Joint Bone Spine 86 (2019) 89–94

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Original article

The popliteal groove region: A new target for the detection of monosodium urate crystal deposits in patients with gout. An ultrasound study

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ARTICLE INFO

Article history:
Accepted 20 June 2018
Available online 17 July 2018

Keywords:
Gout
Tophus
Monosodium urate crystals
Diagnostic performance
Ultrasound
"Double contour" sign

ABSTRACT

Objectives: To determine the prevalence of the ultrasound findings indicating monosodium urate crystal deposits at the popliteal groove region in patients with gout; to evaluate the diagnostic accuracy of ultrasound in detecting monosodium urate crystal deposits at the popliteal groove region, patellar tendon and the knee hyaline cartilage; to investigate the correlation between the ultrasound findings at the popliteal groove region and the clinical features.
Methods: Bilateral ultrasound assessment of the popliteal groove region, patellar tendon and femoral condyles' hyaline cartilage was performed on 47 consecutive patients with gout and 37 controls. The ultrasound findings indicating monosodium urate crystals (aggregates, tophi and "double-contour" sign) were identified according to the Outcome Measures in Rheumatology definitions.
Results: One or more ultrasound abnormalities (aggregates and/or tophi) were found in at least one popliteal groove region in 23 out of 47 patients with gout (48.9%) and in 4 out of 37 controls (10.8%) ($P < 0.001$). Sensitivity, specificity and diagnostic odds ratio of the ultrasound findings at the popliteal groove region, patellar tendon and at the femoral condyles' hyaline cartilage were 0.49/0.89/7.9, 0.62/0.81/6.9 and 0.30/1.0/32.0, respectively. There was a significant correlation between the ultrasound findings at the popliteal groove region and history of knee inflammatory involvement ($P < 0.001$, $V = 0.644$) and number of gouty "attacks" in the previous year ($P = 0.012$, $V = 0.434$).
Conclusions: This study provides new insights into the ultrasound assessment of patients with gout, highlighting the clinical relevance of the popliteal groove region as an area of collection of otherwise undetectable monosodium urate crystals.

1. Introduction

Gout is the most common form of inflammatory arthritis [1]. It is characterized by the deposition of monosodium urate (MSU) crystals in articular and periarticular structures [2–4]. The gold standard for the diagnosis of gout is the synovial fluid analysis with the identification of negatively birefringent needle-shaped crystals under polarized microscope [5,6].

In recent years, ultrasound (US) has been gaining a relevant diagnostic role in gout. A number of studies have shown that US is able to detect MSU crystal deposits at joint, tendon and soft tissue level, both in the early and late stages of the disease [7–10], and also in asymptomatic hyperuricemia [11,12]. The US "double-contour" (DC) sign has been included in the latest Gout American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [13].

The knee is one of the most frequent targets of gout. US findings indicative of MSU crystal deposits have been described at knee joint and periarticular structures [14–20]. It is well known that the topographic distribution of crystal aggregates is inhomogeneous. In a recent study carried out by Naredo et al. [14], three synovial recesses (suprapatellar, lateral and medial), two tendons (patellar and quadriceps), two bursae (gastrocnemius-semimembranous and deep infrapatellar), two ligaments (lateral collateral and medial collateral) and the hyaline cartilage were evaluated in 182 knees of 91 patients with gout. Aggregates within the patellar tendon and DC

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https://doi.org/10.1016/j.jbspin.2018.06.008
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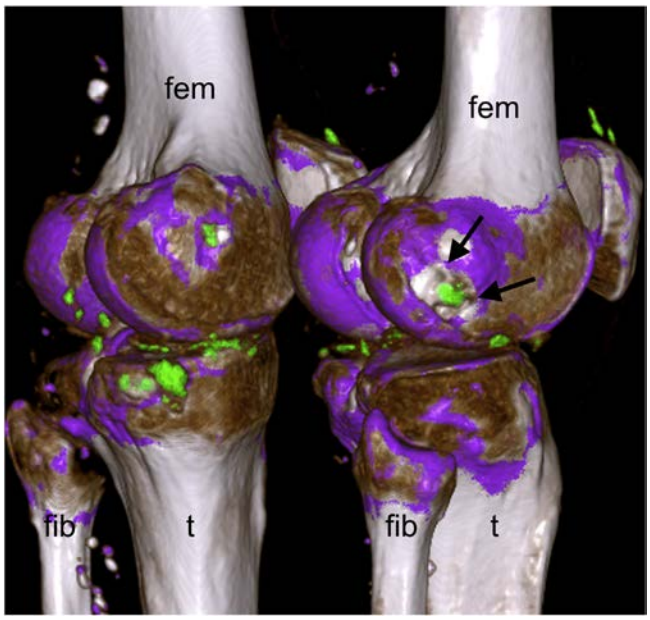

Fig. 1. Three dimensional dual energy computed tomography postero-lateral view of the popliteal groove region in a patient with gout. The popliteal groove (arrow) can be seen as a depression on the postero-lateral side of the lateral condyle of the femur. Monosodium urate crystal deposits are depicted in green. fem: femur; fib: fibula; t: tibia. Courtesy of Dr. Marina Carotti, Radiology Department, Università Politecnica delle Marche.

sign at the hyaline cartilage were the US findings most frequently detected.

Recently, our research group demonstrated the presence of US findings of MSU crystal deposits at the popliteal groove region (PGR) in a small number of patients with gout, raising the hypothesis that urate crystal aggregates have an elective tropism towards this area [21]. The popliteal groove is a depression on the outer side of the lateral femoral condyle and is the site of insertion of the popliteus tendon. At this level, the popliteus tendon has a close connection to the lateral meniscus and is surrounded by the subpopliteal recess, which is in direct communication with the knee joint cavity [22,23]. Fig. 1 shows a three-dimensional dual energy computed tomography scan of the PGR in a patient with gout.

The aims of this US study were:

- to determine the prevalence and topographic distribution of the US findings highly suggestive of MSU crystal deposits at the PGR in patients with gout;
- to evaluate the sensitivity, specificity and accuracy of US at detecting MSU crystal deposits at the PGR, patellar tendon and femoral condyles' hyaline cartilage;
- to investigate the correlation between the US findings at the PGR and the clinical and serological data.

2. Methods

2.1. Patients

Consecutive patients with gout, fulfilling the ACR/EULAR classification criteria [13], and age/body mass index (BMI)/sex-matched controls, diagnosed with other rheumatic diseases according to the international diagnostic/classification criteria, were enrolled.

All the patients were recruited from the outpatient clinic of the "Clinica Reumatologica" of the "Carlo Urbani" Hospital, Jesi, Ancona, Italy.

Exclusion criteria for patients with gout and controls were: "active" knee synovitis at the time of the evaluation, defined as joint swelling with local heat and tenderness; knee joint injections in the six months preceding the recruitment; relevant knee trauma or surgery procedures. Controls with hyperuricemia and/or with family history of gout were excluded.

This study was carried out in compliance with local regulation and the Declaration of Helsinki. All patients gave their informed consent.

2.2. Clinical assessment

An experienced rheumatologist performed the physical examination, mainly focused on the detection of subcutaneous tophi, and gathered demographic and clinical data of all subjects. Lifestyle (smoking and use of alcohol), use of medications (urate-lowering treatments and diuretics) and comorbidities (congestive heart failure, chronic kidney disease, dyslipidemia, hypertension, type II diabetes and metabolic syndrome) were investigated. Serum urate level, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and synovial fluid analysis results were collected. In patients with gout, the following information was also obtained: disease duration since the first diagnosis, family history of gout, gouty "attacks" in the previous year, and previous inflammatory involvement of the knee.

2.3. Ultrasound examination

A second rheumatologist, blinded to clinical and laboratory data, performed the US examination in all subjects. The US examination was carried out with a Logiq 9 US system (General Electric Medical Systems, Milwaukee, WI, USA), working with a linear probe operating at 15 MHz and at a Doppler frequency of 7.5 MHz. The following structures were scanned bilaterally both in longitudinal and transverse views: the PGR, including both the popliteus tendon and the sub-popliteal recess, the patellar tendon, and the femoral condyles' hyaline cartilage.

The PGR was examined with the patients lying supine on the examination bed with the knee flexed at 90° (Fig. 2). The patellar tendon was examined with the patients lying in supine position, both with the knee in extended and in semi-flexed (45°) position.

The femoral condyles' hyaline cartilage was scanned with the patient in supine position with the knee in maximal flexion (> 90°). The following Outcome Measures in Rheumatology (OMERACT) US working group definitions of elementary gout lesions [24] were used:

- aggregates: heterogeneous, hyperechoic foci that maintain their degree of reflectivity even when the gain value is minimized or the insonation angle is changed and which occasionally may generate posterior acoustic shadow;
- tophi: circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (which may or not generate posterior acoustic shadow) which may be surrounded by a small anechoic rim;
- DC sign: an abnormal hyperechoic enhancement of the superficial margin of the articular hyaline cartilage, independent of the angle of insonation and which may be either irregular or regular, continuous, or intermittent and can be distinguished from the cartilage interface sign.

The presence of aggregates and tophi was investigated at the level of the PGR and of the patellar tendon. The DC sign was examined at the level of the femoral condyles' hyaline cartilage.

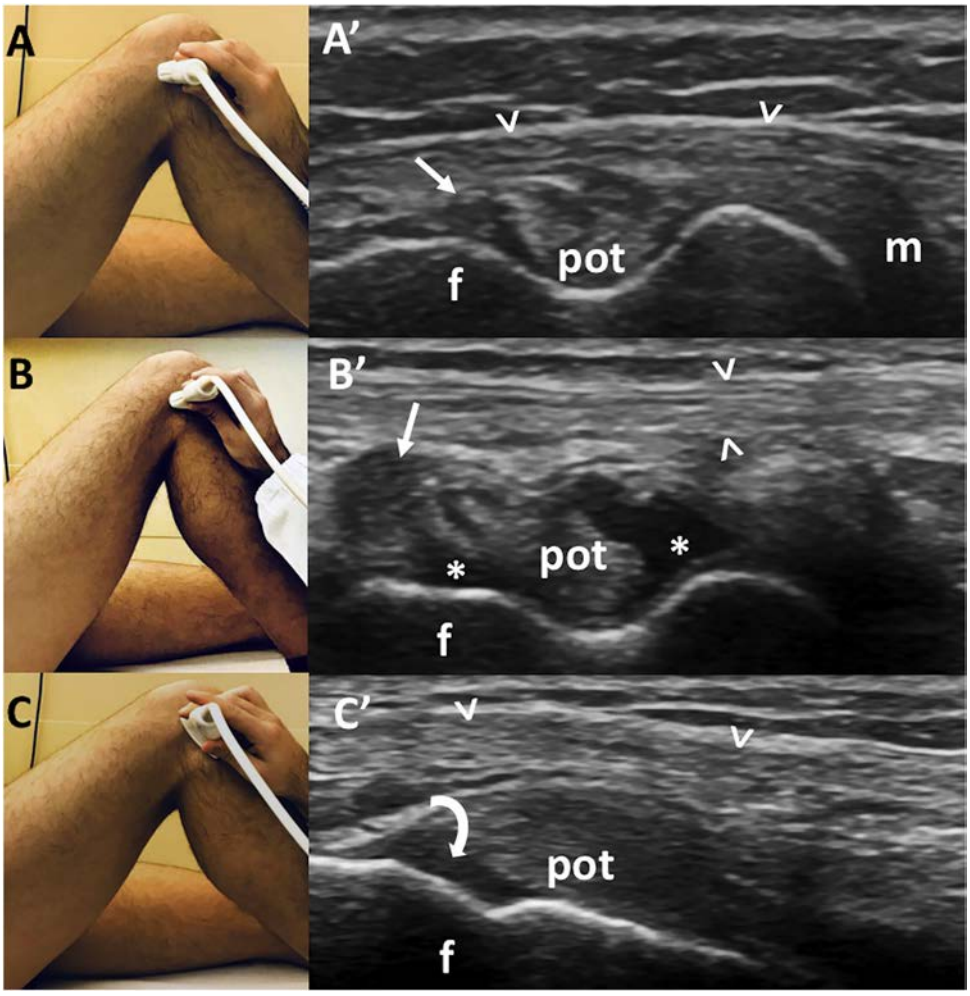

Fig. 2. Main ultrasound views of the popliteal groove region. In transverse view (A, B), the scanning protocol included the movement of the probe from the superior aspect of the popliteal groove (A–A′) to the inferior one (B–B′) using the iliotibial band (arrowheads) as sonographic landmark. In longitudinal scan (C–C′), the popliteal groove region was explored using the insertion of the popliteus tendon at the lateral femoral condyle (curved arrow) as sonographic landmark. Arrow: lateral collateral ligament; asterisks: sub-popliteal recess; f: femur; m: lateral meniscus; pot: popliteus tendon.

2.4. Statistical analysis

Results are reported as median and interquartile range for quantitative variables which were not normally distributed and as mean ± standard deviation (SD) for the ones which had a normal distribution (Kolmogorov–Smirnov test). Results for qualitative variables are expressed as absolute frequency and as corresponding percentage.

The Mann–Whitney test was used for the quantitative variables which were not normally distributed whereas the Student's *t*-test was used for the quantitative variables which had a normal distribution. The Chi^2 test was used for the categorical variables. The sensitivity, specificity and diagnostic odds ratio of US at detecting MSU crystal deposits at the PGR, patellar tendon and the femoral condyles' hyaline cartilage were calculated.

Correlations between the US findings indicating MSU crystal deposits at the PGR and the clinical and serological variables were assessed. Chi^2 test and Cramer's V were used to correlate the US findings with the categorical and/or ordinal variables (gender, previous episodes of knee synovitis, gouty "attacks" in the previous year, presence of subcutaneous tophi and synovial fluid analysis positive for MSU crystals). Point-biserial correlation (Rpb) was used to evaluate the correlation between the US findings and the quantitative variables (age, BMI, disease duration, serum urate levels).

Statistical analysis was performed using SPSS software (version 24.0 for Mac, Chicago, Illinois, USA).

2.5. Role of the funding source

Not applicable.

3. Results

We assessed a total of 168 PGR (94 PGR in patients with gout and 74 PGR in controls) in 84 patients (47 patients with gout and 37 controls).

The control group was made up of 13 patients with rheumatoid arthritis, 6 with calcium pyrophosphate deposition disease (CPPD), 5 with psoriatic arthritis, 4 with osteoarthritis, 4 with systemic sclerosis, 3 with ankylosing spondylitis and 2 with reactive arthritis.

Table 1 illustrates the main clinical and serologic features for both the patients with gout and controls.

Table 2 illustrates the prevalence and distribution of the US findings indicating MSU crystal deposits at the PGR, patellar tendon and femoral condyles' hyaline cartilage in patients with gout and controls.

Representative examples of the US findings of MSU crystal deposits at the PGR are shown in Fig. 3.

Table 1
Demographic, clinical and serological data for both patients with gout and controls.

	Gout patients	Controls
Male/female	46/1	35/2
Age (years)	65.8 ± 10.9	59.5 ± 13.1
Disease duration (years)	11.0 ± 10.1	13.1 ± 14.5
BMI (kg/m^2)	30.3 ± 3.0	30.8 ± 2.2
Subcutaneous tophi	16 (34.0%)	0
History of knee inflammatory involvement	31 (66.0%)	13 (35.1%)
Familiar history of gout	23 (48.9%)	0
High or moderate intake of alcohol (> 2 drinks/day)	24 (51.1%)	20 (54.1%)
Gouty attacks in the previous year	31 (66.0%)	–
Laboratory data		
Serum urate level (mg/dL)	6.9 ± 1.9	5.6 ± 0.9
ESR (mm/h)	26.2 ± 20.5	16.3 ± 15.6
CRP (mg/dL)	1.1 ± 1.4	0.9 ± 1.5
MSU crystals in the synovial fluid analysis	27 (57.4%)	0
Therapy		
Urate-lowering drugs	30 (63.8%)	0
Colchicine	26 (55.3%)	2 (5.4%)
Diuretics	11 (23.4%)	8 (21.6%)
Comorbidity		
Congestive heart failure	6 (12.7%)	5 (13.5%)
Chronic kidney disease	9 (19.1%)	4 (10.8%)
Metabolic syndrome	15 (31.9%)	4 (10.8%)
Type II diabetes	6 (12.7%)	3 (8.1%)
Hypertension	20 (42.6%)	7 (18.9%)
Hypercholesterolemia	20 (42.6%)	7 (18.9%)

BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MSU: monosodium urate.

The sensitivity, specificity and diagnostic odds ratio of US in detecting MSU crystal deposits at the PGR, patellar tendon and femoral condyles' hyaline cartilage are reported in Table 3.

US findings indicative of MSU crystal deposits were observed in at least one PGR in 23 patients with gout. In 7 of these patients (30.4%), they were detected at the PGR, but not at the patellar tendon and/or at the femoral condyles' hyaline cartilage of either the homolateral or contralateral knees. In the remaining 16 patients (69.6%), they were detected at the PGR and at patellar tendon and/or at the femoral condyles' hyaline cartilage of the homolateral and/or contralateral knee. US findings indicating MSU crystal deposits were not observed at the PGR in 24 patients with gout. In 15 of these patients (62.5%), they were detected at the patellar tendon and/or at the femoral condyles' hyaline cartilage of the homolateral and/or contralateral knees. In the remaining 9 patients (37.5%), they were not detected in any of the anatomic areas examined of both knees.

In patients with gout, 46 out of 94 knees (48.9%) were reported as previously involved in the patients' clinical history. MSU crystal deposits were found in 34 out of these 46 knees (73.9%). In these 34 knees, the US exam revealed: 11 DC signs (in 2 cases as isolated finding, in 9 cases in combination with US findings of MSU crystals at the PGR), 32 US findings indicating MSU crystals at the PGR (in 23 cases as isolated finding, in 9 cases in combination with the DC sign). In the 48 knees (51.1%) which were not reported as previously involved in the patients' clinical history, MSU crystal deposits were found in 7 knees (14.6%). In these 7 knees, the US exam revealed: 3 DC signs (in 2 cases as isolated finding, in 1 case in combination with MSU crystals at the PGR), 5 US findings indicative of MSU crystal deposits at the PGR (in 4 cases as isolated finding, in 1 case in combination with the DC sign).

There was a strong association between the US findings of MSU crystal deposits at the PGR and a positive history of previous knee inflammatory involvement ($P < 0.001$, V = 0.644) and a moderate association between the US findings and the number of gouty "attacks" in the previous year ($P < 0.05$, V = 0.434). No correlation was found between the US findings indicating MSU crystal deposits at the PGR and the other variables which had been considered: age ($P = 0.466$), P = gender ($P = 0.322$), disease duration ($P = 0.446$), BMI ($P = 0.990$), presence of MSU crystals at synovial fluid analysis ($P = 0.586$), presence of subcutaneous tophi ($P = 0.181$) and serum urate levels ($P = 0.617$).

4. Discussion

To the best of our knowledge, this is the first study that aimed to explore the presence of US findings indicating MSU crystal deposits at the PGR in patients with gout. The prevalence of US findings indicative of microcrystal aggregates at the PGR was significantly higher in patients with gout than in controls: 23 out of 47 patients with gout (48.9%) vs. 4 out of 37 controls (10.8%) ($P < 0.001$). Three out of the 4 controls with US findings indicative of MSU crystal deposits were patients with CPPD. The sonographic pattern of these 3 patients was indistinguishable from that of the patients with gout. Further investigation in a larger cohort of patients is required to determine whether the PGR can be a specific region of interest also for the detection of calcium pyrophosphate crystal aggregates.

Until now, the PGR has been investigated only by one study using magnetic resonance imaging (MRI). In this observational retrospective study, where Ko et al. reviewed the MRI images of the knees of 30 patients with gout, the presence of tophaceous deposits at the PGR was demonstrated in a considerable number of knees (78.1%) [25].

In the present study, US MSU crystal aggregates were detected more frequently in the sub-popliteal recess than within the popliteus tendon. On the other hand, tophi were found more frequently within the popliteus tendon than in the sub-popliteal recess. The increased concentration of microcrystal deposits at the PGR may be related to the hydrodynamics of synovial fluid ("pooling effect").

Sensitivity and specificity of the US findings varied considerably among the examined anatomical areas. In fact, the sensitivity of the US findings at the PGR was lower than at patellar tendon, but higher than at femoral condyles' hyaline cartilage. On the other hand, the specificity of the US findings at the PGR was higher than at patel-

Table 2
Prevalence and distribution of the US findings indicating MSU crystal deposits at the popliteal groove region, patellar tendon and femoral condyles' hyaline cartilage in patients with gout and controls.

US findings indicating MSU crystal deposits	Number of patients			Number of knees		
	Gout	Controls	*P* value	Gout	Controls	*P* value
Popliteal groove region (in at least one knee)	23 (48.9%)	4 (10.8%)	< 0.001	39 (41.5%)	5 (6.8%)	< 0.001
Intratendinous tophi	10 (21.3%)	1 (2.7%)	0.012	11 (11.7%)	1 (1.4%)	0.010
Tophi in the sub-popliteal recess	7 (14.9%)	0	0.014	7 (7.4%)	0	0.016
Intratendinous aggregates	7 (14.9%)	1 (2.7%)	0.059	7 (7.4%)	1 (1.4%)	0.065
Aggregates in the sub-popliteal recess	14 (29.8%)	3 (8.1%)	0.014	17 (18.1%)	3 (4.1%)	0.005
Popliteal groove region (bilaterally)	16 (34.0%)	1 (2.7%)	< 0.001	–	–	–
Femoral condyles' hyaline cartilage	14 (29.8%)	0	0.002	14 (14.9%)	0	< 0.001
Patellar tendon	29 (61.7%)	7 (18.9%)	< 0.001	40 (42.6%)	9 (12.2%)	< 0.001

MSU: monosodium urate; US: ultrasound. Percentages refer to the total number of patients (gout = 47, controls = 37) and knees (gout = 94, controls = 74), respectively. Of the 4 patients with US findings indicating MSU crystal deposits at the popliteal groove region, 3 had calcium pyrophosphate deposition disease and 1 had osteoarthritis.

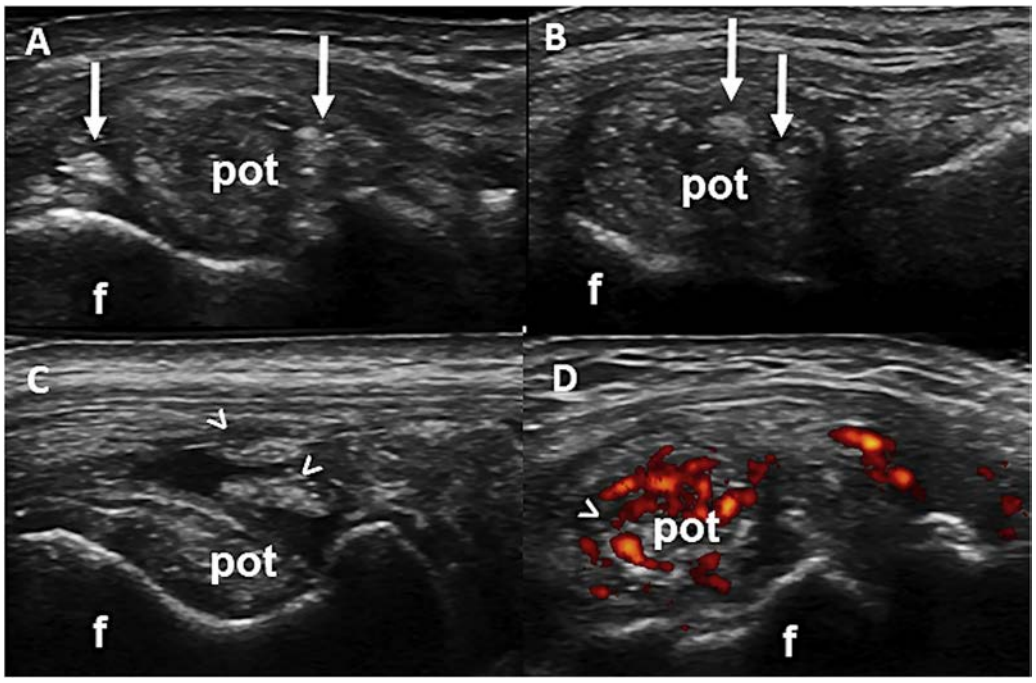

Fig. 3. Ultrasound findings indicative of monosodium urate crystal deposits acquired using transverse scans at the popliteal groove region in patients with gout. In Fig.3A and Fig. 3B, aggregates (arrows) are visible in the sub-popliteal recess and within the popliteus tendon, respectively. In Fig. 3C, two tophi in the sub-popliteal recess are highlighted with arrowheads. Note, in Fig. 3D, the presence of an intra-tendinous tophus (arrowhead), surrounded by power Doppler signal (red spots). f: femur; pot: popliteus tendon.

Table 3
Sensitivity, specificity and diagnostic odds ratio of US at detecting MSU crystal deposits at the popliteal groove region, patellar tendon and femoral condyles' hyaline cartilage.

US findings indicating MSU crystal deposits	Sensitivity	Specificity	Diagnostic odds ratio
Popliteal groove region (in at least one knee)	0.49 (0.34–0.64)	0.89 (0.75–0.97)	7.9 (2.4–26.0)*
Popliteal groove region (bilaterally)	0.34 (0.21–0.49)	0.97 (0.86–1.0)	19.0 (2.3–148.0)*
Patellar tendon (in at least one knee)	0.62 (0.46–0.75)	0.81 (0.65–0.92)	6.9 (2.5–19.0)*
Femoral condyles' hyaline cartilage (in at least one knee)	0.30 (0.17–0.45)	1.0 (0.91–1.0)	32.0 (1.9–566.0)*

MSU: monosodium urate; US: ultrasound. Each result's 95% confidence interval is written in brackets. The significance of the test was determined by Chi^2 Test.
* $P < 0.01$.

lar tendon, but lower than at femoral condyles' hyaline cartilage. The diagnostic accuracy increased when US findings of MSU crystal deposits were found at the PGR of both knees.

In a considerable number of patients with gout, US findings indicative of MSU crystal deposits were found at the PGR but not at the patellar tendon or at hyaline cartilage. Moreover, MSU crystal aggregates were noticeably more frequently detected at the PGR than at the femoral condyles' hyaline cartilage in the knees reported as previously involved in the patients' medical history. In subjects with clinical features suggestive of gout, the standard protocol of US assessment should include not only the patellar tendon and the femoral condyles' hyaline cartilage, but also the PGR because otherwise undetectable MSU crystal deposits can be easily demonstrated in this area.

Imaging has an unquestionable value in the diagnosis of gout, especially in cases where the synovial fluid analysis is not practicable and the clinical examination is not conclusive for a definite diagnosis [26]. To date, the physical examination is considered as the most feasible method in clinical practice to detect the presence of tophi [27], although its sensitivity may be low especially in the early phases of the disease [28]. The newer imaging techniques, such as US and dual energy computed tomography, have the potential to change dramatically the diagnostic algorithm of gout because of their ability to identify even minimal and otherwise undetectable crystal deposits. US allows physicians to explore multiple joints and tendons in the same exam session, increasing the chance to detect MSU crystal deposits also in asymptomatic anatomic sites. With this in mind, the identification of targets of MSU crystal deposits becomes extremely important.

5. Conclusion

This study provides new insights into the US assessment of the patients with gout, highlighting the clinical relevance of PGR as an area of collection of otherwise undetectable MSU crystal deposits.

Disclosure of interest

The authors declare that they have no competing interest.

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