Value of a short four-joint ultrasound test for gout diagnosis: a pilot study

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Abstract

Objective

The goal of this study was to investigate the usefulness of a short ultrasound (US) assessment in gout.

Methods

Patients with gout, confirmed by urate crystal identification, and having at least one symptomatic flare in the last three months were included. Standardised US examinations of sixteen joints and eight tendons in the lower limbs were carried out. Six lesions were studied: hyperechoic spots in the synovial fluid, hyperechoic cloudy areas (HCA), bright stippled aggregates (BSA), the double contour sign (DCS), erosions and the Doppler signal. For reliability, inter-reader analyses were performed by five rheumatologists. With the results, a short US assessment was created.

Results

Twenty-nine consecutive patients were included (93% men). The Doppler signal, HCAs and BSAs appeared in 100%, 97% and 93% of the patients, respectively. The DCS was found in 69% of patients. The locations that were most affected were the first metatarsophalangeal joint (MTP) and the knee joints, both of which are in 93% of patients. Reliability analyses showed consistent results for erosions, the Doppler signal, HCAs and the DCS in the 1st MTP (k=0.818, k=0.958, k=0.739 and k= 0.697, respectively) and for the DCS in the knees (k=0.779). A six-minute US examination of four joints (knees and the 1st MTPs) detected HCAs or DCS in 97% of cases.

Conclusion

A US examination of four joints for two elemental lesions (the DCS and HCAs) is feasible, reliable and has face and content validity as a diagnostic test in patients with crystal-proven gout.

Key words
gout, ultrasound, imaging, diagnostic criteria

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Received on October 13, 2011; accepted in revised form on December 20, 2011.

Competing interests: none declared.

Introduction

Gout is one of the most common forms of inflammatory arthritis in adult men. The prevalence of gout is almost 7% in men aged over 65 years and increase with age (1, 2). The European League Against Rheumatism (EULAR) evidence-based recommendations for gout diagnosis states "the demonstration of monosodium urate (MSU) crystal in synovial fluid or tophus permits a definitive diagnosis of gout" (3). Nevertheless, despite a reasonable understanding of its pathogenesis and the availability of effective treatments, gout is often misdiagnosed or diagnosed late in its clinical course (3). One possible explanation is that physicians do not apply the evidence-based recommendations, and this has been confirmed in the literature (4). Thus, the diffusion and implementation of medical guidelines is the solution. On the other hand, there are some situations, such as cases of intercritical or chronic gout, in which the crystal identification sensitivity can decrease from 84% (in cases of acute gout) to 70% (3, 5). In this situation, a novel approach through imaging modalities, such as US, may improve the diagnosis of gout (6, 7). In recent years, US lesions associated with gout have shown diagnostic value for gout both in early disease and in long-term illness (7-19). The accuracy of US in the diagnosis of gout is supported by previous works. In these studies, US had a sensitivity of 43.7% and a specificity of 99% for detecting double contour signs (DCS) (12), a sensitivity of 79% and a specificity of 95% for detecting the presence of hyperechoic cloudy areas (HCA) in synovial joints and a sensitivity of 80% and specificity of 75% for the detection of bright stippled aggregates (BSA) (15). The combination of BSAs and/or HCAs on US images serves as clear evidence of gout, with high sensitivity (96%) and specificity (73%) (15). Other signs, such as hyperechoic spots in the synovial fluid (HSSF), erosions and the Doppler signal, are also reported, but these signs have lower sensitivities or specificities (7, 15).

US has demonstrated validity against the gold standard in gout diagnosis (7, 12, 15). Nevertheless, specific lesions have only been evaluated in isolated, symptomatic regions and without an extensive standardised examination at the patient level. The aim of our study was to demonstrate the usefulness of a short US assessment in the diagnosis of gout. To achieve this objective we determined, in patients with proven gout, which lesions and joints were present and should be explored at the patient level to aid the clinician in the diagnosis of gout. In doing so, an extended US examination in different areas of the lower limbs was performed to analyse the prevalence of various elementary gout lesions, as well as the face and content validity, the reliability and feasibility of US for the diagnosis of gout.

Materials and methods

Patients

Twenty-nine consecutive, adult patients that arrived to the rheumatology clinic with a history suggestive of gout and at least one symptomatic acute attack in the last three months were included in the study. The demographic, clinical and laboratory characteristics of each patient were recorded. Pain was measure by a visual analogue scale range 0-100. In all patients, a definitive diagnosis was confirmed by the presence of MSU crystals in aspirates from symptomatic joints. The aspirates were examined using polarising light microscopy, and patients without MSU crystals were excluded. Patients with other rheumatic diseases were also excluded. Prior to their inclusion, all patients provided informed consent for participation, and local approval was obtained from the ethics committee and institutional review board of our hospital (Hospital Universitario La Paz)..

Ultrasonographic examinations

US examinations were performed by a second rheumatologist who was blinded to the clinical data. The assessment was completed using Logiq 9 equipment (General Electric Medical Systems, Milwaukee, WI, USA) with a 9-14-MHz probe for grey scale and a 5-7.5-MHz probe for Doppler. Standardised examinations were carried

out over different anatomical areas in the lower limbs. All studies were performed by scanning across the joints and moving the probe from the medial to lateral aspect and from the proximal to distal aspect. Sixteen joints were studied, including the dorsal, medial and plantar aspects of the first metatarsophalangeal joint (MTP); the 2nd-5th MTPs (exclusively in the first 18 patients); the anterior (ANKa) and lateral and medial ankle recesses (ANKlm); the dorsal aspect of the midtarsal (MTAR) joints; and the medial and lateral recesses of the knee. We also examined eight tendons: the peroneal (PER) tendons, the tibialis anterior (TA) tendon, the tibialis posterior (TP) tendon, and the patellar (PAT) tendon. Cartilage was examined in the dorsal and plantar aspect of the MTP joints as was the condylar cartilage with the knee in maximal flexion.

Six gout-related lesions were tested in each joint, including hyperechoic spots in the synovial fluid, hyperechoic cloudy areas, bright stippled aggregates, the double contour sign, erosions and Doppler signals. Three lesions were studied in the tendons, including hyperechoic cloudy areas (THCA), bright stippled aggregates (TBSA), and Doppler signals. HSSFs were defined as spots <1 mm in size with the same echogenicity of the bony cortex (7). HCAs were defined as heterogeneous masses composed of hyperechoic and hypoechoic material, sometimes surrounded by a small hypoechoic rim, and occasionally possessing posterior shadows (9, 15, 20). BSAs were defined as irregular, hyperechogenic deposits without posterior shadows over an anechogenic background (21). DCSs were defined as focal or diffuse echogenic enhancements on the superficial margins of the joint cartilage (13). Erosions were defined as intra-articular breaks of the bone profile that were detectable in at least two perpendicular planes, following the Outcome Measures for Arthritis Clinical Trials (OMERACT) criteria (22). The Doppler gain was adjusted to a level just below its disappearance under the bony cortex. The absence or presence of Doppler was considered for the analysis.

Table I. Gout-related, elementary lesions.

		Total number of affected regions	Median	Mean	Number and % of patients
HSSF	Total	**20**	**0**	**0.69**	**13 (45%)**
HCA	Joint	166	5	5.72	28 (97%)
	Tendon	73	2	2.52	23 (79%)
	Total	**239**	**9**	**8.2**	**28 (97%)**
BSA	Joint	55	1	1.89	25 (86%)
	Tendon	21	0	0.72	15 (52%)
	Total	**76**	**3**	**2.62**	**27 (93%)**
DCS	Total	**38**	**1**	**1.3**	**20 (69%)**
Erosion	Total	**17**	**1**	**0.8**	**16 (55%)**
Doppler	Joint	192	7	6.62	29 (100%)
	Tendon	39	1	1.34	18 (62%)
	Total	**231**	**8**	**7.96**	**29 (100%)**

HSSF: hyperechoic spots in synovial fluid; HCA: hyperechoic cloudy areas; BSA: bright stippled aggregates; DCS: double contour signs.

During the course of the US examination, the presence of predefined, elementary lesions was determined, and sonographic images of each location in every subject were stored independently of the findings. A minimum of 56 images per patient were stored.

To calculate reliability, five rheumatologists carried out an inter-reader analysis using the images from the first fifteen patients included in the study. All of the stored images (with or without pathology) in every patient were evaluated. Two of the readers had more than four years of experience in examining gout ultrasounds, and the others had only a general knowledge of muscle-skeletal sonography. Prior to reading the US images, all of the rheumatologists underwent a one-hour training discussion on each elementary lesion image set according to the previously-reported definitions. The images used in the consensus were different than those images used in the inter-reader exercise. All readers were blind to the clinical data.

Using the results of the study, we aimed to build a feasible, simplified US test that allows the clinician to recognise patients with gout. To create this test, we used the more prevalent and specific US lesions and locations, also taking into account the reliability of every lesion and the area of examination. At the end, we calculated the time required for a complete examination in all of our patients. We also determined the time required to perform the short US test using the time counter that appear in every stored picture of the US examination and calculating the mean and standard deviation.

Statistical analysis

Mean ± standard deviation or median with interquartile range were used to describe the demographic characteristics of the patients and the elementary, ultrasonographic features of the group. The reliability analysis was performed using the kappa correlation coefficient.

Results

Demographic and clinical characteristics

A total of 29 consecutive, adult gout patients, 27 (93%) of whom were men, with a mean age of 58 years (range: 38–75 years), were included for evaluation by diagnostic imaging. The median disease duration was 8.5 years (IQR: 2.7–14 years). The mean serum urate level was 8.86 ± 1.72 mg/dl, and the erythrocyte sedimentation rate (ESR) was 20.5 mm/h (IQR: 6–26.5 mm/h). The median pain score was 20 (IQR 9–38), and the median number of tender and swollen regions were 1 (IQR: 0–2.5) and 1 (IQR: 0–1.5), respectively. Sixty percent of patients had swollen joints, and 59% had joint pain at the moment of the examination. At baseline, 10 patients (34.5%) were treated with allopurinol, 17 patients (59%) were treated with colchicine, and 13 patients (45%) were

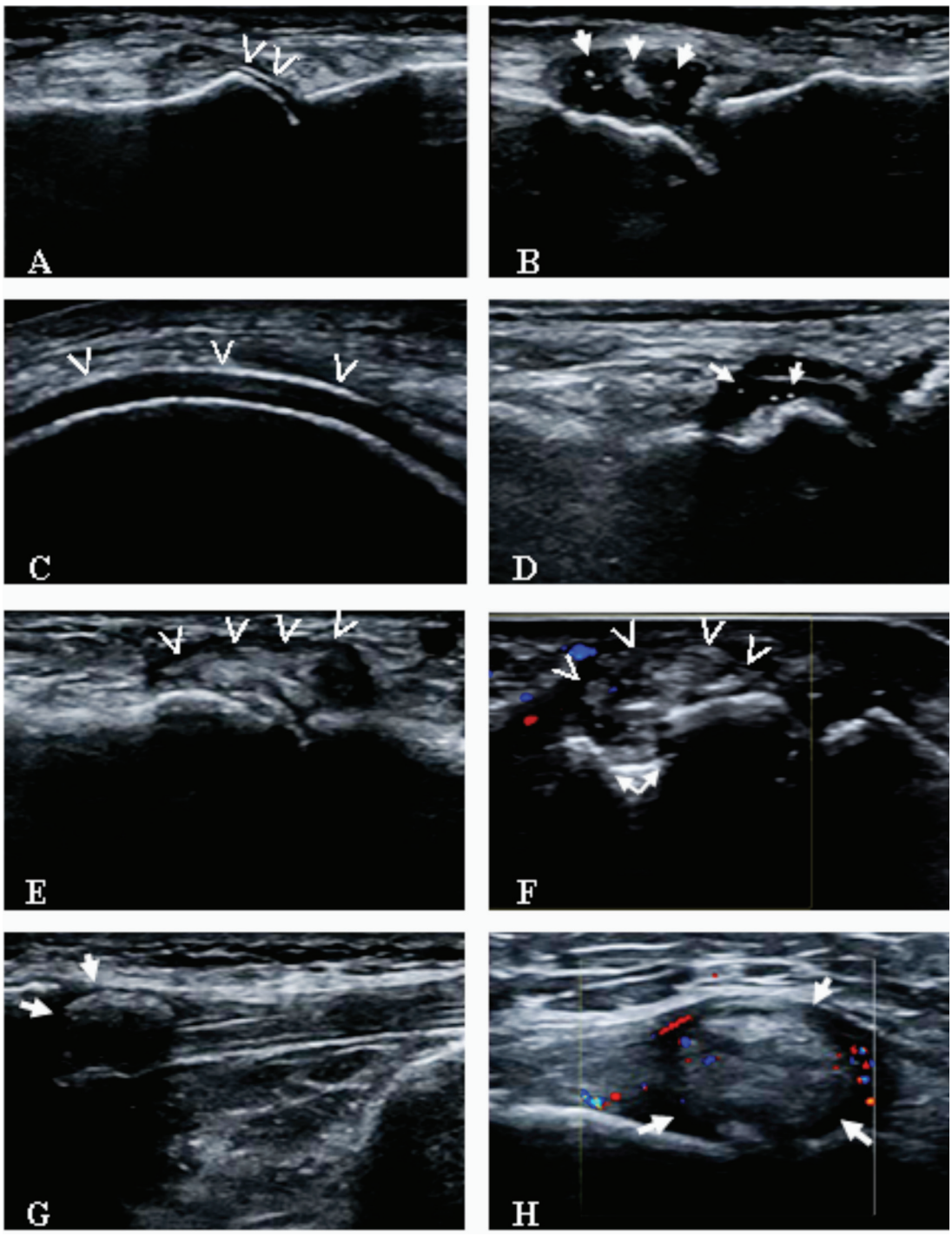

Fig. 1. Ultrasonographic features indicating the presence of gout.
A. Longitudinal ultrasound (US) image at the region of the first metatarsophalangeal joint (1st MTP) revealing hyperechoic enhancement of the chondrosynovial interface due to monosodic urate crystal deposition. Arrowheads indicate the presence of double contour sign (DCS).
B. Longitudinal US image of the dorsal aspect of the 1st MTP showing bright stippled aggregates within the joint space (arrows) .
C. Longitudinal US image of the hyaline cartilage of the femoral condyle showing DCS (arrowheads).
D. Longitudinal US image of the dorsal aspect of the 1st MTP showing anechoic, intra-articular fluid with hyperechoic and floating spots (arrows).
E. Longitudinal US image at the region of the dorsal aspect of the 1st MTP showing a hyperechoic image. The hyperechoic cloudy areas (HCA) represent monosodium urate deposits within the thickened synovial membrane (arrowheads).
F. Longitudinal view of the 1st MTP revealing a HCA with Doppler signal. Bone erosion is seen at the level of the anatomic neck of the metatarsal head (arrowheads).
G. Longitudinal US image of the patellar tendon revealing a HCA (arrows).
H. Longitudinal US image at the medial recess of the knee showing a HCA with Doppler signal (arrows).

treated with non-steroidal anti-inflammatory drugs (NSAIDs).

Ultrasonographic results

– Ultrasound elementary lesions

Table I shows the frequency of the US elementary lesions examined in our cohort, expressed as the mean, median and percentage. According to these results, the Doppler sign, HCAs and BSAs are the most frequently identified elementary lesions, appearing in 100%, 97% and 93% of patients, respectively. DCSs appeared in 69% of the cases. We found that lesions with a high specificity, such as joint and tendon HCAs, were observed in 97% and 79% of patients, respectively (with a median of 5 and 2 per patient, respectively) (Table I). The elementary lesions identified by US are illustrated in Figure 1.

When we exclusively considered more specific ultrasonographic features (HCA, DCS) (12, 15), we found at least one lesion in every patient. Only one patient (3%) had no HCAs in the tendons or joints at the time of examination, but the patient did have bilateral DCSs in the 1st MTP.

– Ultrasound scan areas

Twenty-seven patients (93%) had at least one characteristic lesion in the 1st

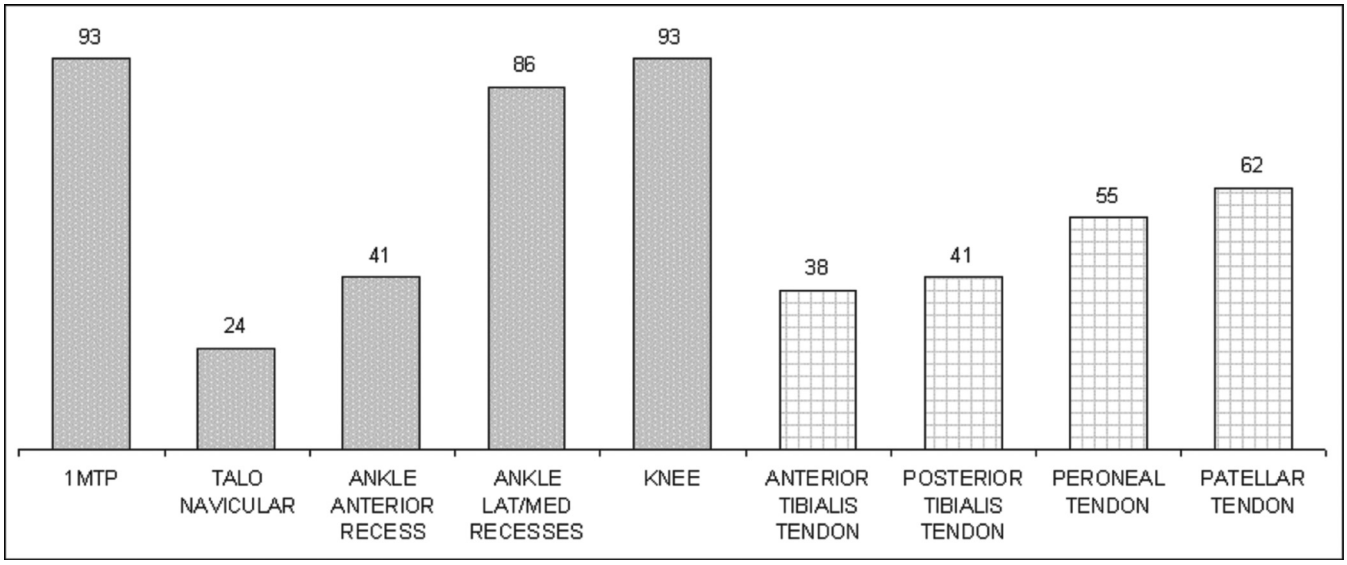

Fig. 2. Percentage of patients with ultrasonographic findings, segregated by joint or tendon type.

MTP, and the same number of patients had characteristic lesions in the knees. The lateral and medial recesses of the ankles were also affected in most patients (86.2%). The tendons that were most frequently affected included the patellar tendon (in 18 patients [62%]) and the peroneal tendons (in 16 patients [55%)]) (Fig. 2).

Preliminary analyses of the 2nd-5th MTPs in the first 18 patients revealed only a few features (1 patient with DCS, 3 patients with HCA) and did not add information beyond that obtained by imaging the 1st MTP. Based on this observation, we decided not perform this examination with subsequent patients, and we did not consider these joints in the analyses.

– Reliability

The inter-reader reliability analysis of the different lesions in each of the examined joints (1st MTP, midtarsal [MTAR], ankle, and knee) is shown in Table II, which includes the number of elementary lesions that were found and the number of patients affected (in parentheses). The last column represents the kappa correlation coefficients. Table III shows the reliability analysis of the lesions in each of the examined tendons (patellar, tibialis anterior, tibialis posterior and peroneal). As the tables illustrate, reliability depends not only on the specific elementary lesion but also on the anatomical site of the lesion.

– Short US assessment (feasibility)

As explained in the methods, based on the results of the study, a simplified assessment was created. This assessment included the locations that were the most specific, prevalent and reliable for gout. Ankles, midtarsal locations, BSF and HSSF lesions were excluded because of their moderate-to-low reliability (Tables II, III). Other specific and reliable lesions, such as tendon HCAs, showed redundant information to that obtained from examination of the knee or the 1st MTP joints. Doppler signals and erosions were excluded because they are present in other diseases and are not specific to gout. The analysis of our results (Tables I–III, Fig. 2) showed that seeking only two lesions (DCS and HCA) in four joints (both knees and the 1st MTPs) identified the 97% of patients tested (Fig. 3). Specifically we found HCA located in 1st MTPs and knees in 20 (69%) and 23 (79%) of patients, respectively; and DCS located in 1st MTPs and knees in 14 (48%) and 12 (41%). Only one patient did not have a DCS or HCA according to this short test exploring the knees and 1st MTP joints; however, this patient did have HCAs in both ankle medial recesses and THCAs in the tibialis anterior tendon (which are not included in the proposed short test). The full lower-limb US examination in every patient (looking for six lesions in sixteen joints and eight tendons) required a mean of 42.88±16.22 minutes, and the simplified assessment required 6.14±1.18 minutes of examination time per patient.

Discussion

Currently, the most highly recommended and accepted gold standard for gout diagnosis is the identification of crystals in the joint fluid or tophi (3). However, crystal identification is not always performed in clinical practice, and clinical judgment is frequently used (4, 23). Ultrasound is not included in the guidelines as a diagnostic tool; however, due to its physical properties, it is a precise technique for the detection of crystalline material. Monosodium urate crystals produce a US wave reflection that is stronger than the surroundings tissues and can easily be identified (9). For this reason, US can be a useful tool for the diagnosis of gout. Furthermore, guided arthrocentesis could improve crystal aspiration procedures by facilitating selection of the best areas from which synovial fluid should be collected (17).

As mentioned in the introduction, the challenge and validity of using US for gout diagnosis emerges from previous works that have demonstrated specific US elementary lesions with a high sensitivity and specificity (7, 12, 15). Our study accepts these results and focuses on the usefulness of US. The question to resolve is what is the minimum number of lesions and areas examined needed to reliably identify specific gout lesions.

Table II. Inter-reader reliability analysis for elemental lesions of the joints (n=15).

		Reader 1	Reader 2	Reader 3	Reader 4	Reader 5	κ coeff
1st MTP	HSSF	6 (5)	8 (6)	5 (5)	8 (7)	11 (10)	**0.391**
	HCA	18 (12)	17 (10)	17 (11)	19 (11)	18 (11)	**0.739**
	BSA	8 (7)	11 (9)	11 (8)	7 (7)	13 (10)	**0.137**
	DCS	4 (3)	6 (5)	6 (4)	5 (4)	6 (4)	**0.697**
	Erosion	6 (5)	9 (7)	7 (5)	8 (6)	7 (6)	**0.818**
	Doppler	12 (8)	12 (8)	12 (8)	11 (7)	11 (7)	**0.958**
MTAR	HSSF	0	0	0	0	0	---
	HCA	2 (1)	2 (2)	4 (2)	4 (3)	0	**0.506**
	BSA	6 (5)	3 (3)	2 (2)	2 (2)	0	**0.423**
	DCS	0	0	0	0	0	---
	Erosion	1	1	2 (2)	2 (2)	2 (2)	**0.322**
	Doppler	6 (3)	8 (5)	7 (4)	7 (4)	8 (5)	**0.958**
ANKa	HSSF	0	0	0	0	0	---
	HCA	2 (2)	1	1	1	5 (4)	**0.636**
	BSA	1	4 (4)	1	1	1	**0.426**
	DCS	0	0	0	0	0	---
	Erosion	0	0	0	0	0	---
	Doppler	5 (5)	3 (3)	4 (4)	2 (2)	4 (4)	**0.634**
ANKlm	HSSF	0	0	0	3 (2)	1	---
	HCA	31 (13)	44 (15)	50 (15)	44 (14)	25 (13)	**0.220**
	BSA	16 (11)	10 (5)	8 (5)	8 (5)	18 (12)	**0.309**
	DCS	0	1	1	0	0	---
	Erosion	0	0	0	0	1	---
	Doppler	32 (11)	37 (13)	34 (13)	31 (11)	36 (14)	**0.774**
Knee	HSSF	0	0	0	0	0	---
	HCA	15 (9)	25 (11)	27 (11)	33 (13)	22 (8)	**0.402**
	BSA	13 (9)	7 (4)	6 (3)	2 (1)	6 (5)	**0.303**
	DCS	9 (8)	9 (8)	7 (6)	10 (8)	9 (7)	**0.779**
	Erosion	0	0	0	0	0	---
	Doppler	23 (13)	26 (12)	25 (12)	24 (11)	24 (12)	**0.790**

1stMTP: first metatarsophalangeal; MTAR: midtarsal; ANKa: ankle anterior recess; ANKlm: ankle lateral and medial recesses; K coeff: kappa coefficient; HSSF: hyperechoic spots in the synovial fluid; HCA: hyperechoic cloudy area; BSA: bright stippled aggregates; DCS: double contour sign. The number of elementary lesions is followed by the number of patients affected (in parentheses).

Table III. Inter-reader reliability analysis for elemental lesions of the tendons (n=15).

		Reader 1	Reader 2	Reader 3	Reader 4	Reader 5	κ coeff
PAT	THCA	15 (7)	21 (7)	14 (7)	13 (6)	14 (7)	**0.848**
	TBSA	0	6 (6)	0	2 (1)	1 (1)	---
	TDS	6 (5)	7 (6)	6 (5)	5 (4)	6 (5)	**0.860**
TA	THCA	2 (2)	3 (3)	5 (5)	1	3 (3)	**0.614**
	TBSA	1	1	2 (2)	0	2 (2)	---
	TDS	0	1	3 (2)	1	2 (2)	---
TP	THCA	3 (3)	4 (3)	1	3 (3)	4 (3)	**0.704**
	TBSA	0	0	3 (2)	2 (2)	1	---
	TDS	1	0	2 (2)	1	2 (2)	---
PER	THCA	1	0	2 (2)	4 (3)	4 (3)	---
	TBSA	2 (2)	3 (3)	6 (5)	2 (2)	1	**0.344**
	TDS	4 (4)	2 (2)	2 (2)	3 (3)	2 (2)	**0.504**

PAT: patellar tendon; TA: tibialis anterior tendon; TP: tibialis posterior tendon; PER: peroneal tendon; THCA: hyperechoic cloudy area in tendon; TBSA: bright stippled aggregates in tendon; TDS: Doppler signal in tendon. The number ofelementary lesions is followed by the number of patients affected (in parentheses).

Face validity represents credibility, in this case if US can see what it is intended to see. Along these lines, our work investigated the prevalence of different US elementary lesions in various joints and tendons that seem to be representative of the disease at the patient level. Our results show that every patient included in the study had at least one specific gout lesion and a median of five highly specific lesions (HCA) in the synovial joint (Table I). The prevalence of DCSs was quite similar to previous reports that found DCSs in 14 of 32 knees (43.7%) (12), or in 25 of 60 knees (41.6%) (18), or in 17 of 78 1st MTP joints (22%) (7). These frequencies were even higher in other reports when the examinations were focused on the symptomatic joints, with DCSs found in 92% of joints and HCAs found in 100% (9). On the contrary, other studies made in early stage gout found similar percentages in the prevalence of DCS in the knees and MTPs (46.7% and 40% respectively) but lower results for tophi (26.7%) for both sites (19). These differences could be related to the longer disease duration of the patients enrolled in our study and are more evident for the HCA lesions than for the DCS. But even in 11 out of 26 asymptomatic hyperuricaemia patients these lesions have been demonstrated (17).

As a second step, we analysed content validity. Content validity is the same as comprehensiveness or whether a test covers all aspects of the attribute to be measured. In our cohort, at the patient level, US showed alterations in the synovial tissue, synovial fluid, tendons, tendon sheaths, cartilage, bone cortex and vascular flow, all aspects of which have been related to urate arthritis deposition diseases.

Next, we investigated reliability. Exercises that explore the reliability of US in gout diagnosis are sparse and focused at isolated regions for only a few specific US features. Perez-Ruiz *et al*. have shown that the intra-observer, intraclass correlation when observing lesions in tophi was >0.90 for diameters and volume, while the inter-observer correlation was 0.71 to 0.83 (24). In a study by Wright *et al*., the US data from two sonographers were analysed; however, only the reliability results of erosions and soft tissues were shown (kappa=0.87 and 0.76, respectively) (7). Filippucci *et al*. (12) reported an inter-explorer kappa of 0.68 for DCSs

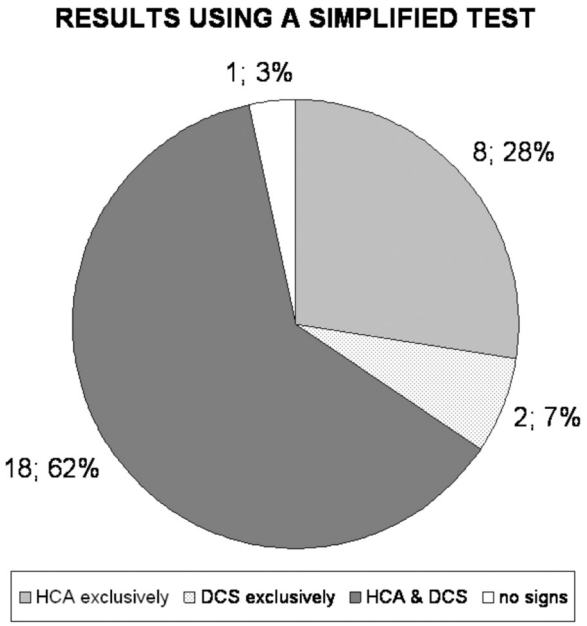

Fig. 3. Number and percentage of patients with highly specific and reliable gout lesions identified by a short US test (knees and 1st MTPs). HCA: hyperechoic cloudy area. DCS: double contour sign.

in the knee cartilage. Our work confirms that there is an excellent kappa coefficient (k) for erosions and Doppler, good results for HCAs and DCSs in the 1stMTP, good results for DCSs in the knees and excellent kappa values for HCAs in patellar tendons. Yet, the most interesting result that has not been previously reported is that the reliability of US gout diagnosis depends not only on the specific, elemental lesion but also on the anatomical site of the lesion, as shown in Tables II and III.

As a last step, our study looked at feasibility. A feasible US test means that it can be applied easily, including constants of time, money and interpretability. In this way, after analysing our results we proposed a short test that, through the examination of only DCSs and HCAs in the knees and 1stMTP joints from at least sixteen joints and six elemental US lesions, we could use to identify specific and reliable gout US elementary lesions in 97% of the studied patients.

Our study design has some limitations. For one, our reliability analysis was calculated from previously obtained pictures rather than from newly acquired images. This process could artificially increase the reliability results; however, performing reliability analyses using five independent rheumatologists with such a high number of elemental lesions and sites in every patient is impractical because of the time it takes. Another limitation is the variability in the skillfulness of the gout ultrasound readers, which could cause lower reliability; however, such differences in skill can also produce closer-to-expected results if the technique is generally used. In our work, we decided to exclusively explore the lower limbs; we based this decision on our opinion and experience that gout less often affects the upper limbs. Investigations of the use of US to diagnose gout using lesions in the upper limbs would be interesting, but the current examination seems to be enough to properly diagnose patients. Another limitation was that we did not have a control population, thus we could not calculate the accuracy of the proposed US test. However, our aim was not a validity study against the gold standard but rather a useful and feasible short US test with face and content validity in patients with proven gout. Finally, the frequency of lesions could be influenced by the disease stage, disease duration and previous gout treatments; our score seems to be face and aspect validated in gout proven patients with a mean time disease duration of 8.5 years. In the future it would be interesting to assess this short test in early disease, asymptomatic hyperuricaemia or other conditions.

In conclusion, our results show that a six-minute-long US examination of four joints (bilateral knees and the 1st MTP joints) and two elemental lesions (double contour sign and hyperechoic cloudy areas) is feasible and reliable in diagnosing gout and has both face and content validity. Other elemental lesions, including bright aggregates, or other involved anatomical locations, such as ankle recesses, are also frequent, but their usefulness in diagnosing gout is restricted because of the lower reliability. Doppler signs and erosions had good or excellent reliability, but these were excluded because they are not specific for gout. Our study supports the use of US as a complementary test in the diagnosis of gout and for future longitudinal studies on disease course and response to treatment.

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