An exploratory ultrasound study of early gout

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Abstract

Objective

We aimed to determine by ultrasonography (US) the prevalence of articular monosodium urate deposits in patients with gout who do not require urate lowering therapy (ULT) according to international recommendations.

Methods

In this prospective study, we enrolled patients with proven gout demonstrated by crystals in synovial fluid but who did not require ULT. Two trained ultrasonographers assessed 10 joints per patient (metatarsophalangeal [MTP] joints 1-2, knees, metacarpophalangeal [MCP] joints 2-3) to determine the prevalence of the double-contour (DC) sign and tophi in each site.

Results

We studied 150 joints from 15 patients (median age 56.9 years [interquartile range 31.7] years; 14 males). The median number of acute attacks per patient was 2.0 [0.7]. Interobserver agreement was good to excellent for all articular sites. The prevalence of the DC sign in the knees and MTP joints was 46.7% and 40% respectively, whereas that of tophi was 26.7% for both sites. No urate deposits were found in MCP joints. The DC sign and tophi were found in at least one articular site in 60% and 46.7% of patients, respectively. All patients with urate levels > 600 µM (10 mg/dl) had a DC sign in at least 1 assessed joint. Urate levels were positively correlated with presence of the DC sign in knees (p=0.005) and MTP joints (p=0.03) but not presence of tophi.

Conclusions

In this study, ultrasonography allowed for detecting articular urate deposits in 60% of gouty patients not requiring ULT by international recommendations.

Key words

gout, ultrasonography, diagnosis, imaging, hyperuricemia

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Introduction

Clinical manifestations of gout are related to monosodium urate (MSU) crystal deposition in articular or peri-articular tissues and in the renal tract. The natural history of articular gout typically consists of 3 periods: asymptomatic hyperuricaemia, episodes of acute attacks of gout with asymptomatic intervals, and chronic gouty arthritis (1).

Both the British Society for Rheumatology and the European League Against Rheumatism (EULAR) recommend starting urate lowering therapy (ULT) in patients with complicated gout defined by the presence of tophi, radiographic evidence of changes in gout, or uric acid stones (2, 3), all features that reflect high urate crystal load within the body.

However, agreement is lacking on the initiation of ULT in recent uncomplicated gout, that is, for patients with the first and unique acute attacks within a year or just 2 or 3 previous acute attacks. One argument for not initiating treatment for these patients is that slightly less than half will not experience further attacks within a year (2, 3). In contrast, treating and curing gout is probably easier for cases of relatively small urate crystal load (2), but we lack information on the prevalence of urate deposits in joints of patients with uncomplicated gout.

Ultrasonography (US) is a useful tool to detect intra-articular urate deposits (4). Two sonographic features are considered characteristic of gout: the double contour (DC) sign, produced by deposition of urate crystals on the surface of articular cartilage, and hyperechoic cloudy areas, which represent urate deposits within the joint and tendons or soft tissues (4-8).

We aimed to use US to assess the prevalence of urate deposits in the subset of patients with recently diagnosed gout who do not require ULT according to international recommendations.

Patients and methods

Ethics statement

The Institutional Review Board (IRB No. 00006477) of Paris North Hospitals approved this study. All patients gave their written informed consent to participate.

Subjects and study design

To be included in this prospective study, patients had to have gout proven by demonstration of MSU crystals in synovial fluid and ≤1 acute attack in the previous year, ≤3 total acute attacks and none of the following features of chronic gout: tophi on clinical examination, radiographic evidence of gouty arthropathy in the foot and/or affected joint and uric acid nephropathy.

All subjects underwent a detailed clinical evaluation, including disease history, clinical examination, laboratory testing (including urate levels) and radiologic assessment. Patients were asked to recall the number of acute attacks they had. If a patient declared a history of acute arthritis, we used the Janssens score to facilitate the diagnosis of acute gouty arthritis (9).

As recommended (10), synovial fluid was obtained for all patients from inflamed joints or asymptomatic joints (knee or metatarsophalangeal [MTP] joints) and then analysed by trained rheumatologists (SO, PR and TB) who used a compensated polarising microscope to investigate the presence of negatively birefringent MSU crystals.

Ultrasonography assessment

Two rheumatologists (SO and AA) trained in musculoskeletal ultrasonography (Master of Musculoskeletal Ultrasound) performed US assessment. All scans involved use of an Esaote Technos MP machine (Esaote, Genoa Italy) equipped with a 9- to 13-MHz broadband linear transducer.

We assessed the first and second MTP joints, both knees, and the second and third metacarpophalangeal (MCP) joints for each patient, which corresponds to 10 screened joints per patient. All joints were scanned in the longitudinal plane and dorsal side. Knees were explored on the transverse and longitudinal suprapatellar plane in maximal flexion according to guidelines for musculoskeletal US (11).

For each joint, we recorded 2 features of urate deposits (Fig. 1) as present or absent: 1) the DC sign, which corresponds to a hyperechoic, irregular band over the superficial margin of the articular cartilage; and 2) tophi within

the joint, which appear as iso- or hyperechoic nodular deposits (4-7).
The set of US images acquired for each patient by one rheumatologist (SO) was digitally stored and read by a second rheumatologist (AA) who was blinded to clinical details and US results of the other observer. Any discrepancies in results between the 2 sonographers were resolved by consensus. Inter-reader agreement was assessed by computing the κ-coefficient for determining the DC sign and the presence of tophi for each joint site.

Statistical analysis
Data are presented as mean (SD) and median [interquartile range] and percentages. We arbitrarily defined the severity of hyperuricemia by a urate level ≥600 μmol/l (10 mg/dl). This cut-off was associated with a high risk of recurrence of gouty acute attacks (12, 13). Associations between US features and urate levels were tested by the non-parametric Mann-Whitney U-test, and comparisons of hyperuricemia involved the Student *t*-test. A two-sided $p<0.05$ was considered statistically significant. All tests involved use of StatView v5.0 (SAS, Gary, IN, USA).

Fig. 1. US features: tophi (panel A) and the DC sign (panel B)
Panel A. 1st MTP: isoechoic cloudy area with anechoic rim corresponding to intraarticular tophus (white arrows).
Panel B. Femoral cartilage of the knee in suprapatellar plan: hyperechoic band over the superficial margin of cartilage corresponding to the "double contour" sign (white arrowheads).

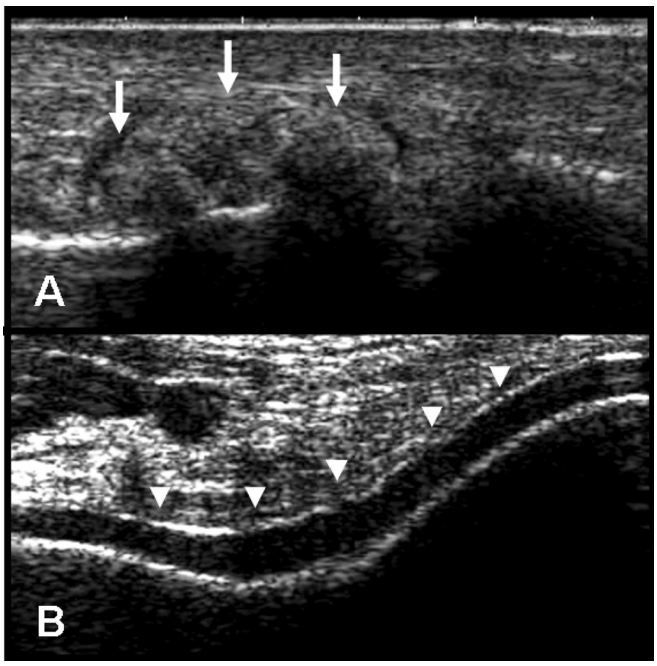
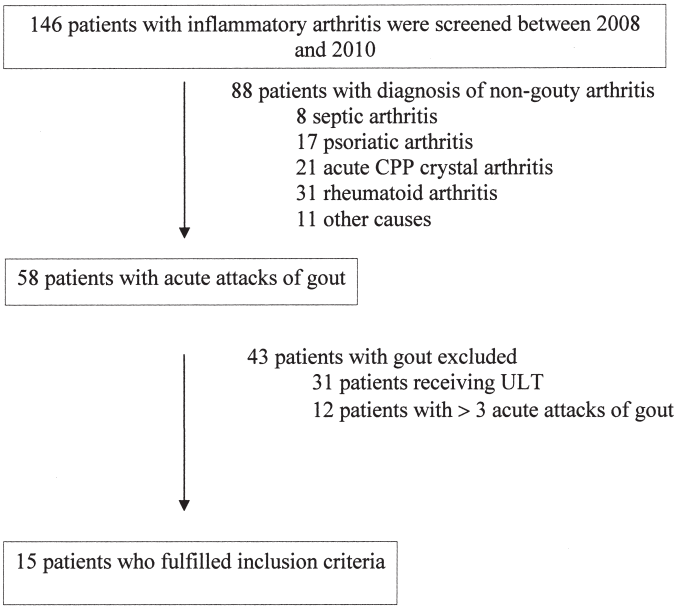


Fig. 2. Flowchart of the study.



CPP: calcium pyrophosphate; ULT: urate-lowering therapy.

Results

Characteristics of patients with gout
We screened 58 patients who had acute attacks of gout between November 2008 and October 2010. Of these 58 patients, 43 were excluded because they had had more than 3 acute attacks and/or had chronic gout and received ULT (Fig. 2).
Finally, we included 15 patients who did not require ULT according to international recommendations (median [IQ] age 56.9 [31.7] years and body mass index 25 [2.2] kg/m^2; 14 males) (Table I). In all patients, MSU crystals were identified by compensated polarised-light microscopy. The median delay between the first acute attack and the US assessment was 17.7 [30.2] months, and the patients had a median of 2.0 [0.7] episodes of acute arthritis before inclusion. The joints involving acute attacks mainly involved the MTPs and the knees. Median urate levels and creatinine clearance were 577 [176] μM (9.7 [0.2] mg/dl) and 65 [35] ml/min, respectively.

Ultrasonography findings
We assessed 150 joints in the study population. The inter-reader agreement between the 2 sonographers for the DC sign was κ=0.98, κ=0.92 and κ=0.95 for MCPs, knees and MTPs, respectively, and for presence of tophi κ=1, κ=0.97 and κ=0.98, which indicates excellent agreement for all articular sites.

The prevalence of the DC sign in the knees and MTPs was 46.7% and 40%, whereas that of tophi was 26.7% for both sites (Table II). We found no urate deposits in MCPs. Considering all assessed joints, the DC sign and tophi were found in at least one articular site in 60% and 46.7% of patients, respectively.
We next assessed, for each articular site, the prevalence of the DC sign in joints with intra-articular tophi. The DC sign was found in all knees and

Table I. Characteristics of patients with gout.

Patients	Age (years)	BMI (kg/m^2)	Total number of attacks	Delay between first attack and US (months)	Uricemia (μmol/l)	Creatinine clearance (ml/min)	Affected joints
1	33.2	24.2	2	48.2	577	120	MTP, Knee
2	74.9	31.1	3	36.1	771	29	MTP, Knee
3	84.0	24.7	2	17.5	571	59	MTP
4	77.0	25.0	2	120.4	631	33	MTP
5	84.9	28.7	3	109.6	382	51	Knee
6	42.4	22.6	1	0.5	807	53	MTP
7	59.2	25.2	2	26.2	574	65	Ankle
8	57.0	24.2	2	17.8	547	67	Knee
9	54.7	25.0	2	13.2	476	87	MTP
10	70.0	26.7	1	0.0	570	15	DIP
11	50.6	23.0	1	0.0	707	56	Knee
12	41.7	28.4	1	2.3	1087	71.8	MTP
13	65.2	26.1	2	0.3	426	85	Knee
14	33.0	24.8	3	24.0	736	95	MTP, Knee
15	38.6	25.9	2	26.9	685	109	Knee
Mean (SD)	57.8 (17.8)	25.7 (2.2)	1.9 (0.7)	30.0 (37.3)	636.5 (174.5)	66.4 (29.3)	NA
Median [IQ]	56.9 [31.7]	25 [2.2]	2 [0.7]	17.7 [30.2]	577 [176]	65 [35]	NA

US: Ultrasonography; BMI: body mass index; MTP: metatarsophalangeal; DIP: Distal interphalangeal; NA: not applicable.

MTPs showing tophi. By contrast, the prevalence of tophi in the knees and MTPs showing the DC sign was 42.9% and 66.7%, respectively.

Association of urate levels and presence of the DC sign and tophi

The study population was subdivided according to the last urate levels, using a cut-off of 600 μM (10 mg/dl), as shown in Table III. The prevalence of the DC sign in patients with ≥600 μM (10 mg/dl) urate was 75% and 62.5% in knees and MTPs, respectively, as compared with 12.5% for both sites for patients with urate levels <600 μM (10 mg/dl) (Table III). Moreover, all patients with urate levels ≥600 μM (10 mg/dl) had a DC sign in at least one assessed joint.

By contrast, the 2 groups showed less difference in prevalence of tophi (Table III). Finally, we found a significant association of urate level and DC sign at the knees (p=0.005) and MTPs (p=0.03) but not presence of tophi.

Discussion

Recent studies have called attention to the potential usefulness of US in investigating gout (5, 6). These studies have shown that US can detect bone erosions – a potential feature of urate arthropathy – even with normal radiography results (5, 14), and have suggested that US can help in the diagnosis of gout by demonstrating intra-articular or tendinous MSU crystal deposits.

Our exploratory study of early gout focused on the US demonstration of intra-articular urate deposits, which can be visualized on the cartilage surface (the DC sign) or within the synovium (intra-articular tophi). The specificity of the DC sign and intrasynovial deposits was considered very good (>90%) in two studies (5, 7). Moreover, intrasynovial tophi were seen in all gouty MTP and MCP joints but in no control joints (6), which suggests that US scan can be an attractive tool for the diagnosis of gout.

However, the sensitivity of US for the diagnosis of gout has varied among published studies (5-7, 15). The DC sign was found in 22% of 1st MTPs (5) to 92% of symptomatic joints (6) and intra-articular tophi in 32% (5) to 100% (6). These discrepancies could be explained in part by the quality of the apparatus used, different joint assessment, and the experience of the investigators but also to the amount of crystal deposits. In our experience, nearly every patient with tophaceous gout shows US features of urate deposits in the MTP and/or knee joints (unpublished data). Additionally, detection of the DC sign in the MTP joints can be impaired by loss of cartilage, which sometimes occurs during gouty arthropathy. The presence of tophi at the dorsal side of MTPs can also impair the ability to detect the DC sign, by attenuating the penetration of ultrasound. US might be helpful in measuring changes in tophi size and showing the disappearance of the DC sign in patients receiving ULT (16, 17).

In this study, we aimed to explore the efficiency of US for patients with incipient disease, in whom clinical diagnosis is less easy and the crystal load is believed to be low. Indeed, 60% of our small series of patients with crystal-proven gout and a maximum of 3 attacks had at least one US feature of urate deposits in MTP and/or knee joints. Interestingly none had intra-articular tophi or the DC sign in MCP joints, which suggests that screening MCP joints might be less useful in early gout. Additionally, the relation we found between serum urate levels, an important factor of gout (12), and US findings further suggests the good ability of US to demonstrate urate deposits and their extent (*i.e.* severity of gout) in joints.

A previous US study detected tophi and increased vascularity in one-third and one-quarter, respectively, of asymptomatic hyperuricemic patients (18), which demonstrates a continuum between asymptomatic hyperuricemia and gout (4). A recently published study found a DC sign in 25% of first MTP and 17% in knee joints from asymptomatic hyperuricemic patients (19).

Table II. Prevalence of patients with the DC sign and/or tophi detected by US according to joint site.

	DC sign	Tophi	DC sign and tophi
MCPs	0	0	0
Knees	46.7	26.7	20.0
MTPs	40.0	26.7	26.7
At least one site	60.0	46.7	60.0

Data are percentages of patients. US: ultrasonography; DC: double contour; MCP: metacarpophalangeal; MTP: metatarsophalangeal.

Table III. Clinical and US findings according to levels of uricemia.

	Uricemia <600 µmol/l (10mg/dl) (n=8)	Uricemia >600 µmol/l (10 mg/dl) (n=7)	*p*-value
Age (years)	63.5 ± 16.8	51.2 ± 17.7	ns
Delay between first attack and US (months)	29.1 ± 35.9	31.0 ± 41.7	ns
Number of attacks	2 ± 0.5	1.9 ± 0.9	ns
Creatinine clearance (ml/min)	68.6 ± 30.5	63.8 ± 30	ns
DC sign			
Knees	12.5	75	0.005
MTPs	12.5	62.5	0.03
At least one site	25	100	0.003
Tophi			
Knees	12.5	37.5	ns
MTPs	12.5	25	ns
At least one site	25	62.5	ns

Data are mean ± SD or percentages. US: Ultrasonography; DC: double contour. MCP: metacarpophalangeal; MTP: metatarsophalangeal.

These results suggest that substantial urate deposits in joints could pre-date crystal-induced flares. In our study, we assessed the intra-articular urate deposits by evaluation of intra-articular tophi and the DC sign. It should be noted that US assessment of tendons or entheses, which are frequently involved in early gout (15) could also be helpful to find urate deposits. Importantly, our data show that the DC sign, which was previously reported to be a sonographic finding of late stages of gout, can also be found in the early stages of the condition. If US findings can provide an indication of the amount of deposited crystals, US features could be taken into account in assessing the severity of the disease and could help in clarifying the indication for ULT in early gout. Because the outcome of gout is uncertain in patients who have experienced 1 or only a few flares and because ULT exposes the patient to safety hazards, the indication for this therapy is uncertain in early gout. Indeed, after a first attack, some patients do not have another for years. The recurrence rate was reported to be 62 in the first year, 78% by 2 years and 89% by 5 years (20).

International bodies have recommended that ULT be limited to severe gout (*i.e.* tophaceous gout or urate arthropathy or recurrent gout) (2, 3). However, crystal deposition in early gout is likely to worsen if uricemia is above the saturation point of MSU, and crystals are known to take longer to dissolve with delayed ULT. Indeed, the time required for crystal disappearance within the joint is associated with disease duration (21), mainly because the higher the amount of the urate pool, the longer it takes to deplete (22).

Additionally, since the use of new imaging modalities for gout (23), conventional radiography, used traditionally to detect gouty arthropathy, has been found poorly sensitive in detecting bone damage. Typical erosions, which are closely linked to tophus (24), may not be seen with plain radiographs until 6-12 years after the initial acute attacks (25). In addition, recent reports have suggested that gouty arthropathy, especially in MTPs, might occur in clinically "silent" joints and might be detected only by advanced imaging such as MRI and/or US, when plain radiography results are normal (5, 14, 25).

In conclusion, our exploratory study of patients with gout who did not meet the criteria for ULT revealed that on US, 60% had significant crystal deposits, a finding that could support an indication for ULT. Prospective studies are needed to assess the benefit-risk balance of early ULT in patients with gout in whom articular urate deposits are detected**.**

US may be effective in detecting crystal deposits in patients with early gout.

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