

The validity of gout diagnosis in primary care, results from a patient survey

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Objective

Validate primary care diagnosis of gout by the Mexico and Netherlands classification criteria.

Methods

Questionnaires on gout characteristics was sent to all individuals aged ≥ 18 with ≥ 1 ICD-10 diagnosis of gout at 12 primary care centers.

Results

Positive predictive values for gout diagnosis ranged from 71% for the Netherlands criteria to 80% for the Mexico criteria. Maximum inflammation within 24 hours was the most common reported symptom (86%).

Conclusion

The vast majority of gout cases in primary care fulfill classification criteria and are valid for research purposes.

Introduction

Gout is mainly diagnosed and managed in primary care (PC). The diagnostic gold standard for gout is detection of monosodium urate (MSU) crystals in synovial fluid, a procedure rarely performed in PC (1). To enable uniform definition of diseases, especially in research, classification criteria have been developed. The first gout classification criteria, Rome 1963 (2) and New York 1966 (3), were developed using expert opinion and relied largely on the presence of tophi and MSU crystals. The 1977 American Rheumatism Association (ARA) criteria (4), the 2010 Mexico criteria (5) and the 2010 Netherlands criteria (6) incorporated several clinical characteristics of gout and are not primarily based on synovial fluid analysis. Although widely used historically, the ARA criteria are still only preliminary criteria since they have not been extensively validated and it should also be noted that they were developed for acute arthritis of gout. The ACR/EULAR criteria (7) from 2015 also includes imaging modalities. Of the currently available criteria only the Rome, New York and ARA criteria have been validated in PC populations (8, 9). It is of great importance to know how valid a clinical diagnosis of gout in PC is, especially to facilitate subject recruitment for PC gout researchers. In this study we wanted to validate the PC diagnosis of gout against published classification criteria using self-reported data from patients overall and by sex.

Methods

All individuals aged ≥ 18 years with ≥ 1 ICD-10 diagnosis of gout (M10) recorded by a physician during a two year period (2015-2017) were identified at 12 PC centers in the Western Sweden Health Care Region. Patients were sent a questionnaire with questions on

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demographics, comorbidities and gout characteristics. All participants were informed in writing that the reported data would be published and returning the questionnaire was considered informed consent.

Specifically related to gout they were asked about items included in the Mexico (5) and Netherlands (6) gout classification criteria: knowledge of elevated serum urate, presence of tophi (with illustration), podagra/MTP-1 involvement, >1 attack of acute arthritis, maximum inflammation within 24 hours, redness over the joints, unilateral tarsal joint attack, mono- or oligoarticular attacks, male sex, hypertension and/or cardiovascular disease (CVD) defined as previous myocardial infarction or stroke.

These two sets of classification criteria stem from an experienced need for classification and diagnostic tools in a setting where joint fluid isn't easily obtained, like in PC. The Mexico criteria is based on items from the ACR (4) and EULAR (10) criteria and were developed in patients seen at rheumatology units. In the Netherlands criteria a broader array of clinical and laboratory variables were tested for their ability to diagnose MSU crystal positive versus negative PC patients with acute monoarthritis, groups which entailed men in 96% and 90 %, respectively.

The Netherlands criteria require ≥ 8 points for classifying patients as highly likely to have gout. A score of 4-8 calls upon further investigation, e.g. joint fluid analysis. The importance of male sex is demonstrated by the fact that this item is rewarded with 2 points. In the current setting with 20% postmenopausal women, average age 76 years, we also applied the Netherlands criteria disregarding sex as an item and requiring only 6 points ($8-2=6$) for high likelihood of gout diagnosis. The Mexico criteria consists of 8 items and ≥ 4 is required for classification as gout.

The ARA (4) and the ACR/EULAR (7) criteria were not used since they are dependent upon imaging and joint fluid analysis.

Thus, the ICD-10 gout diagnosis was used as index test and the Mexico and Netherlands criteria as reference tests.

Primary non-responders received a second mailing of the questionnaire. Ten percent randomly selected among those still not responding were interviewed by telephone to characterize the group of non-responders.

Ethical approval was granted from the Ethical Review Board of Gothenburg, Sweden (519-16).

Positive predictive values (PPV) were calculated by dividing the number of patients who met the Mexico/Netherlands classification criteria by the total number of patients who were diagnosed with gout in the medical record. Gender differences regarding fulfilment of classification criteria and frequency of reported gout characteristics were calculated using Chi-square test.

Results

A total of 1444 individuals with a gout diagnosis were identified and sent the questionnaire. After one reminder questionnaire, 784(54.3%) individuals responded. Non-responders were overrepresented in young men. Among responders, mean age was 72 years and 80% were men. Ever smoking and history of kidney stone were significantly more common in men, $p=0.0003$ and $p=0.0007$ respectively, whereas women were significantly older, $p=0.0001$ (Table 1). Women reported a non-significant higher frequency of tophi and prescription of urate lowering treatment(Table 1). 738(94%) gave valid answers to all classification criteria items. The PPV in the total cohort ranged from 71 to 80% for the different criteria used(Table 2). Applying the criteria sets on men and women separately rendered no difference for the Mexico criteria while for the Netherlands criteria women had a PPV of only 46% compared to 77% for men(Table 2). When disregarding sex as an item in the Netherlands criteria the PPV increased to 76% in women (Table 2). Including only subjects who reported knowledge of increased serum urate rendered PPV of 94% and 93% for the Mexico and Netherlands criteria respectively. Similar results were found among those interviewed only by telephone (not shown). The five most common classification criteria items reported were experienced by the vast majority of respondents(Table 2). Podagra/MTP-1 involvement was significantly more common in men ($p=0.004$) whereas CVD and tophi were slightly but not significantly more common in women(Table 2). Knowledge of increased serum urate was reported by only 42% of the patients(Table 2).

Discussion

In the present study, we found that the PPVs for being classified as having gout ranged from 71 to 80 %. The five most common classification criteria items reported were maximum inflammation within 24 hours, CVD, redness over the joints, podagra/MTP-1 involvement and >1 attack of acute arthritis.

These PPVs were similar to the results in a previous validation study in the same geographical region, based on medical records (1), supporting the validity of the current findings.

The Mexico and Netherlands criteria have been validated in two published studies compared to MSU crystal assessment in rheumatology settings. Taylor (11) and Jatuworapruk (12) collected 983/233 persons in the United States/Thailand with suspected gout/acute arthritis, average age 60/65 years, 14%/19% women. For the Netherlands criteria sensitivity was 73-88% for patients with recent onset symptoms and 92-96% for patients whose symptoms began at least two years earlier, with specificities of 75-86% and 47-50% respectively. The Mexico criteria performed slightly better with sensitivity of 87-89% for patients with recent onset symptoms and 99% for patients whose symptoms began at least two years earlier and with specificities of 66-82% and 31-34% respectively. Thus, both criteria sets displayed high sensitivity although it should be kept in mind that these studies were performed in rheumatology settings and therefore possibly have included patients with more severe gout, compared to the PC setting in the current study. Many items are similar between the two criteria sets although in the Netherlands criteria the items are weighed from 1 to 3.5 points while all items are weighed equally in the Mexico criteria.

Gout is predominantly a male disease especially in the age spans of premenopausal women. In our study, the women were postmenopausal, average age 76 years, and had a low PPV (46%) for the Netherlands criteria. If we on the other hand disregarded sex as an item in the criteria set 76% would be classified as gout cases. In the published validation studies (11, 12) subanalysis by sex were not performed.

A minority of the patients in our study were aware of increased urate levels, probably due to gaps in information(13), lack in recall and maybe also partly due to physician non-adherence to guidelines recommendation of urate monitoring (14).

A limitation of this study is the response rate at 54.3%, which may have hampered generalizability, particularly since it was slightly skewed with regard to age and sex. It is however a common phenomenon in our setting that younger men are poor responders to questionnaires (15-17). Furthermore, the 10% of the non-responders that were interviewed by telephone reported similar frequencies for the gout classification items as responders. A second possible limitation is the low awareness of increased serum urate among the respondents; however, this could at least partly reflect poor adherence to guidelines. A third limitation to the study is that we were not able to apply the 2015 ACR/EULAR (7) criteria. Finally, some of the items reported by the patients as well as the ICD-10 code is generated by the PC physician, thus not completely independent from each other.

A strength of this study is the population based health care setting.

To conclude, the vast majority of patients diagnosed with gout in PC have clinical symptoms compatible with the disease and fulfill the Mexico and Netherlands classification criteria. A gout diagnosis in PC is valid for identifying patients for research purposes.

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	Total, n=738	Men, n=598	Women, n=140	p-value
Age, mean (SD)	71.9 (11.5)	70.9 (11.4)	75.8 (11.5)	0.0001
BMI, mean (SD)	28.5 (9.8)	28.3 (10.6)	29.0 (5.2)	0.45
Smoking ever, n (%)	389 (53)	335 (56)	54 (39)	0.0003
Diabetes, n (%)	173 (23)	141 (24)	32 (23)	0.8
Myocardial infarction, n (%)	112 (15)	95 (16)	17 (12)	0.2
Stroke, n (%)	73 (10)	60 (10)	13 (9)	0.7
Kidney disease, n (%)	57 (8)	42 (7)	15 (11)	0.1
Kidney stone, n (%)	101 (14)	94 (16)	7 (5)	0.0007
Hypertension, n (%)	488 (66)	389 (65)	99 (71)	0.18
Dyslipidemia, n (%)	249 (34)	194 (32)	55 (39)	0.1
Tophus, n (%)	102 (14)	75 (13)	27 (19)	0.07
ULT ever, n (%)	497 (67)	408 (68)	89 (64)	0.36

Table 1 Characteristics of the gout questionnaire respondents, SD=standard deviation, ULT=urate lowering therapy,

Gout classification criteria	Total, n=738	Men, n=598	Women, n=140	p-value
Fulfilling Mexico criteria, n PPV % (95% CI)	588 80 (77-82)	481 80 (77-83)	107 76 (69-83)	0.29
Fulfilling Netherlands criteria, n PPV % (95% CI)	522 71 (67-74)	458 77 (73-80)	64 46 (38-54)	< 0.0001
Fulfilling Netherlands criteria without item sex, n PPV % (95% CI)	564 76(73-79)	458 77 (73-80)	106 76(68-82)	0.8
Individual classification criteria items	Total, n=738	Men, n=598	Women, n=140	p-value
Maximum inflammation developed within 1 day, n (%)	636 (86)	520 (87)	116 (83)	0.2
Hypertension or ≥ 1 cardiovascular disease*, n (%)	580 (79)	464 (78)	116 (83)	0.19
Redness observed over the joints, n (%)	564 (76)	459 (77)	105 (75)	0.62
A history or observation of podagra/MTP-1 involvement, n (%)	464 (63)	391 (65)	73 (52)	0.004
More than one attack of acute arthritis, n (%)	437 (59)	353 (59)	84 (60)	0.8
High serum urate, n (%)	309 (42)	251 (42)	58 (41)	0.8

Table 2 Positive predictive values (PPV) for gout diagnosis and the six most common individual classification criteria items reported with the exception of male sex, CI=confidence interval,

**cardiovascular disease here defined as myocardial infarction or stroke,*