

Gout in Women – A Diagnostic Challenge

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ABSTRACT

Objectives Gout predominantly affects men (male: female; 9: 1). The clinical presentation of acute monarthritis of the lower extremity in men is usually highly suggestive of the diagnosis. In contrast, data on gout in women are limited. In women, gout is therefore often not included in the differential diagnosis of arthritis. We therefore studied the epidemiology and clinical presentation of gout in women and compared them to classical male gout. As a result, the data were analyzed for features that

distinguish gout from arthritis of other origin in women, thus helping to avoid misdiagnosis.

Patients/Methods For the year 2012 to 2018, we retrospectively analyzed all patients who were discharged with a primary discharge diagnosis of gout (ICD-10 M10.XX) from the University Medical Center at the TU Dresden. Clinical, laboratory and radiological findings were recorded and analyzed by descriptive and multivariate statistics, using SPSS and R. In a second step, the data from women with gouty arthritis were compared to those with monarthritis of a different origin, defining parameters that showed significance in differentiating gout from other arthritis.

Results A total of 238 gout patients (71 women, 167 men) were included. Women in this cohort were on average 20 years older than men at the time of diagnosis. They then more frequently had several comorbidities: 92% of all female gout patients suffered from hypertension (men 74%), 84% had an eGFR <60 mL/min (men 52%) and 40% had previous cardiovascular events (men 14%). 90% were on diuretics (men 47%). Almost half (47%) of the women already had overt osteoarthritis (men 30%). Clinically, classic MTP I arthritis occurred less frequently in women (69 vs. 84%). A comparison of women with gout confirmed by microscopic crystal detection and women with crystal-negative monarthritis showed that women with gout were older and significantly more likely to suffer from hypertension or cardiovascular disease, type 2 diabetes, or obesity, and were taking diuretics. Such risk factor, combined with impaired kidney function and hyperuricemia, made gout very likely.

Conclusion It is essential to consider gout in the differential diagnosis of acute monarthritis in postmenopausal women. This is particularly true if they suffer from hypertension, cardiovascular disease, and type 2 diabetes mellitus, or obesity and regularly take diuretics. Impaired kidney function and serum uric acid >390 µmol/l (>6.5 mg/dL) make gout very likely.

Introduction

With a prevalence of 1.6%, gout is the most common inflammatory arthritis, but it predominantly manifests in men of working age [1, 2]. The classical clinical picture of the first typical attack of gout in the metatarsophalangeal joint (podagra) is usually associated with men [3–5].

In all studies on gout, at least 70% men are found; women with gout are also the exception in randomized therapy studies. However, looking at the latest prevalence and incidence data on gout in

Germany, it is noticeable that women are also affected by gout as they get older. In the 6th decade of life, women already have a gout prevalence of over one percent, which corresponds to the prevalence of rheumatoid arthritis [1, 6]. With increased age, the prevalence and incidence of gout continue to increase, also in women. Therefore, gout is an important differential diagnosis in older female patients with acute arthritis [1]. Unfortunately, the evidence on gout in women is sparse. Searching the term “gout AND women” in the literature mainly resulted in hits on papers describing epide-

miological differences between men and women [7, 8]. A Swedish registry study analyzed data from men and women with gout [7]. At the time of initial diagnosis, women were 6 years older than men on average and had more comorbidities. Obesity and the use of diuretics were more common in women with gout, while men had more cardiovascular disease. In contrast, a study from the Netherlands found higher rates of cardiovascular disease in women with gout [8]. Regardless of gender, gout is associated with higher cardiovascular risks as well as increased risks for cardiovascular and overall mortality [9, 10].

Very limited information can be found on clinical presentations of gout in women [11]. Our literature search in the PubMed database (with the search term “Woman AND Gout”) from the years 2000–2020, when limited to clinical manifestations, yielded 61 papers; these mostly described individual cases or case series of women with atypical or complicated gout, who often could not be primarily identified as gout.

Studies especially focusing on how to suspect and diagnose gout in women do not exist. If the clinical classification criteria for gout are considered, the male sex and an affected MTP-I joint are given high weightings (2 and 2.5 of 8 required points, respectively) (► **Table 1**) [5, 12]. It is in fact not yet clear whether and how the primary clinical manifestation of gout in women differs from that in men. There are at least indications that gout may present clinically different in older women [13, 14]. This could mean that – unlike in men – gout is not immediately included into the differential diagnosis and potentially overlooked.

In the present study, we collected data of patients who were treated as inpatients with confirmed gout, and analyzed epidemiological as well as clinical, laboratory and imaging findings with a special focus on gender-specific differences. Differentiating features in contrast to other acute arthritis are presented. Considera-

tion of these differences might be helpful in the future to identify female patients with gout.

Patients/Material and Methods

Cohort I – Comparison of Men and Women with Gout

All patients with arthritis who were hospitalized at the Dresden University Hospital between 2012 and 2018 and who were discharged with a confirmed main diagnosis of gout (ICD-10 M10.XXG) were retrospectively included in the study (cohort I, n = 238) (► **Fig. 1**). In addition to epidemiological information, data on gout, such as the time of diagnosis, affected joints, gout attacks in the last 12 months, comorbidities and comedications as well as gout-specific therapies (lowering of uric acid, prophylaxis of attacks, and medication for gout attacks) were recorded. In addition, routine clinical, laboratory and radiological findings were collected. Men (n = 167) and women (n = 71) with gout were compared.

Cohort II – Comparison of Women with Gouty Arthritis and Arthritis of other origins

In a second step, the data of women with confirmed gout (urate crystal-positive in polarization microscopy; n = 42) and women with monoarthritis of a different origin (urate crystal-negative in the joint puncture, n = 43) were compared (cohort II) (► **Fig. 1**).

Results

Comparison of men and women with gout (Cohort I)

Between 2012 and 2018, a total of 238 patients (167 men and 71 women) with confirmed gout were treated as inpatients. Gout was diagnosed much earlier in men, who aged 53 ± 16 (mean \pm SD) years, than in women, who were 74 ± 11 years old at the time of the initial diagnosis (► **Fig. 2**).

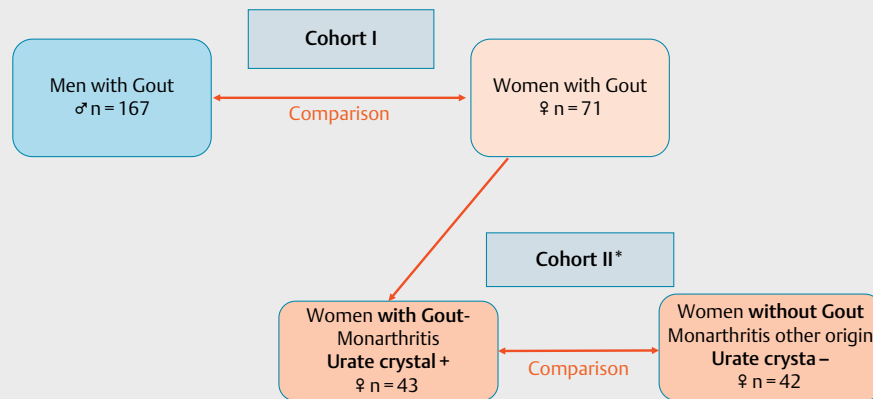
Comorbidities in men and women with gout

The examination of pre-existing cardiovascular, renal and metabolic disease revealed more comorbidities in women than in men. The gout patients suffered from an average of 4 comorbidities (in descending order: arterial hypertension, hyperlipidemia, chronic kidney failure, type 2 diabetes, obesity, coronary artery disease, transient ischemic attack, myocardial infarction) (► **Fig. 3**).

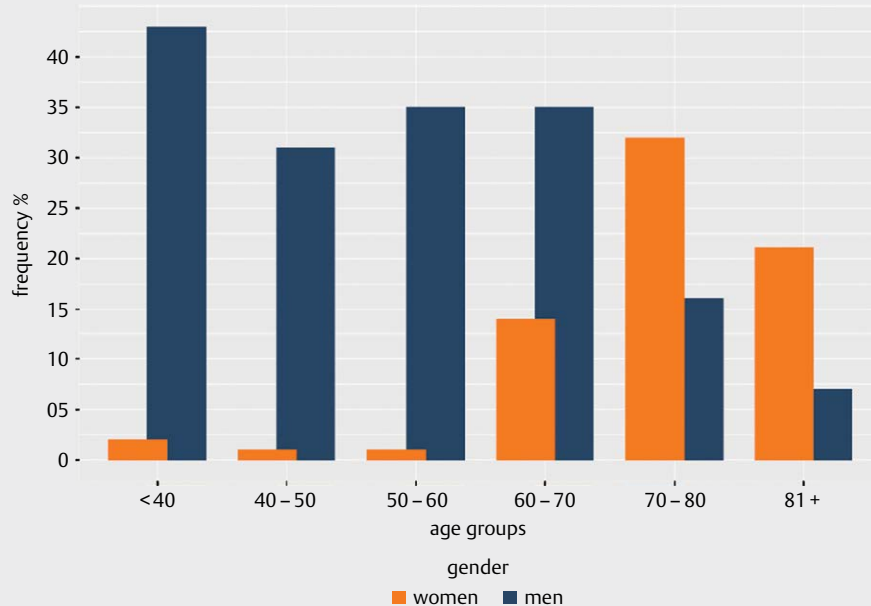
Almost all (n = 66, 94 %) women with gout had arterial hypertension, compared to three in four men with gout (n = 124, 74 %) (► **Table 2**). Almost half of the women (n = 30) had a history of coronary heart disease, as compared to every 7th man (n = 23). There were no significant differences with regard to other cardiovascular disease patterns (transient ischemic attack and myocardial infarction). Almost half of the women (n = 34) had type 2 diabetes mellitus, compared with a quarter of the men (n = 43). Almost half of the female gout patients and a quarter of the men were obese (BMI > 30) (► **Table 2**). More than half of women with gout (n = 55) had impaired kidney function, corresponding to less than a third of men (n = 46). 75 % of the women had an estimated glomerular filtration rate (eGFR) < 55 ml/min, in a quarter the eGFR was below 34 ml/min.

► **Table 1** Gout calculator (Gout Calculator App): In acute arthritis, the clinical diagnosis of gout can be made or ruled out very easily by weighting clinical criteria and the serum uric acid level [5, 12].

			Points
Male Gender	No	Yes	2
Previous arthritis attack	No	Yes	2
Onset within 1 day	No	Yes	0.5
Joint redness	No	Yes	1
MTP-1 involvement	No	Yes	
Hypertension or CVD	No	Yes	2.5
Uric acid > 5.88 mg/dl (350 μ mol/l)	No	Yes	1.5
	No	Yes	3.5
Diagnosis score points:			0.00
Gout diagnosis:	Very unlikely		
≤ 4 Points: consider other non-gout diagnoses			
> 4 und < 8: consider additional diagnostic strategy			
≥ 8 Punkte: make diagnosis of gout			



► **Fig. 1** Patient Recruitment. Cohort I: inpatients with gout as the main diagnosis; men and women are compared. Cohort II: patients with acute monarthrits microscopic confirmation of the diagnosis. Women with confirmed gout (urate crystal +) vs. other arthritis (urate crystal-).



► **Fig. 2** Cohort I: Age distribution at first diagnosis of gout of inpatients treated with gout at the Dresden University Hospital (2012–2018; n = 238; women = 71; men = 167; f: m 1: 3): women treated with gout are predominant >60 years old, men significantly younger.

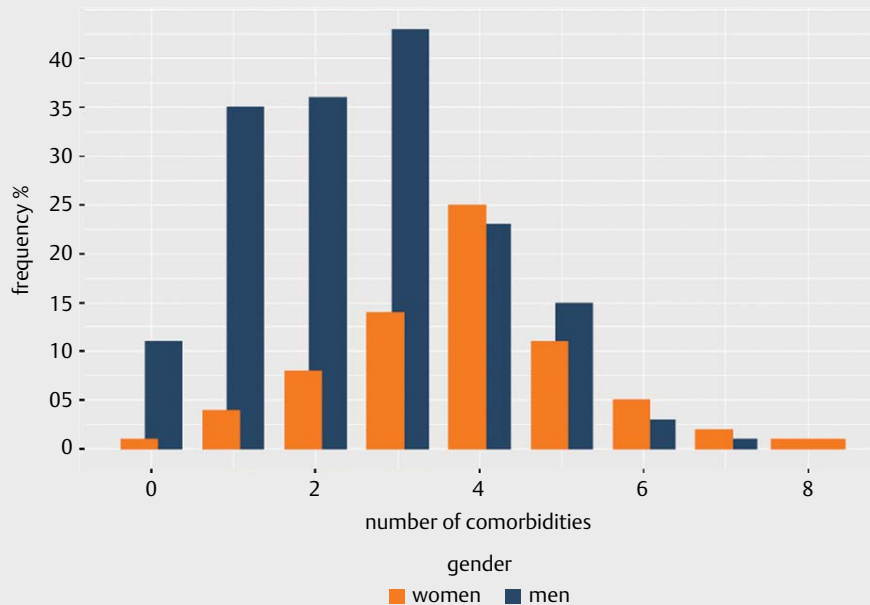
Osteoarthritis (possibly predisposing to gout attacks) was found in half of all women (n = 36); significantly less often in men (less than a third, n = 50). The incidence of concurrent seropositive rheumatoid arthritis in women (n = 5) was not significantly higher than in men (n = 8).

When analyzing the comedications, it is noticeable that almost all women (n = 64, 90%) were on diuretics (furosemide, torasemide, thiazide diuretics), as long-term therapy compared with a good half of men (n = 88, 53%). The other concomitant medications did not differ significantly.

Comparison of women with gouty arthritis and acute arthritis of other origins (Cohort II)

Case vignette

A 65-year-old woman presented to the surgical emergency room on a late Saturday afternoon (► **Fig. 6**). About 2 days ago, painful swelling of her right hand suddenly set in, and even cooling did not bring any real relief. The hand became more and more swollen despite taking a pain reliever and the fingertips were now hypesthetic. Since the family doctor could not be reached, her son brought her to the emergency room. The patient did not remember any injury – and had never experienced a similar problem before. Except for medication for high blood pressure and an occasional swelling



► **Fig. 3** Cohort I: Number of comorbidities in inpatient women and men with gout (2012–2018 n = 238; women = 71; men = 167; f: m 1: 3); inpatient women tend to have more comorbidities than men.

► **Table 2** Cohort I: Comorbidities in gout patients – comparison between men and women.

	Men n = 167 (%)	Women n = 71 (%)	Significance
Arterial hypertension	124 (74%)	66 (94%)	P < 0.001
Transient ischemic attack	16 (10%)	10 (14%)	P = 0.39
Coronary heart disease	23 (14%)	30 (43%)	P < 0.001
Myocardial infarction	15 (9%)	5 (7%)	P = 0.85
Type 2 diabetes mellitus	43 (26%)	34 (49%)	P < 0.001
Obesity	44 (26%)	29 (42%)	P < 0.05
Hyperlipidemia	117 (70%)	40 (60%)	P = 0.17
Chronic renal failure	46 (28%)	55 (77%)	P < 0.001

tendency of both lower legs, against which she took diuretics, she reported herself actually healthy. She did not need any medication for a slight diabetes. The patient was admitted under suspicion of septic arthritis. Intravenous antibiotic therapy was started immediately after arthrocentesis, since the synovial fluid appeared purulent. In the synovial analysis, however, urate crystals were found en masse, no bacteria were detected. Laboratory results were notable for impaired kidney function (eGFR 55 mL/min) and a serum uric acid of 520 µmol/L (8.6 mg/dL).

When analyzing the data on women with gout, it was found that women often initially presented with a different suspected diagnosis (► **Fig. 4**). Antibiotic therapy was very often started, because

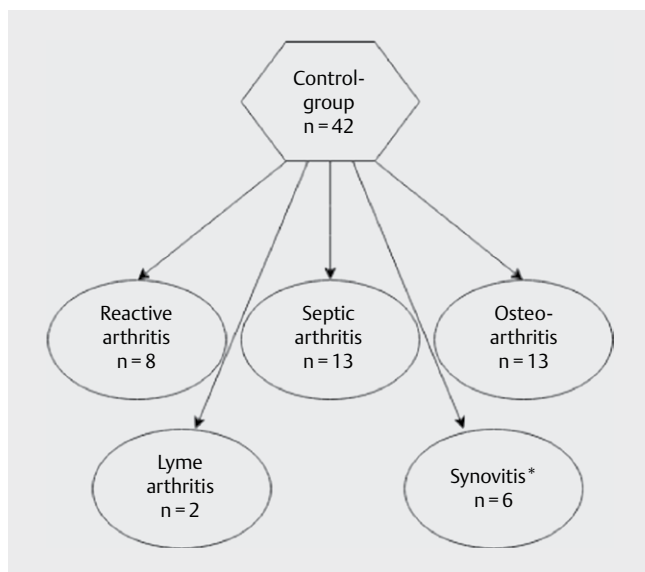
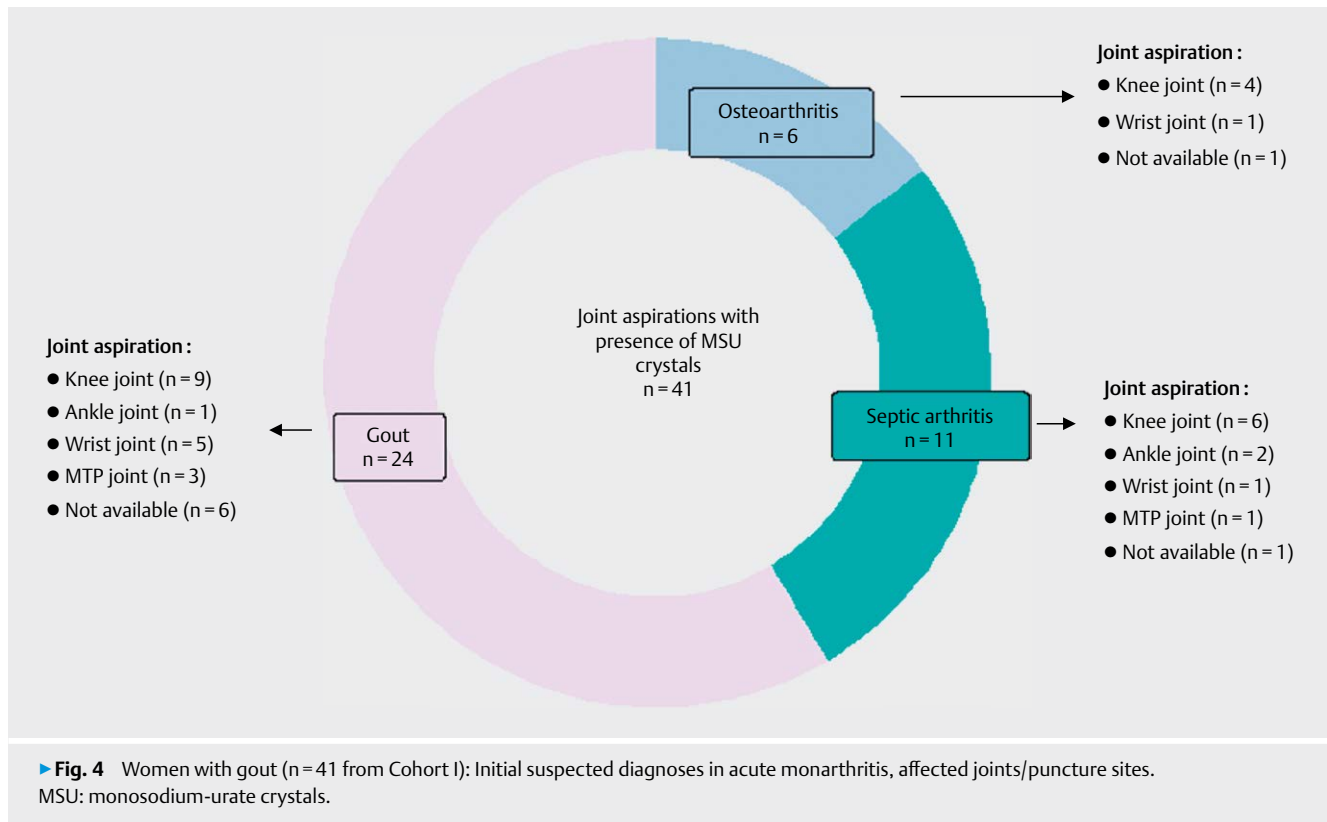
septic arthritis was suspected. In only about half of the patients was gout even considered in the primary differential diagnosis.

For this reason – and because the gout classification criteria apparently do not adequately reflect women with gout – the comparison was made between women with confirmed gout (with uric acid crystal detection) arthritis with those of other origins (uric acid crystals negative). 85 patients were included in cohort II: a group of women with confirmed gout (reference group, n = 43, including 2 additional gout patients not included into cohort I) and a group of women with acute arthritis of other origins (Control group, n = 42) (► **Fig. 5**). Both groups had a comparable median age: women with gout were a median of 78.5 years (SD ± 7.3), women with non-gouty arthritis had a median of 76.0 years (SD ± 6.7).

The differences in the localization of the joints affected by monarthritis were interesting: While the wrist and ankle were more often affected in gout, it was mostly the knee joint in patients with other monarthritis. The ankle joints were affected equally often in both groups (► **Fig. 4**).

Comorbidities

When looking at the comorbidities of both groups, significant differences were particularly noticeable in the cardiovascular risk profile. Patients with gout were significantly more likely to have cardiovascular comorbidities, impaired kidney function, type 2 diabetes, and a BMI of over 30. When analyzing other medications, only one clear difference was found with regard to diuretics: patients with gout were significantly more likely to have diuretics in long-term medication than patients with other forms of monarthritis. The results of the univariate logistic regression can be interpreted as follows in the presence of acute monarthritis:



- Ongoing diuretic therapy ($p < 0.001$): Patients on diuretics as long-term therapy were 46.5 times more likely to have urate crystals in the synovial fluid than patients who are not taking diuretics;
- Hyperuricemia (uric acid $> 390 \mu\text{mol/L}$; 6.5 mg/dL) ($p < 0.001$): women with a serum uric acid level $> 390 \mu\text{mol/L}$ had a 30.2-fold

increased probability of urate crystals in their synovial fluid than women with values $< 390 \mu\text{mol/L}$;

- Impaired kidney function (eGFR $< 60 \text{ mL/min/1.73 m}^2$) ($p < 0.001$): in women with impaired kidney function, urate crystals in the synovial analysis were found 24.3 times more often than in women with an eGFR value $> 60 \text{ mL/min/1.73 m}^2$;
- Diabetes mellitus type 2 ($p < 0.001$): Patients with diabetes were 8.4 times more likely to have urate crystals in the synovial fluid than those without;
- Age > 63 years of age ($p = 0.011$): women older than 63 years were 8.1 times more likely to have urate crystals in the synovial fluid than women younger than 63;
- Hypertension and/or atherosclerosis ($p = 0.02$): Women with arterial hypertension, transient ischemic attack or coronary heart disease were 6.1 times more frequently positive for urate crystals than women without one of these diseases;
- Obesity ($p = 0.01$): Patients with a BMI > 30 had a 4.6 times higher probability of having gout than patients with a BMI < 30 .

Discussion

Gout in women has so far been little explored. One reason for this is that gout is viewed as a disease of men [2, 15]. On the one hand, this is due to the fact that more men are affected by the disease (gout is the most common arthritis in men), on the other hand, gout usually affects men for the first time at their “prime” age [1]. Accordingly, therapeutic studies predominantly include men. Up to menopause, women are largely protected from developing hyperuricemia and gout by the uricosuric effect of the estrogens. With

the loss of hormones, however, there is also an increase in serum uric acid and an increase in the incidence of gout, even in women [4].

If one looks at current epidemiological data, there is a significant increase in gout incidence and prevalence also in women, especially after the age of 60. The prevalence of gout in women in the 6th decade of life is 1.3% and increases to over 3% in those over 80 [1, 2]. Therefore, gout is an important differential diagnosis in acute joint inflammation in older patients. Recent epidemiological studies from Sweden and the Netherlands show that women with gout have more comorbidities than men [7, 8]. Women with gout even have a higher cardiovascular risk profile than men with gout in the corresponding age group [10, 11].

The present analysis included patients who had been treated as inpatients for confirmed gout. The unusually high proportion of women (male: female: female; 2.4: 1, usually 9: 1) is partly explained by the selection of patients who were admitted to hospital because of the age of the patients, the severity of their illness, and the common suspicion of a septic process. When looking at the comorbidities, it becomes clear that women with gout usually had more than four other comorbidities. Almost all of them had a manifest cardiovascular disease.

In addition to the severity of the disease and an overall higher morbidity index among women as possible causes for the higher proportion of women in the population examined, the consideration of cohort II allows another conclusion. It turns out that only about half of the patients were initially diagnosed with gout. Other causes, mostly septic arthritis, were mostly assumed for their monoarthritis. Inpatient admission was often achieved by presenting women with acute monoarthritis to an emergency room (► Fig. 6). This is undoubtedly correct if septic arthritis is suspected. However, synovial fluid was frequently not analyzed beyond microbiology. The microscopic detection of urate crystals in the joint puncture continues to be the gold standard for confirming the diagnosis of gout [20–23]. If nobody with sufficient expertise is on site, this diagnostic step can also be carried out on the following days [24].

As an older publication indicates, the clinical presentation of gout in women often differs from that in men [11]. Podagra, which is typical for men, is less common. This is confirmed in our small cohort: the joints of the hands were more frequently affected.



► Fig. 6 First manifestation of gout in a 65-year old woman who presented to the surgical emergency room.

Women also had osteoarthritis significantly more often. Out of an attack, the clinical differentiation between activated osteoarthritis and gout can be a diagnostic challenge, especially since the cartilage damage caused by osteoarthritis promotes the precipitation of crystals [11, 14]. Radiological diagnostics do not help to detect early gout; mostly only the arthritic changes can be shown. This essentially also applies to dual-energy computed tomography DECT, which has its strength in the detection of tightly packed urate deposits (tophi), which can then often already be felt and seen clinically [18]. DECT can be helpful in differentiating changes in symmetrical joint changes from rheumatic nodules in rheumatoid arthritis [19]. In florid gouty arthritis with effusion, DECT is not sensitive. Moreover, the method is usually only available at centers [17]. Arthroscopic ultrasonography should always be used to detect typical early changes, such as urate crystal deposits on the cartilage (double contour) [16, 17]. In osteoarthritis, the representation of particularly small joints with regard to sonographic differentiation from gout in women has not yet been systematically investigated.

Analysis of the factors in patient history and clinical findings revealed that it was essentially the comorbidities that helped differentiate gout in women from other form of arthritis. Impaired kidney function, diabetes, obesity, hypertension or other cardiovascular concomitant diseases are significantly more common in women with gout. Osteoarthritis or hyperlipidemia, however, were not significantly different. Diuretics in women were associated with gout at a high level of significance; Women over the age of 60 were almost twice as likely to develop a gout attack when taking diuretics as women who were not taking diuretics. The connection between loop and thiazide diuretics, but not potassium-sparing diuretics, with the development of gout is well known [23]. Diuretics preferentially inhibit uric acid excretion via renal OAT1/4 transporters [25], resulting in hyperuricemia (and gout). Another relevant factor for the development of gout is kidney function. With functional impairment with reduced glomerular filtration (eGFR) <60 ml/min, the risk of gout increases significantly [26].

If the following health issues are present in the previous history of a female patient with acute monoarthritis, gout should definitely be high in the differential diagnosis: older age (from the age of 63), hypertension, diabetes, obesity and diuretic use. If there is also impaired kidney function (eGFR <60 ml/min) and increased serum uric acid (HSR >390 µmol/L; >6.5 mg/dL), this speaks all the more for gout (► Fig. 6).

Since the data were collected from a selected cohort of inpatient arthritis patients, further review in a larger arthritis cohort in women is necessary. Also, because the data were collected in an inpatient setting, the transferability of the statements obtained to the outpatient sector requires further examination.

In spite of all the enthusiasm for using the patient's history for making a diagnosis, thus can in no way replace the implementation of further decisive diagnostic measures, especially if septic arthritis cannot be ruled out with certainty [27, 28]. In the hands of the rheumatologist, arthrocentesis with both Gram stain and culture for pathogens and microscopic analysis of the synovial fluid to detect crystals continues to be the gold standard.

Conclusions

These comparisons of gout in men and women (cohort I) reveal relevant gender-specific differences in clinical and laboratory characteristics. When gout is first diagnosed, women are older, have more comorbidities and often show a different clinical presentation. The clinical gout diagnostic score, which has been tried and tested for men, does not seem to be transferable to women.

Since the incidence and prevalence of gout increases significantly, especially in women over the age of 60, gout needs to be considered in all female patients with cardiovascular and metabolic disease. If combined with severely impaired renal function and/or long-standing diuretics, any monoarthritis likely is gout.

Conflicts of interest

AKT has received speakers fee related to the topic: lecture and consultancy fees from Berlin Chemie Menarini, Novartis, Grünenthal. Research grants from Menarini, Astra Zeneca. Co-author of recommendations for gout: DGRh and EULAR. AG and MA declare no conflict of interest related to the topic.

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