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An optimal ultrasonographic diagnostic test for early gout: A prospective controlled study

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Abstract

Objective: To identify the optimal sites for classification of early gout by ultrasonography.

Methods: Sixty patients with monosodium urate crystal-proven gout (25 with early gout [≤2-year symptom duration], 35 with late gout [>2-year symptom duration], and 36 normouricemic healthy controls) from one centre were prospectively evaluated. Standardized blinded ultrasound examination of 36 joints and the triceps and patellar tendons was performed to identify tophi and the double contour (DC) sign.

Results: Ultrasonographic sensitivity was lower in early than late gout. Binary logistic regression analysis showed that two ultrasonographic signs (tophi in the first metatarsophalangeal joint [odds ratio, 16.46] and the DC sign in the ankle [odds ratio, 25.18]) significantly contributed to the final model for early gout diagnosis (sensitivity and specificity of 84% and 81%, respectively). The inter-reader reliability kappa value for the DC sign and tophi was 0.712.

Conclusions: Four-joint investigation (both first metatarsophalangeal joints for tophi and both ankles for the DC sign) is feasible and reliable and could be proposed as a screening test for early ultrasonographic gout classification in daily practice.

Keywords

Gout, ultrasound, tophus, double contour sign, diagnostic test

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Introduction

Gout is considered the most common form of arthritis in adults, with a prevalence ranging from 2.5% to 6.1% in the general population.[1–5] Gout has been recognized as an independent risk factor for mortality and morbidity.[6] Early diagnosis, possibly even in the asymptomatic hyperuricemic stage, is needed to prevent poor outcomes. The gold standard diagnostic technique for gout is detection of monosodium urate (MSU) crystals in synovial fluid.[7–9] However, this is an invasive procedure and does not allow for evaluation of either the extent of urate deposition or the response to urate-lowering treatments. Ultrasonography (US) has recently been proposed for these purposes.[10,11] The new American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) gout classification criteria are the first to incorporate US evidence of the double contour (DC) sign, an articular cartilage abnormality related to the deposition of crystals on the surface of the hyaline cartilage, as a sign specific to gout.[12] The specificity and sensitivity of other gout-related elementary US lesions, such as the presence of tophi, still need to be evaluated in prospective trials.[12,13] The sensitivity and negative predictive value of US signs of MSU deposition in symptomatic joints is only about 60%, while examination of multiple joints gives better results.[14] Naredo et al.[15] proposed a 12-site US examination including the upper and lower extremities and two tendons; this technique showed 84.6% sensitivity and 83.3% specificity for gout diagnosis. Peiteado et al.[16] performed an uncontrolled study of a time-saving 6-minute US examination of four joints in the lower extremities (knees and first metatarsophalangeals [MTPs]), which allowed for the detection of "hyperechoic cloudy areas" and/or the DC sign in 97% of cases. Since the aforementioned studies, most gout US imaging studies have investigated patients with advanced-stage gout[17] with an average disease duration of 7 years. Therefore, which and how many sites should be investigated for optimal US gout classification in patients with early-stage gout remains unclear.

Our goal was to compare the diagnostic value of US in early- versus late-stage gout and to establish an optimal multiple-site US test for early gout classification.

Methods

The prospective case-control single-centre study was performed from 2013 to 2016. The study was approved by the Lithuanian University of Health Sciences Kaunas Region Biomedical Research Ethics Committee. Written informed content was obtained from all patients before study entry.

Participants

For inclusion in the study, participants had to be >18 years old and meet one of the following two criteria: (1) have a diagnosis of gout as stated by a rheumatologist and confirmed by the study investigators according to the presence of MSU crystals in a symptomatic (ever) joint or bursa and have no acute gout attack at the time of US examination, or (2) have a healthy clinical status with a serum uric acid (UA) concentration of ≤404 μmol/L (6.8 mg/dL) without objective or subjective joint symptoms. Patients with gout were recruited from those who had been referred from a primary care facility for a rheumatology consultation. Patients with other inflammatory diseases or psoriasis were excluded. The participants were divided into four groups for statistical analysis: whole gout (all patients with gout), early gout (≤2 years from the first attack), late gout (>2 years from the first attack), and healthy controls.

Sample size calculation

The primary effect variable used for the power calculation was the proportion of tophi or DC signs found per joint site on US examination. With an assumption of a calculated expected sensitivity of 49% for tophi or the DC sign in patients with advanced gout, 23% in patients with early gout, and 2% in healthy controls; based on the sensitivity reported at different joint sites in previous studies[15,18–20]; and aiming for a power of 0.80 and a risk of 0.05 for type 1 errors, a minimum of 49 joints was required per site for comparison between patients with early and late gout, and a minimum of 29 joints was required for comparison between patients with gout and healthy controls. Because bilateral assessment of each site was planned, a minimum of 25 participants was required in each group.

Clinical and laboratory assessment

All participants underwent a clinical assessment and blood sampling by a rheumatologist. Demographic data (age and sex), height, weight, and the serum concentrations of UA, C-reactive protein, and creatinine were obtained for all participants. Disease history (symptom duration and the numbers of gout attacks throughout life and within the last year) and the presence of subcutaneous tophi were recorded for all patients with gout.

US assessment

Standardized US examinations were performed for all participants by one rheumatologist (M.P.) who had 10 years of experience in musculoskeletal US and was blinded to the patient groups and clinical data. The LOGIQ e US system with a 12-MHz linear transducer on a B-mode scale was used for all US examinations. Obtained views were recorded to the digital file for each participant. Thirty-six joints (both wrists, metacarpophalangeals [MCPs], hand proximal interphalangeals, knees, ankles, and MTPs and four tendons [both triceps and patellar tendons]) of each participant were assessed. All joints were scanned in the longitudinal plane on the dorsal side. Knees were explored in the longitudinal and transverse planes in the suprapatellar and parapatellar joint recesses on full extension of the leg for joint cavity evaluation, longitudinally at 20 degrees of flexion for patellar tendon evaluation, and transversally at maximal flexion for femoral cartilage evaluation. The ankles were investigated in the longitudinal plane on the dorsal and lateral sides. These views were chosen according to the guidelines for musculoskeletal US.[21–23] The areas scanned were defined based on typical gout clinics and previously published literature.[15,24,25] Joints were investigated for the presence of the DC sign and tophi. Tendons were investigated for tophi. US features of MSU crystal deposition (Figure 1) were chosen based on the literature[15,21,26–29] and personal experience. Specifically, an intraarticular tophus was defined as a circumscribed heterogeneous, hyperechoic/isoechoic (relative to subdermal fat) mass, sometimes with hypoechoic inclusions and with or without a small anechoic rim. The DC sign was defined as a hyperechoic band over the superficial margin of the articular hyaline cartilage, visible independent of the angle of insonation. An intratendinous tophus was defined as a circumscribed heterogeneous, hyperechoic/isoechoic (relative to the tendon fibres) aggregation with poorly defined margins and with or without areas of acoustic shadowing, changing the normal course of the tendon fibres.

US reliability

Prior to the study, two investigators (M.P. and E.N.) scanned 10 patients with gout

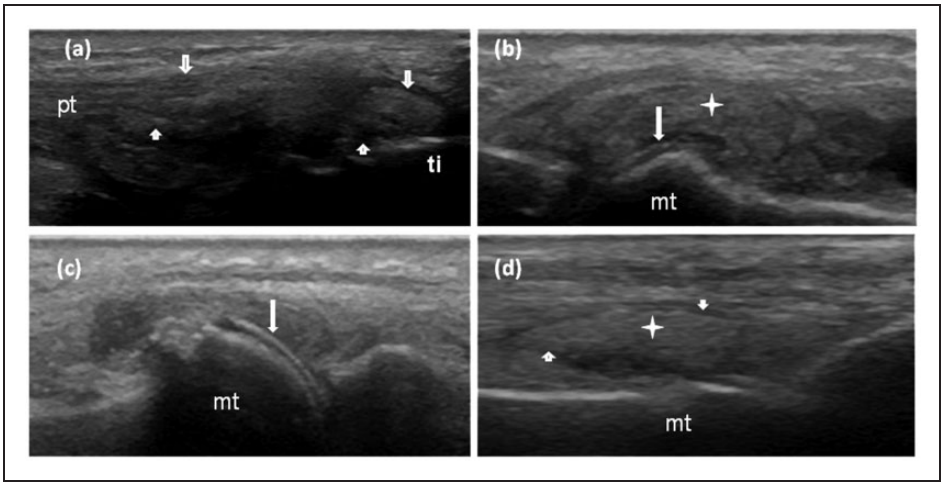

Figure 1. Specific ultrasonography (US) changes in gout. (a) Longitudinal US image at the lower part of the patellar tendon, revealing intratendinous heterogeneous tophaceous deposits (arrows) with poorly defined margins and posterior acoustic shadowing. (b) Longitudinal dorsal US image of the first metatarsophalangeal (MTP) joint with a nonhomogeneous (hyperechoic with hypoechoic inclusions) tophus-like mass (star) and double contour sign (arrow). (c) Longitudinal dorsal US image of the first MTP joint: double contour sign (arrow). (d) Longitudinal dorsal US image of the third MTP, revealing a homogeneous hyperechoic mass: tophus (star) with a visible small anechoic rim (between the arrows) without posterior acoustic shadowing. pt, patellar tendon; ti, tibia; mt, metatarsal bone.

(not included in the study) who had visible subcutaneous tophi to discuss the scanning technique, clarify previously reported definitions of gout lesions, and identify typical signs of gout deposits. To calculate the reliability and reproducibility of the US assessment, a Web-based exercise was performed at the start of the study. Eighty-four digitally recorded US images with or without urate deposits in different investigated areas of both patients and controls were randomly selected from the database and evaluated twice at a 3-week interval for the presence or absence of MSU deposits by two rheumatologists: M.P. (the investigator who obtained the US images) and E.N. (4 years of experience in US and special skills in gout US). Both rheumatologists were blinded to the patients' clinical data. The results reported by investigator M.P. or upon agreement were used for statistical analysis.

Synovial fluid investigation

US-guided aspiration from symptomatic (ever) joints or bursas was performed by the two above-mentioned study investigators (M.P. and E.N.) in all patients with gout before inclusion in the study. Healthy controls underwent aspiration when they had pathological US findings (tophus or DC sign) and if they agreed to undergo an intervention. Synovial fluid was analysed for MSU crystals by polarized light microscopy on the same day as the aspiration. Analysis was performed by two trained rheumatologists. One of them was an independent assessor who was blinded to the patients' clinical data and US results. Discrepancies between estimators were resolved by consensus.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 20.0

(IBM Corp., Armonk, NY, USA). Continuous variables are presented as as mean ± standard deviation or median, and categorical variables are presented as frequency and percentage. The frequencies of US findings were calculated first as proportions (displayed by participants) and second at individual investigated sites. Paired means between groups were compared using the Mann–Whitney test or Student's t test and Pearson's chi-square test or Fisher's test for categorical variables, as appropriate. All tests were two-tailed. The reliability analysis was performed using unweighted Cohen's k-statistic for dichotomous assessment (i.e., presence or absence), and the k-statistic was interpreted as follows: 0.00–0.20, slight reliability; 0.21–0.40, fair reliability; 0.41–0.60, moderate reliability; 0.61–0.80, substantial reliability; and >0.80, almost perfect reliability.[30] To identify the most important sites and signs for US gout classification, only variables with a p-value of <0.05 in the chi-square test and a Cramer's V of >0.3 were subjected to binary logistic regression with the forward stepwise conditional method. The diagnostic value of the developed set of US features for US gout classification was estimated using a classification table: sensitivity of prediction (percentage of patients classified correctly) and specificity of prediction (percentage of controls classified correctly). All p-values of <0.05 were considered statistically significant.

Results

The data of 96 participants were chosen for analysis: 60 patients (53 men) with primary gout proven by the presence of crystals (25 classified as early gout, 35 as late gout) and 36 healthy controls (28 men). Seventeen patients clinically suspected to have gout were screened for the study, but gout was not confirmed by crystal microscopy and the patients were not analysed. The demographic and clinical characteristics of the study participants are displayed in Table 1. There were no differences in sex or age between the two groups. The median disease duration in the whole gout group was 3 (0, 1–33) years. A total of 35% (21/60) of the patients with gout were undergoing treatment with hypouricemic agents, but only 13% (8/60) had a serum UA concentration of <360 μmol/L. Tophi were clinically identified in 40% (24/60) of the patients with gout. Patients in the early and late gout subgroups were similar in terms of the UA concentration, C-reactive protein concentration, glomerular filtration rate, diuretic use, and body mass index; however, patients with early gout had fewer gout attacks during the last year/throughout life and had no tophi compared with patients in the late gout group (all $p < 0.0001$).

US gout lesions: Frequencies and comparison between groups

In total, 2160 joints and 240 tendons of the patients with gout were evaluated and compared with 1296 joints and 144 tendons of the healthy controls. The investigated US signs in patients and controls, expressed as the number and percentage of affected anatomical sites, are shown in Figure 2. Comparisons of the tophus and DC sign frequencies in the investigated anatomical areas between the early and late gout subgroups are shown in Figure 3; tophi and DC signs were less often found in all investigated areas in the early than late gout subgroup on US examination. The frequencies of tophi and DC signs, expressed as the number and percentage of participants with affected anatomical regions between patients and controls, are displayed in Table 2; a tophus and DC sign in one or more joint areas (36 investigated joints) were found more often in the patients than controls, with a sensitivity of 85% and 87% and specificity of 83% and 86%, respectively

Table 1. Clinical and demographic data of the study population
Data are presented as mean ± standard deviation or n (%) unless otherwise indicated.

	Early gout group (N = 25)	Late gout group (N = 35)	Healthy control group (N = 36)	p value
Sex (male/female), n	19/6	33/2	28/8	ns
Age, y	52.6 ± 12.4	54.6 ± 10.1	51.5 ± 15.3	ns
Serum UA, μmol/L	501.1 ± 122.3[a]	496.7 ± 145.3[a]	320.47 ± 50.6	<0.0001
GFR, mL/min	99.6 ± 44.0	104.9 ± 42.5	96.9 ± 30.5	ns
CRP, mg/L	13.7 ± 13.3[a]	16.3 ± 18.4[a]	3.5 ± 5.6	<0.0001
BMI, kg/m^2	32.37 ± 5.9[a]	32.35 ± 4.6[a]	26.77 ± 4.4	<0.0001
Diuretic use	5 (20.8)[a]	11 (31.4)[a]	1 (2.8)	<0.01
UA < 360 μmol/L	5 (20.8)	3 (8.6)	NA	ns
Tophus found on clinical examination	0 (0.0)[b]	24 (68)[b]	NA	<0.0001
ULT use	2 (8.0)[b]	19 (54.3)[b]	NA	<0.0001
Duration of gout symptoms, y	0.84 ± 0.60 (median, 0.83)[b]	10.47 ± 8.40 (median, 8.00)[b]	NA	<0.0001
Gout attacks in last year, n	2.5 ± 1.4 (median, 3.0)[b]	16.1 ± 24.8 (median, 6.0)[b]	NA	<0.0001
Gout attacks in life	3.4 ± 2.3 (median, 3.0)[b]	114.6 ± 186.3 (median, 34.0)[b]	NA	<0.0001

GFR, glomerular filtration rate; CRP, C-reactive protein; BMI, body mass index; UA, uric acid; ULT, urate-lowering therapy; NA, not applicable; ns, not significant
[a]Significant difference compared with control group
[b]Significant difference between early and late gout groups

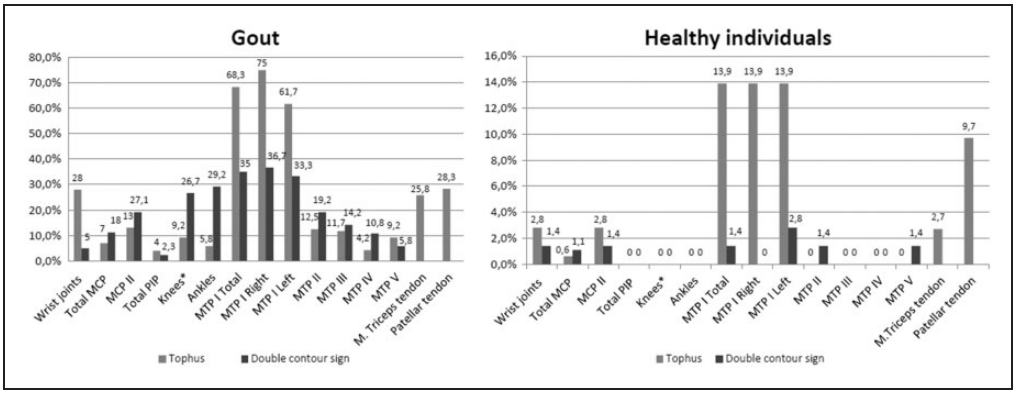

Figure 2. Ultrasonography findings in patients with gout and controls in different anatomical sites displayed as number (%) found with the pathology in the investigated anatomical site. MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; T, tophus; DC, double contour. *Suprapatellar and parapatellar joint recesses or femoral cartilage.

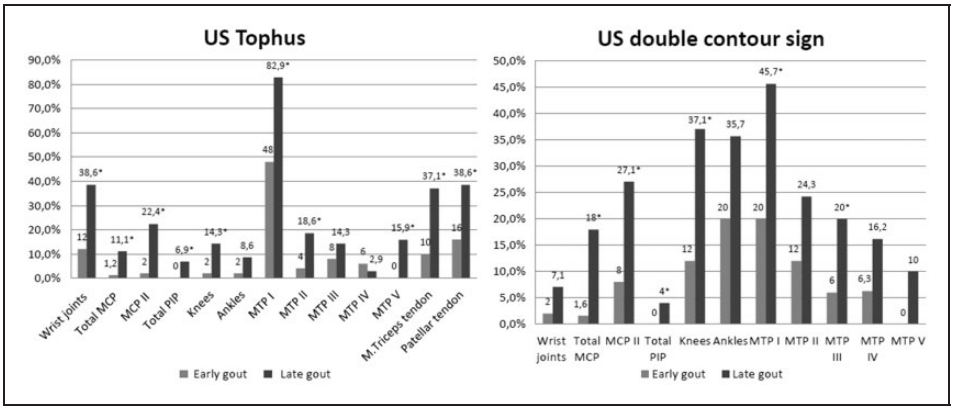

Figure 3. Difference between early gout (symptom duration of ≤2 years) and late gout (symptom duration of >2 years) according to the percentage of tophus and double contour sign at different anatomical sites. US, ultrasonography; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal joint. *$p < 0.05$.

Table 2. Ultrasonographic lesions by anatomic location (unilateral or bilateral) in patients and controls.

Investigated sign and location	Gout (N = 60)	Healthy controls (N = 36)	p-value	Kramer's V*
T ± DC sign, all sites (40)	58 (97.0%)	16 (44.0%)	<0.001	ne
T ± DC sign, joints (36)	57 (95.0%)	11 (30.6%)	<0.001	ne
DC sign, all joints (36)	52 (86.7%)	5 (13.9%)	<0.001	ne
T, all sites (40)	56 (93.0%)	11 (30.6%)	<0.001	ne
T, all joints (36)	51 (85.0%)	6 (16.7%)	<0.001	ne
T, wrists	23 (38.3%)	1 (2.8%)	<0.0001	0.398
T, MTP I	50 (83.3%)	6 (16.7%)	<0.0001	0.655
DC sign, MCP II	19 (31.7%)	1 (2.8%)	0.001	0.344
DC sign, knee	19 (31.7%)	0 (0.0%)	0.001	0.344
DC sign, ankles	24 (40.0%)	0 (0.0%)	<0.001	0.411
DC sign, I MTP	20 (50.0%)	1 (2.8%)	<0.001	0.489
DC sign, II MTP	17 (28.3%)	1 (2.8%)	0.002	0.317
DC sign, III MTP	13 (21.7%)	0 (0.0%)	0.003	0.307
T, m. triceps tendon	22 (36.7%)	2 (5.6%)	0.001	0.348
T, patellar tendon	24 (40.0%)	6 (16.7%)	0.02	0.244
T, all tendons (4)	32 (53.0%)	8 (22.0%)	0.003	ne

Data are presented as n (%).

US, ultrasound; T, tophus; DC, double contour sign; MCP, metacarpophalangeal; MTP, metatarsophalangeal; ne, not evaluated.

*A measure of association between two nominal variables (sign and gout diagnosis)

(all $p < 0.001$). Any sign of crystal deposition (tophus and/or DC sign) in one or more investigated areas with 56% specificity was found in 97%, 100%, and 92% of our whole, late, and early gout patients, respectively. A tendon tophus with 78% specificity was found in 53% of patients with gout ($p < 0.01$).

Optimal set of US lesions for gout classification

The parameters entered into the binary logistic regression model were wrist tophus, second MTP tophus, triceps tendon tophus, second MCP DC sign, knee DC sign, first MTP tophus, ankle DC sign, first MTP DC sign, and second MTP DC sign (all with Cramer's V of >0.3) (Table 2). The predictors that contributed to the model and were therefore considered to be independently associated with US gout classification using the whole gout group and controls were a tophus in the first MTP joint (odds ratio [OR], 20.21; 95% confidence interval [CI], 4.42–92.31; $p < 0.0001$), a tophus in the triceps tendon (OR, 8.80; 95% CI, 0.96–80.65; $p = 0.054$), the DC sign in the ankle (OR, 30.01; 95% CI, 2.42–372.92; $p = 0.008$), the DC sign in the first MTP joint (OR, 11.11; 95% CI, 0.95–130.55; $p = 0.055$), and the DC sign in the second MTP joint (OR, 27.06; 95% CI, 2.02–361.84; $p = 0.013$), with a sensitivity and specificity of prediction of 93% and 78%, respectively. When the same parameters were entered into a binary logistic regression analysis, only two signs contributed to the model in the early gout subgroup: a tophus in the first MTP joint (OR, 16.46; 95% CI, 4.04–67.13; $p < 0.0001$) and the DC sign in the ankle (OR, 25.18; 95% CI, 2.30–276.35; $p = 0.008$), with a sensitivity and specificity of 84% and 81%, respectively (Table 3). Inclusion of the upper extremity joints, patellar tendons, and knee joints in the regression model did not improve the model at any stage of the disease. Using Pearson's chi-square test, we also checked the sensitivity and specificity of two tests for US gout classification proposed in the literature[15,16] using our whole gout cohort and the early and late gout subgroups (Table 4). The sensitivity and specificity of all tests (including those created with the regression analysis (Table 3) and those proposed in the literature (Table 4)) were similar, with

Table 3. Parameters associated with ultrasonographic gout classification* on binary logistic regression, tested in the whole gout group and early gout subgroup.

	OR	95% CI	p-value
Whole gout group (all 60 patients)**			
Tophus, I MTP	20.21	4.42–92.31	0.000
Tophus, m. triceps tendon	8.80	0.96–80.65	0.054
Double contour sign, ankle	30.01	2.42–372.92	0.008
Double contour sign, I MTP	11.11	0.95–130.55	0.055
Double contour sign, II MTP	27.06	2.02–361.84	0.013
Sensitivity of the model, 93%			
Specificity of the model, 78%			
Early gout subgroup (25 patients)***			
Tophus, I MTP	16.46	4.04–67.13	0.000
Double contour sign, ankle	25.18	2.30–276.35	0.008
Sensitivity of the model, 84%			
Specificity of the model, 81%			

CI, confidence interval; OR, odds ratio, MTP, metatarsophalangeal; MCP, metacarpophalangeal

*With parameters entered into the regression model: tophus in wrist, tophus in II MTP, tophus in patellar tendon, double contour sign in II MCP, double contour sign in knee.

**Negelkerke R^2 statistic was 0.731 in step 5

***Negelkerke R^2 statistic was 0.521 in step 2

Table 4. Sensitivity and specificity of two ultrasonographic gout tests proposed in the literature, evaluated in the whole study population and in the late and early gout subgroups.

Investigated anatomical areas; signs	SW (N = 60)	SL (N = 35)	SE (N = 25)	SP
12 areas (8 J + 4 Te), 12 signs*: DC knees (DC II MCP), DC ankles, DC I MTPs, T wrists, T PTs, T MTTs	88 (85)	94 (94)	80 (72)	75 (72)
4 J, 8 signs**: DC knees, DC I MTPs, T knees, T I MTPs	87	94	76	81

J, joint; Te, tendon; T, tophus; DC, double contour sign; MTPs, metatarsophalangeals; PTs, patellar tendons; MTTs, musculus triceps tendons; MCP, metacarpophalangeal; SW, sensitivity whole gout; SL, sensitivity late gout; SE, sensitivity early gout; SP, specificity

*Described by Naredo et al.[15]

**Described by Peiteado et al.[16]

better sensitivity in late versus early gout in all cases.

Intra- and inter-reader agreement (κ) of US findings

The κ value for inter-reader agreement for cartilage was 0.671 and that for tophus was 0.773; the mean κ value for inter-reader agreement was 0.712. The intra-reader (M.P.) agreement for cartilage was 0.657 and that for tophus was 0.770; the mean κ value was 0.740. The intra-reader (E.N.) agreement for cartilage was 0.727 and that for tophus was 0.828; the mean κ value was 0.809. The strength of agreement was considered good or very good.

Concordance between US findings and microscopic evaluation of MSU crystals

Forty-five intra-articular tophi found by US examination (39 randomly selected from patients with gout and 6 from healthy controls) were aspirated. MSU crystals were microscopically identified in 80% of participants (36/45). Six crystal-negative samples were from the healthy control group, and three were from the clinically suspected gout group (all from the first MTP joint). Thirty-six tophi found in the first MTP joint on US examination were confirmed by MSU crystal identification in 75% of participants. Aspiration of these tophi in patients with gout revealed MSU crystals in 90% (27/30) of patients. In five joints with only the DC sign present on US examination, crystals were found in 80% of cases (one crystal-negative sample was from the healthy control group). The combination of a tophus plus the DC sign on US examination showed 100% concordance (12/12) with MSU crystal identification.

Discussion

To meet the study goals, only patients with gold standard-proven gout (confirmed by MSU crystal detection in synovial fluid) and who fulfilled the recent 2015 ACR-EULAR diagnostic criteria for gout[12] were included in the study and compared with healthy controls. The median duration of the gout symptoms in our whole cohort was 3 years, and 40% of the patients with gout had subcutaneous tophi. This is characteristic for a typical gout population but differs from most previous studies[15,16,18,19,31] that reported the value of US in patients with advanced tophaceous gout. We separately analysed 25 patients with early (median disease duration, 0.83 years)

non-tophaceous gout; this group of patients could serve as a representative example of the gout population in primary care, for which information about the value of US is still missing.

Previous US studies have demonstrated that the presence of tophi and the DC sign have high sensitivity and specificity in late gout.[18,19,31] The largest and most well-controlled US multicentre observational cross-sectional study was recently performed by Ogdie et al.[32] That study included 824 participants (416 patients with gout and 408 controls) in whom a single swollen joint was investigated. The authors found that the sensitivity for tophus, ''snowstorm,'' and the DC sign on US was only 46.0%, 30.3%, and 60.1% and that the specificity was 94.9%, 90.9%, and 91.4%, respectively. In patients with a gout symptom duration of <2 years, sensitivity was limited (tophus, 34%; snowstorm, 32%; and DC sign, 51%). That study did not evaluate the sensitivity and specificity of multi-site investigation in the early stage. Comparison of the results of their study and ours is difficult because of the different descriptions used for specific gout lesions and the different anatomical sites investigated. Our understanding of ''tophus'' and ''DC sign'' is in line with the definitions proposed by the Outcome Measures in Rheumatology (OMERACT) group[13] except that we did not differentiate ''tophus'' from ''aggregates,'' and some of our ''tophi'' could be considered ''aggregates'' according to the OMERACT criteria. The feasibility of the latter definition is doubtful because the latest efforts of the OMERACT US group to validate the definitions of US gout lesions in patients showed poor interobserver agreement for ''aggregates.''[13] The double-validity control performed in our study exhibited good value for specific US signs of MSU deposition: 83% specificity for tophi and 86% specificity for the DC sign according to healthy normouricemic controls, and 80% concordance of US tophi and the DC sign according to synovial fluid investigation for MSU crystals.

To check the spread and specificity of US signs of MSU deposition in different disease stages, we systemically scanned 36 joints (including the upper and lower extremities) and two tendons (patellar and triceps) in the present study. We found a tophus and/or the DC sign in at least one investigated area (40 sites) in 97% of patients with gout, which is comparable with the findings reported in previous studies.[16,17,24] The joints most often affected in the lower extremities, similarly reported in other studies,[16,18,25] included the first MTP joints, knees, and ankles. We identified fewer DC signs in the first MTPs; the DC sign was found in 35% of the joints in our whole gout group compared with 64% to 67% in previous reports.[18,25] This last finding can be explained by the shorter duration of symptoms in our whole cohort. Because we investigated only the suprapatellar and parapatellar recesses (without the lateral and medial compartments) of the knee, we reported many fewer intra-articular knee tophi than did the authors of some studies[16,18,31] but an amount very similar to that reported in the suprapatellar knee recesses in one study.[15] Our study confirms the findings reported by Naredo et al.[15], who stated that the wrists and second MCP joints are the most often affected joints in the upper extremities.

Our direct comparison of the urate deposit load (tophi or the DC sign) between patients with a disease duration of <2 versus >2 years, even with our relatively small number of participants, showed that urate deposition was significantly lower in the earlier stage of the disease in all sites (including the upper and lower extremities and both investigated tendons). Tophi and the DC sign were seldom or not found in the MCP or proximal interphalangeals in patients with early gout. Our examination

findings for small hand joints are comparable with those of Ottaviani et al.,[18] who found no tophi or DC signs in MCP joints in early gout.[20] The most specific signs found in the present study included tophi and the DC sign in the knees, ankles, and foot joints, showing up to 97% specificity for healthy controls. We found that the presence of a tophus in the first MTPs was the most sensitive US sign for gout in all stages, although it was less specific (83%) with the blinded assessment performed in our study than in some previous studies reporting 100% specificity for tophi in toes with a nonblinded investigator. False-positive tophi on US could be explained by degenerative changes in a toe, which are found in 17% of healthy persons, and confirmed by the absence of crystals in synovial fluid in our study.

To create an optimal US test for early diagnosis of gout, we first performed binary logistic regression analysis for all patients with gout. The US predictors that contributed to the regression model and were therefore estimated to be independently associated with gout were tophi in the first MTP joint, tophi in the triceps tendon, the DC sign in the ankle, the DC sign in the first MTP, and the DC sign in the second MTP joint cartilage; these signs had a sensitivity and specificity of 93% and 78%, respectively. Parameters such as the DC sign in the knee, tophi in the wrist, and tophi in the patella did not improve the diagnostic model for US gout classification. While testing the same predictors for early gout classification (excluding patients with a disease duration of >2 years), we found that only two US signs—tophi in the MTP joint and the DC sign in the ankle—were independently associated with gout in the final step of the regression analysis, with a sensitivity of 84% and specificity of 81%. This finding suggests that the first MTP joint and ankle might be the joints most often involved in gout at the beginning of the disease. Both tests, including the one recommended for US gout classification in the literature[15,16] and the one tested in our cohort, showed good value and were comparable in terms of sensitivity and specificity in patients with a disease duration of >2 years. The sensitivity of all diagnostic tests, including the "12-sites" US examination,[16] the 4-joint (knees and first MTPs) investigation,[15] and the set of 5 joints, generated from the results of our study was lower (80% versus 94%, 76% versus 94%, and 88% versus 100%, respectively) in patients with a disease duration of ≤2 than >2 years. The best balance between the sensitivity (84%) and specificity (81%) of early gout diagnosis was reached with investigation of the first MTPs for tophi and the ankles for the DC sign in our study.

Several limitations of our study should be mentioned. Twenty-one of 60 patients with gout (35%) were reportedly undergoing hypouricemic therapy, which might have had an impact on US sensitivity;[31,33] however, most were not within the therapeutic window (87% of the patients had a UA concentration of >360 μmol/L), and there was no difference in the use of hypouricemic treatment between the early and late gout subgroups. For ethical reasons, all US assessments (long-lasting US assessment of 40 sites) were performed by a single investigator; however, validity control showed good concordance between the US findings and crystal detection in the synovial fluid as well as between the two investigators in the Web-based exercise. The lack of a universally accepted definition of tophus during the planning phase of the study might have resulted in overestimation of the percentages of tophi found per participant because some of them might now be defined as aggregates.[13] Finally, exclusion of the lateral and medial knee compartments from the examination protocol in our study could have impacted the final test results.

This study is the first attempt to compare the spread of specific US gout symptoms in early versus late gout using a multiple-site investigation. Our findings create a paradigm for future US studies, suggesting that the MSU deposition load increases proportionally with the disease duration at all anatomical sites, demonstrating the highest sensitivity in the first MTP joint and ankle in the early stage of the disease. The value of the diagnostic test for early gout proposed in our study should be assessed using the most recent definition of tophus[13] and in asymptomatic patients in the hyperuricemic stage.

Conclusions

The present study has shown that the US sensitivity for specific US signs of MSU deposition (tophus and the DC sign) was lower in patients with a gout symptom duration of ≤ 2 than >2 years.

The four-joint investigation, which includes both first MTPs for tophi and both ankles for the DC sign, is feasible and reliable and could be proposed as a screening test for early US classification of gout in daily practice based on the results of our study.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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References

1. Zhu Y, Pandya BJ and Choi HK. Prevalence of gout and hyperuricemia in the US general population: the national health and nutrition examination survey 2007–2008. *Arthritis Rheum* 2011; 63: 3136–3141.
2. Bardin T, Bouée S, Clerson P, et al. Prevalence of gout in the adult population of France. *Arthritis Care Res (Hoboken)* 2016; 68: 261–266.
3. Kuo C-F, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015; 74: 661–667.
4. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. *Ann Rheum Dis* 2008; 67: 960–966.
5. Winnard D, Wright C, Taylor WJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. *Rheumatology (Oxford)* 2012; 1: 901–909.
6. Perez-Ruiz F, Martínez-Indart L, Carmona L, et al. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis* 2014; 73: 177–182.
7. Perez-Ruiz F, Dalbeth N and Bardin T. A review of uric acid, crystal deposition disease, and gout. *Adv Ther* 2014; 32: 31–41.
8. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; 65: 1301–1311.
9. Dalbeth N, Fransen J, Jansen TL, et al. New classification criteria for gout: a framework for progress. *Rheumatol (Oxford)* 2013; 52: 1748–1753.
10. Scirocco C, Rutigliano IM, Finucci A, et al. Musculoskeletal ultrasonography in gout. *Med Ultrason* 2015; 17: 535–540.
11. Codreanu C and Enache L. Is ultrasound changing the way we understand rheumatology? Including ultrasound examination in the classification criteria of polymyalgia rheumatica and gout. *Med Ultrason* 2015; 17: 97–103.
12. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League

Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2015; 74: 1789–1798.
13. Terslev L, Gutierrez M, Schmidt WA, et al. Ultrasound as an Outcome Measure in Gout. A Validation Process by the OMERACT Ultrasound Working Group. *J Rheumatol* 2015; 42: 2177–2181.
14. Zufferey P, Valcov R, Fabreguet I, et al. A prospective evaluation of ultrasound as a diagnostic tool in acute microcrystalline arthritis. *Arthritis Res Ther* 2015; 17: 188.
15. Naredo E, Uson J, Jiménez-Palop M, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? *Ann Rheum Dis* 2013; 73: 1522–1528.
16. Peiteado D, de Miguel E, Villalba A, et al. Value of a short four-joint ultrasound test for gout diagnosis: A pilot study. *Clin Exp Rheumatol* 2012; 30: 830–837.
17. Ogdie A, Taylor WJ, Weatherall M, et al. Imaging modalities for the classification of gout: systematic literature review and meta-analysis. *Ann Rheum Dis* 2015; 74: 1868–1874.
18. Ottaviani S, Richette P, Allard A, et al. Ultrasonography in gout: a case-control study. *Clin Exp Rheumatol* 2012; 30: 499–504.
19. Wright S, Filippucci E, McVeigh C, et al. High-resolution ultrasonography of the first metatarsal phalangeal joint in gout: a controlled study. *Ann Rheum Dis* 2007; 66: 859–864.
20. Ottaviani S and Allard A. An exploratory ultrasound study of early gout. *Clin Exp Rheumatol* 2011; 29: 816–821.
21. Backhaus M, Burmester G-R, Gerber T, et al. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60: 641–649.
22. Filippucci E, Meenagh G, Delle Sedie A, et al. Ultrasound imaging for the rheumatologist XXXVI. Sonographic assessment of the foot in gout patients. *Clin Exp Rheumatol* 2011; 29: 901–905.
23. Filippucci E, Scire CA, Delle Sedie A, et al. Ultrasound imaging for the rheumatologist. XXV. Sonographic assessment of the knee in patients with gout and calcium pyrophosphate deposition disease. *Clin Exp Rheumatol* 2010; 28: 2–5.
24. Huppertz A, Hermann K-G a, Diekhoff T, et al. Systemic staging for urate crystal deposits with dual-energy CT and ultrasound in patients with suspected gout. *Rheumatol Int* 2014; 34: 763–771.
25. Roddy E, Menon A, Hall A, et al. Polyarticular sonographic assessment of gout: a hospital-based cross-sectional study. *Joint Bone Spine* 2013; 80: 295–300.
26. Dalbeth N and Doyle AJ. Imaging of gout: an overview. *Best Pract Res Clin Rheumatol* 2012; 26: 823–838.
27. Dalbeth N, McQueen FM, Singh J, et al. Tophus measurement as an outcome measure for clinical trials of chronic gout: progress and research priorities. *J Rheumatol* 2011; 38: 10.
28. Howard RG, Pillinger MH, Gyftopoulos S, et al. Reproducibility of Musculoskeletal Ultrasound for Determining Monosodium Urate Deposition: Concordance Between Readers. *Arthritis Care Res (Hoboken)* 2011; 63: 1456–1462.
29. Ottaviani S, Bardin T and Richette P. Usefulness of ultrasonography for gout. *Joint Bone Spine* 2012; 79: 441–445.
30. Barnhart HX, Yow E, Crowley a. L, et al. Choice of agreement indices for assessing and improving measurement reproducibility in a core laboratory setting. *Stat Methods Med Res* 2016; 25: 2939–2958.
31. Perez-Ruiz F, Martin I and Canteli B. Ultrasonographic measurement of tophi as an outcome measure for chronic gout. *J Rheumatol* 2007; 34: 1888–1893.
32. Ogdie A, Taylor WJ, Neogi T, et al. Performance of ultrasound in the diagnosis of gout in a multicenter study: comparison with monosodium urate Monohydrate crystal analysis as the gold standard. *Arthritis Rheumatol* 2017; 69: 429–438. Oct 16 [cited 2016 Nov 22]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/27748084.
33. Ottaviani S, Gill G, Aubrun A, et al. Ultrasound in gout: a useful tool for following urate-lowering therapy. *Joint Bone Spine* 2015; 82: 42–44.