, 38]). Furthermore, no sex differences were noted in the presence of tophi (5/6 studies [12, 13, 23, 34-36]), while findings on articular manifestations were conflicting. In our study, we used age of onset ≥ 55 years as a surrogate to explore the role of oestrogens on gout characteristics while the mean age of menopause in western European women is 51 years of age and therefore almost all women above 55 years are postmenopausal (28). We demonstrated as first that age of onset ≥ 55 years attenuated the sex differences in comorbidities. Our results therefore suggest that below the age of 55 years women are protected by oestrogens against the impact of classic gout risk factors such as decreased renal function, hypertension, heart failure, and frequency of alcohol consumption. Of note, independent of age of onset, lifestyle factors played always a role in sex differences, as sex differences were attenuated when adjusting for BMI, smoking,

and alcohol consumption. Lifestyle factors consistently attenuated the association between sex and comorbidities but somewhat stronger among those with onset ≥ 55 years. Interestingly, above the age of 55 years obesity played a more important role in sex differences.

In gout, the relationship between sUA and comorbidities is a complex interaction, whereby comorbidities can be both cause and effect of elevated sUA levels. Moreover, comorbidities are interrelated, complicating the exploration of their independent role. Finally, lifestyle factors and medication (especially diuretics) play a key role in the complex interplay of sUA and comorbidities in gout patients (39). Notwithstanding, we cannot ignore the role of sex on gout characteristics. On this line, it was a remarkable finding that women referred to the gout-clinic used 3.51 times more frequent diuretics. Starting diuretics has previously been associated with hyperuricemia, and thus an increased risk of gout in women (40, 41). Although diuretic use has been shown to be a safe and effective first-line treatment for hypertension, our female gout population is characterized by more frequent diuretic use when compared with the male gout population, partly related to the higher prevalence of hypertension. Yet, the differences in diuretic use disappeared in the group with gout onset ≥ 55 years after adjustments for age and lifestyle factors (model 2). When including additionally hypertension in multivariate analyses, no influence on the observed association was found, but confounding between obesity and hypertension was found (data not shown). Possibly, obese women are prescribed more frequently diuretics. Also, striking differences in the prevalence of DM2 were revealed even after adjustments for lifestyle factors (and thus BMI). While the reduced renal function of the female patients might well mediate the relation between DM2 and sUA and thus gout, sUA has also been identified as an independent risk factor for DM2, and it has been suggested that female patients with gout are at a higher risk of developing DM2 than male gout patients (42, 43). This could be a possible explanation for the striking differences in DM2, also when limiting the analyses to those with gout onset above the age of (female) menopause. Moreover, DM2,

together with hypertension, increases independently the risk of heart failure in women (44), and this relation is 3-fold stronger in women compared to men (45).

Furthermore, we compared the FEUa between sexes for patients older than 55 years, when the presumed (protective) uricosuric effect of oestrogens disappears. The average FEUa was similar in women older than 55 years as it was in men ≥ 55 years, yet the classical male gout profile of underexcretor was still less frequently encountered in the female gout population above the age of 55 years. Adjusting the relation between sex and FEUa with potential confounders (age, diuretics use, and BMI) had no relevant impact on the results (data not shown). While we hypothesized that women above 55 years would be as frequently underexcretors as men, we could not confirm this hypothesis. Whether this is due to residual confounding, the small sample or a gene-sex interaction of the urate transporter genes, cannot be further analysed/studied in our sample, but warrants exploration as this might have therapeutic consequences.

Studies on clinical differences between men and women received much attention in the last decade. In this research area, it is recommended to distinguish gender difference from sex differences (21). In gout, a limited number of studies explored the potential role of biological differences (i.e. sex related research) but fewer studies explored the role of gender such as behavior, lifestyle, life experience, and health care access (i.e. gender associated research) (21, 22). In our study, it seems artificial to make a strong distinction between gender and sex as both aspects seem to play a role in the observed sex differences in gout. For example, women are more often obese compared to men in our study population as well as in the general population (46). 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 also by behavioral and socio-cultural factors (gender specific). More-over, hypertension, more prevalent among obese gout patients, might be treated more frequently with diuretics in women compared to men, partly based on biological grounds but partly also on behavioral choices of the prescribing physician.

Results of this study should be interpreted in the light of several limitations. The cross-sectional character of this study, the incomplete information about the date of onset of comorbidities, date of gout onset, age of menopause and urinary UA excretion, the actual data of menopause either plasma oestrogen of women, and finally residual confounding, impedes strong conclusions on pathways explaining sex differences and the role of menopause on sUA metabolism and clinical characteristics. For example, the number of females with an onset of the 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 in sex differences in these subgroups. Despite these limitations, the current study is the first that gives a better understanding of sex differences in gout patient profiles which highlights the need for awareness and potential impact of sex specific pathophysiology and management of gout.

Conclusion

Analyses of our currently identified population confirms 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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Figures legend

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

Variable	Females (n=161)	Males (n=793)	p-value
Age; *mean (SD)*	64.9 (14.9)	62.3 (13.0)	0.040
BMI; *mean (SD)*	31.1 (7.4)	28.9 (4.9)	0.001
<25 kg/m^2*; n (%)*	29 (19.2)	125 (16.6)	
25–29.9 kg/m^2*; n (%)*	40 (26.5)	357 (47.3)	
≥30 kg/m^2*; n (%)*	82 (54.3)	273 (36.2)	
Tophi; *n (%)*	40 (25.0)	180 (22.7)	0.534
MSU crystal confirmed; *n (%)*	142 (93.4)	688 (90.8)	0.291
sUA; *mean (SD)*	0.53 (0.13)	0.49 (0.11)	<0.001
Current smoking; *n (%)**	17 (13.9)	100 (18.1)	0.227
Alcohol consumption; *n (%)**	57 (47.1)	400 (71.9)	<0.001
Comorbidities; *n (%)*			
Hypertension	125 (77.6)	442 (55.7)	<0.001
Peripheral arterial disease	9 (5.6)	61 (7.7)	0.351
CVA	16 (9.9)	50 (6.3)	0.098
MI	20 (12.4)	118 (14.9)	0.419
Heart failure	37 (23.0)	91 (11.5)	<0.001
Heart arrhythmia	36 (22.4)	141 (17.8)	0.173
Dyslipidaemia	41 (25.5)	168 (21.2)	0.231
DM2	63 (39.1)	136 (17.2)	<0.001
Nephrolithiasis	15 (9.3)	65 (8.2)	0.640
Hepatic steatosis	24 (14.9)	85 (10.7)	0.128
eGFR; *mean (SD)*	58.3 (66.3)	73.2 (30.7)	<0.001
eGFR <60	100 (64.1)	237 (30.6)	<0.001
Diuretic use; *n (%)*	97 (60.2)	239 (30.1)	<0.001

Table 1: Baseline characteristics of the female and male patients with gout (total sample). SD= standard deviation, BMI= Body Mass Index, MSU= monosodium urate, sUA= serum uric acid, CVA= cerebrovascular Accident, MI= myocardial infarction, DM2= Diabetes Mellitus type 2, eGFR= estimate Glomerular Filtrate Rate. *data only available in sample B

	Descriptive data		Univariable association		Multivariable model 1*		Multivariable model 2#	
	Females n (%)	Males n (%)	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	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
DM2	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	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 years	**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
DM2	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	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)	87 (36.6)	2.33	1.35-4.02	2.83	1.59-5.04	2.77	1.53-5.03

Table 2: Uni- and multivariable logistic regressions presenting the influence of sex (female opposed to male) on comorbidities and clinical characteristics in the subsample with date of gout onset and lifestyle factors available (sample B). *Multivariable model 1 includes age and #multivariable model 2 includes age, body mass index (where appropriate), smoking and alcohol consumption. DM2= Diabetes Mellitus type 2, eGFR= estimate Glomerular Filtrate Rate.

Variable	Females (n=26)	Males (n=143)	p-value
sUA; *mean (SD)*	0.46 (0.13)	0.45 (0.12)	0.726
Urinary UA; *mean (SD)*	1.5 (1.1)	1.8 (1.2)	0.293
Serum creatinine; *mean (SD)*	108.6 (38.9)	121.7 (51.1)	0.214
Urinary creatinine; *mean (SD)*	71.1 (45.4)	97.8 (66.6)	0.052
eGFR; *mean (SD)*	49.8 (20.1)	59.2 (20.7)	0.035
FEUa (%); *mean (SD)*	4.6 (1.9)	4.4 (1.5)	0.510
<4.0%; *n (%)*	9 (34.6)	64 (44.8)	0.337
≥4.0%; *n (%)*	17 (65.4)	79 (55.2)	

Table 3: Biochemical gout characteristics of the female and male patients with gout older than 55 years (sample A). SD= standard deviation, sUA= serum uric acid, UA= uric acid, eGFR= estimate Glomerular Filtrate Rate, FEUa= fractional excretion of uric acid.

	Country	Study design	Population	Diagnose	Sample size (n (%))	Age (years (SD))	Female after menopause (n (%))	Differences in outcomes female compared to male*		Non-significant outcomes
								Clinical and lifestyle	Comorbidities	
Lally (1986)[12]	USA	Cross-sectional	Rheumatology clinic	MSU	**M:** 75 (77) **F:** 23 (23)	**M:** 50 (-) **F:** 58 (-)*	21 (91%)	- Alcohol intake (10 vs 45%) - Diuretics (78 vs 25%)	- Renal insufficiency (30 vs 12%)	Podagra, tophi, hypertension
Meyers (1986)[34]	South Africa	Retrospective cohort	Rheumatology clinic	ACR	**M:** 178 (66) **F:** 92 (34)	**M:** 58 (-) **F:** 67 (-)	-	- Diuretics (78 vs 48%) - Mono-articular gout (27 vs 61%) - Alcoholism (2 vs 11%)	- Renal insufficiency (25 vs 15%)	Tophi, hypertension, dyslipidaemia, DM2
Deesomchok (1989)[37]	Thailand	Cross-sectional	Rheumatology clinic	ACR	**M:** 172 (89) **F:** 22 (11)	**M:** 52 (14) **F:** 59 (11)*	18 (82%)	- Podagra (32 vs 69%)	- Haematologic malignancy (23 vs 3%)	Articular features, hypertension, DM2, renal insufficiency
Puig (1991)[13]	Spain	Cross-sectional	Rheumatology clinic	MSU/ACR	**M:** 220 (86) **F:** 37 (14)	**M:** 51 (13) **F:** 61 (14)*	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%) - Hypertension (78 vs 33%) - Osteoarthritis (81 vs 40%)	Articular features, obesity, DM2
Tickly (1998)[38]	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%)	- Hypertension (65 vs 59%)	DM2
Chang (2004)[36]	Taiwan	Population-based cohort	GP	ACR	**M:** 101 (79) **F:** 27 (21)	**M:** 49 (15) **F:** 63 (11)*	22 (81%)	- Ccr (5.6 vs 8.6 mmol/L)	- Renal dysfunction (85 vs 65%)	Tophi
Souza (2005)[35]	Brazil	Observational cohort	Rheumatology clinic	MSU/ACR	**M:** 31 (53) **F:** 27 (47)	**M:** 61 (9) **F:** 64 (11)	19 (70%)	- Less podagra* - More upper limb manifestation*	- Osteoarthritis (56 vs 26%)	Diuretics, alcohol intake, tophi, hypertension, DM2, renal insufficiency, dyslipidaemia
Harrold (2006)[1]	USA	Population-based cohort	GP	ACR	**M:** 4975 (81) **F:** 1158 (19)	**M:** 58 (14) **F:** 70 (12)*	-	- Diuretics (77 vs 40%)	- Renal insufficiency (18 vs 10%) - Hypertension (81 vs 57%) - Dyslipidaemia (42 vs 38%) - DM2 (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)	**M:** - **F:** -	-	- Obesity (36 vs 26%) - Diuretics (47 vs 29%) - Heavy alcohol intake (13 vs 43%)	- Hypertension (82 vs 69%)	-
Harrold (2017)[23]	USA	Observational cohort	Rheumatology clinic	ACR	**M:** 1011 (79) **F:** 262 (21)	**M:** 61 (14) **F:** 71 (11)*	-	- BMI (33.5 vs 31.9 kg/m^2) - Alcohol intake (OR: 0.13) - Diuretics (51 vs 22%)	- Hypertension (77 vs 57%) - DM2 (28 vs 17%) - Renal disease (24 vs 13%) - Osteoarthritis (46 vs 25%)	Tophi, heart disease
Drivelegka (2018)[24]	Sweden	Case-control	GP	ICD	**M:** 9513 (67) **F:** 4600 (33)	**M:** 65 (15) **F:** 71 (15)*	-	- Obesity (12 vs 10%) - Diuretics (53 vs 39%) - Alcoholism (2 vs 5%)	- DM2 (18 vs 15%) - Hypertension (72 vs 65%) - CHF (21 vs 16%) - COPD (7 vs 5%) - Thromboembolism (14 vs 10%)	Coronary heart disease, renal disease

Table 4: Literature review of sex differences in patients with gout according to 11 articles. SD= standard deviation, USA= United States of America, GP= general practice, MSU= Monosodium urate crystals, ACR= diagnosed according to the ACR criteria of gout, ICD= International Classification of Disease, M= male, F= female, sUA= serum uric acid, FEUa= fraction excretion of uric acid, Ccr= creatinine clearance, DM2= diabetes mellitus type 2, BMI= body mass index, CHF= congestive heart failure, COPD= chronic obstructive pulmonary disease. *$p<0.05$ of univariate analyses

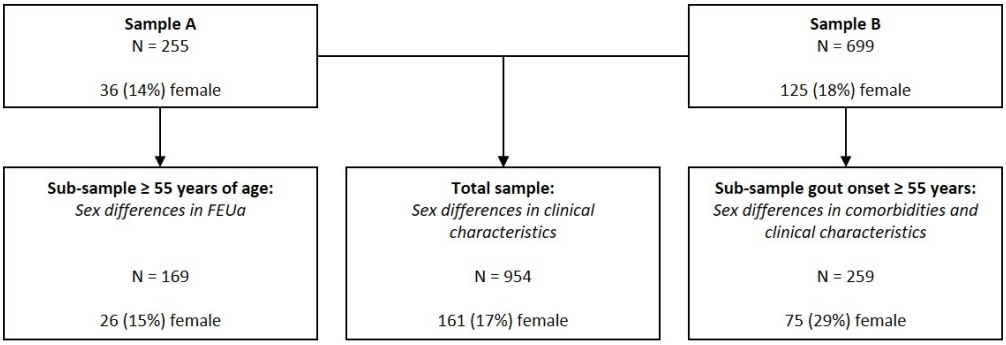

Figure 1: Flowchart of the study and data analyses. FEUa= Fractional excretion of uric acid

191x65mm (150 x 150 DPI)