Review

One year in review 2017: ultrasound in crystal arthritis

E. Naredo[1], A. Iagnocco[2]

[1]Department of Rheumatology, Joint and Bone Research Unit, Hospital Universitario Fundación Jiménez Díaz and Autónoma University, Madrid, Spain; [2]Dipartimento di Scienze Cliniche e Biologiche - Reumatologia, Università degli Studi di Torino, Turin, Italy.

Esperanza Naredo, MD
Annamaria Iagnocco, MD

Please address correspondence and reprint requests to:
Dr Esperanza Naredo,
Department of Rheumatology,
Doctor Alvarez Sierra 4, 4º A,
28033 Madrid, Spain.
E-mail: enaredo@ser.es

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ABSTRACT

Musculoskeletal ultrasound (MSUS) has become a relevant part of rheumatology practice and research. This imaging modality substantially allows us to optimise the management of inflammatory, degenerative and crystal-related musculoskeletal diseases. MSUS is a valuable point-of-care tool to accurately assess intra-articular and periarticular abnormalities involved in rheumatic diseases. Furthermore, MSUS is a bedside aid for guiding accurate and safe musculoskeletal diagnostic aspirations and therapeutic injections. This review provides an overview of the last year's literature on the role of MSUS in crystal arthritis.

Introduction

Gout and calcium pyrophosphate deposition (CPPD) disease are common rheumatic disorders caused by deposition of monosodium urate crystals (MSU) or calcium pyrophosphate crystals, respectively, inside and around joints, where they can produce acute and/or chronic arthritis (1, 2). Definitive diagnosis of these diseases requires identification of crystals in synovial fluid, synovial tissue or crystal deposits. Nevertheless, imaging can provide helpful diagnostic information as well as insights into a better understanding of crystal-related disease pathology.

In the 21st century, musculoskeletal ultrasound (MSUS) has been progressively incorporated into rheumatology clinical practice as a valuable tool to optimise the management of patients with rheumatic and musculoskeletal diseases (RMD) (3, 4). US is now also increasingly being used in the diagnosis and monitoring of crystal arthritis (5-9). Furthermore, MSUS is a valuable bedside tool for guiding accurate and safe diagnostic fluid aspiration or therapeutic injections in joints or periarticular structures (10). MSUS has many advantages such as non-invasiveness, availability, relative low cost, repeatability, and high patient-acceptance; however, it is highly operator-dependent. The Outcome Measures in Rheumatology (OMERACT) MSUS group has made a great effort to standardise and validate MSUS in the diagnosis and monitoring of gout and CPPD disease in order to make this technique applicable to clinical trials and clinical practice (11). Recently, we have witnessed the first incorporation of MSUS findings in gout and CPPD disease classification criteria (12, 13). This review provides an evidence-based update on the role of MSUS in crystal arthritis, particularly in gout and CPPD disease. Figures 1–6 show illustrative MSUS images of these diseases.

We carried out a literature search in PUBMED and EMBASE databases for English language articles published from January 2016 to December 2016. We review all the published articles and selected the most relevant according to the following criteria; involving humans, focus on MSUS advancements, relevance to clinical rheumatology, journal impact factor and expert opinion of the authors. We included original articles and international consensus and recommendations. Narrative reviews, case reports or abstracts from scientific congresses were not included.

Validation

Recently, the OMEACT MSUS group produced consensus-based definitions of the MSUS elementary lesions in gout as well as tested their reliability in still images and patients (14, 15). The group agreed on four statements defining MSUS elementary lesions: double contour, tophus, aggregates and erosion. These definitions were as follows.

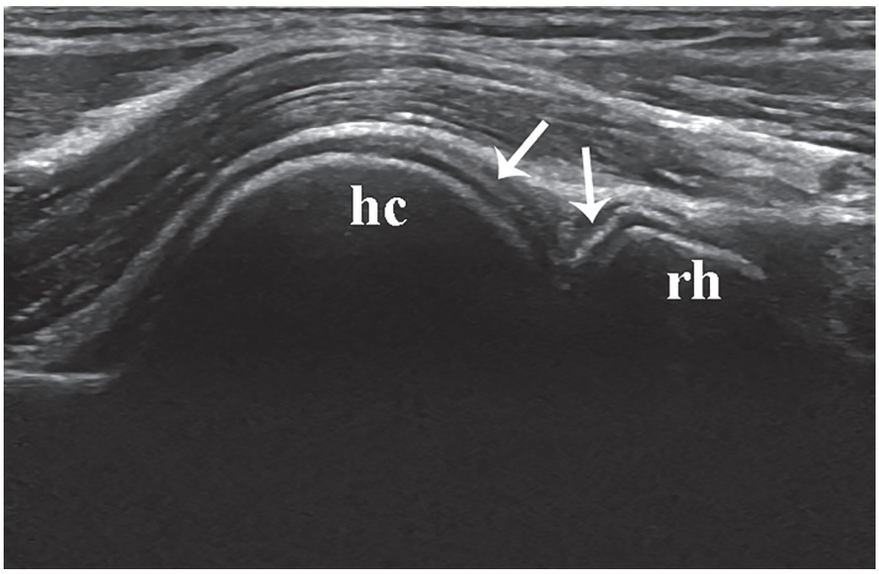

Fig. 1. Longitudinal ultrasound image of the anterior aspect of the elbow joint of a patient with CPPD disease that shows a hyperechoic band within the hyaline cartilage (arrows). **hc**, humeral capitulum; rh, radial head.

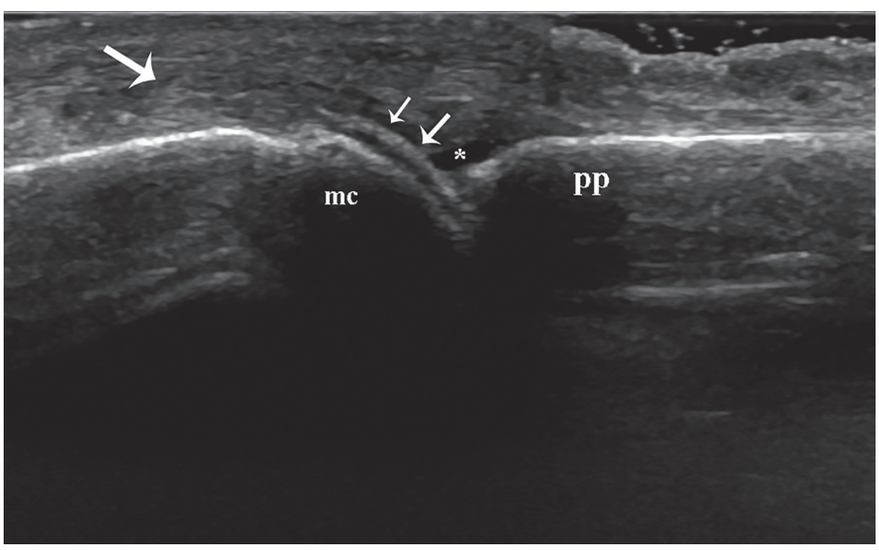

Fig. 2. Longitudinal ultrasound image of the dorsal aspect of the second metacarpophalangeal joint of a patient with gout that shows synovitis with hyperechoic material (arrow) and hypoechoic fluid (asterisk) and the cartilage double contour sign (small arrows). **mc**, metatarsal head; **pp**, proximal phalanx.

- Double contour: Abnormal hyperechoic band over the superficial margin of cartilage independent of angle of insonation and which may be either irregular or regular, continous or intermittent and can be distinguished from the cartilage interface sign.
- Tophus: A circumscribed inhomogeneously, hyperechoic and/or hypoechoic aggregration, (which mayor may not generate posterior acoustic shadow), which may be surrounded by small anechoic rim.
- Aggregates: Heterogeneous hyperechoic foci that maintain their high degree of reflectivity even when the gain setting is minimised or the insonation angle is changed, and which occasionally may generate posterior acoustic shadow.
- Erosion: An intra- and/or extra-articular discontinuity of the bone surface (visible in two perpendicular planes).

The inter-observer and intra-observer reliability of the above consensus-based definitions on images were good for double contour, tophus and erosions and acceptable for aggregates (*i.e.* inter-observer κ values 0.98, 0.71, 0.54 and 0.85, respectively; intra-observer κ values 0.93, 0.78, 0.65 and 0.78, respectively). In the patient-based assessment, the inter-observer reliability was good for tophus and erosions, but fair to moderate for aggregates and double contour, respectively, being the highest reliability for erosions (κ 0.74) and the lowest for aggregates (κ 0.21). The intra-observer reliability was good for tophus, aggregates and erosions and moderate for double contour, being the best for tophus (κ 0.73) and the worst for double contour (κ 0.53).

Over the last two years, the OMERACT MSUS group has started to work in validation of MSUS in CPPD disease. In 2015, a systematic literature review and meta-analysis concluded that US has high sensitivity [87.9% (95% CI 80.9%–94.9%] and specificity [91.5% (95% CI 85.5% to 97.5%] for the diagnosis of CPPD disease (16). In 2016, Filippou *et al*. (17) published a systematic literature review and meta-analysis on the definitions of MSUS elementary lesions and the diagnostic accuracy of MSUS in CPPD disease. The authors included 37 articles for the review and 13 articles for the meta-analysis on MSUS diagnostic accuracy. Description of MSUS elementary lesions at the hyaline cartilage, fibrocartilage, tendons and synovial fluid. were variable and heterogeneous in the published studies. At hyaline cartilage, CPP crystals were generally described as hyperechoic deposits, placed within the layer of the cartilage that reach large dimensions. At fibrocartilage, CPP crystals were usually described as hyperechoic, rounded or amorphous-shaped deposits placed within the structure. In tendons, CPP crystals were mostly described as linear deposits within the fibrillar echotexture (multiple or single lines or thick solid band), but in some studies these deposits were described also as punctate. In the synovial fluid, CPP crystals were reported as hyperechoic spots or ovoid aggregates. Regarding the evaluation of US diagnostic accuracy in CPPD disease, the results were as follows. At the patent level, the pooled sensitivity and specificity of MSUS

for diagnosing CPPD disease was 0.89 (95% CI 0.72–0.97) and 0.94 (95% CI 0.87–0.98), respectively. Regarding the MSUS diagnostic accuracy at the anatomic structure level, the highest sensitivity was obtained at the hyaline cartilage with a pooled sensitivity of 0.77 (95% CI 0.63–0.87) and specificity of 0.92 (0.16–1.00) and at the fibrocartilage with a pooled sensitivity of 0.77 (95% CI 0.31–0.96) and specificity of 0.96 (95% CI 0.75–1.00), while for the tendons the sensitivity and specificity were respectively 0.34 (95% CI 0.16–0.58) and 1.00 (95% CI 0.89–1.00). When MSUS was compared to synovial fluid analysis as gold standard, the pooled sensitivity was 0.87 (95% CI 0.76–0.99) and specificity 0.98 (0.96–1.00) and when the reference standard was the presence of radiographic chondrocalcinosis, the sensitivity was 0.58 (95% CI 0.09–1.00) and specificity 0.84 (95% CI 0.52–1.00). The authors concluded that although MSUS is a potential useful tool for the diagnosis of CPPD disease, further work on agreed definitions and validation of this imaging modality in the diagnosis of this disease should be done before its implementation in clinical practice and trials.

Diagnostic performance

The performance of MSUS in the diagnosis of crystal arthritis has been addressed in a number of recent studies over the last decade (18-24). Recently, further research has provided new insights into this field. Zufferey *et al*. (25) evaluated the diagnostic performance of MSUS for gout and CPPD disease in 109 patients who presented with acute arthritis of suspected microcrystalline aetiology. Patients underwent MSUS of the symptomatic joint(s) and knee, ankle and first metatarsophalangeal (MTP) joints. Fifty-one patients had MSU, 28 CPP and 9 had both crystals by microscopic analysis. The presence of MSUS findings of gout in the symptomatic joint was highly predictive of this diagnosis [Positive predictive value (PPV) = 92%]. In the absence of MSUS signs, CPPD arthritis was unlikely [Negative predictive value (NPV) = 87%].

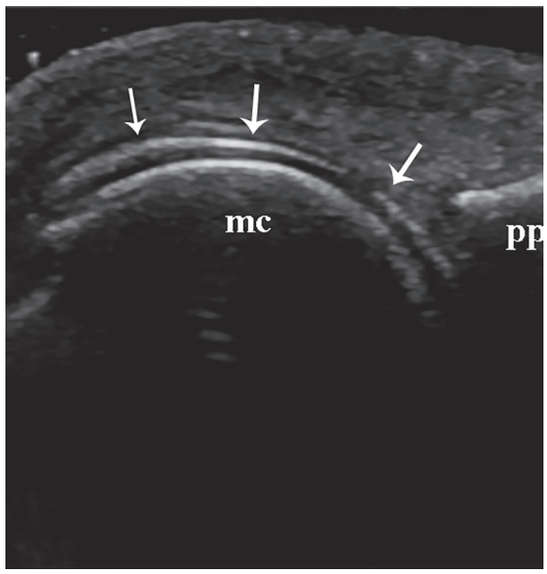

Fig. 3. Longitudinal ultrasound image of the dorsal aspect of the second metacarpophalangeal joint in maximal flexion of a patient with gout that shows the cartilage double contour sign (arrows). **mc**, metacarpal head; **pp**, proximal phalanx.

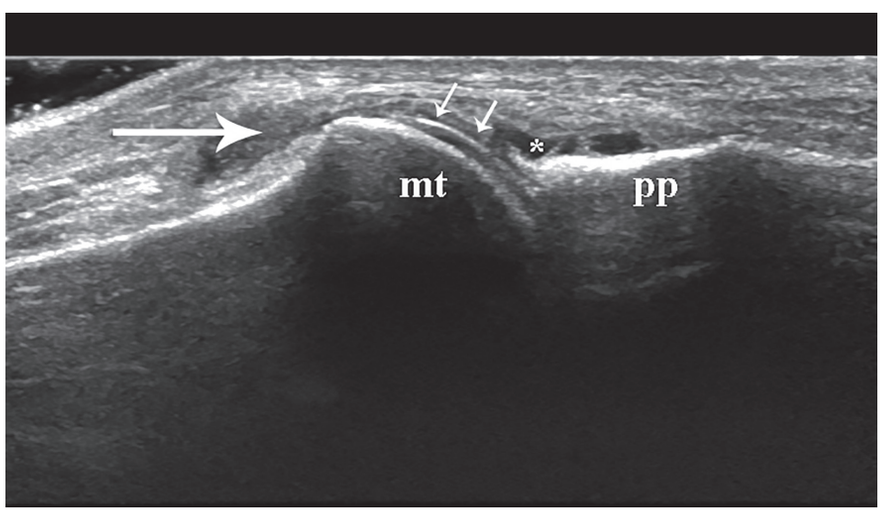

Fig. 4. Longitudinal ultrasound image of the dorsal aspect of the first metatarsophalangeal joint of a patient with gout that shows synovitis with hyperechoic material (arrow) and hypoechoic fluid (asterisk) and the cartilage double contour sign (small arrows). **mt**, metatarsal head; **pp**, proximal phalanx.

Ottaviani *et al*. (26) and Ruta *et al*. (27) compared the capability of MSUS and radiography to detect knee CPPD in 51 and 75 patients, respectively, with knee effusion using microscopic identification of CPP crystals in knee synovial fluid as reference standard. The results of the study by Ottaviani *et al*. (26) showed that sensitivity and specificity were 100% and 92.3%, respectively, for MSUS and 64% and 100%, respectively for radiography. Ruta *et al*. (27) reported a sensitivity and specificity for MSUS of 60% and 96.7%, respectively, and a sensitivity and specificity for radiography of 40 % and 83.3%, respectively. Overall, MSUS seemed to perform better than conventional radiography for diagnosing CPPPD disease in both studies.

Filippou *et al*. (28) assessed the diagnostic performance of MSUS, radiography, and microscopic analysis of synovial fluid for CPPD disease using histology as a gold standard method. They included 42 patients with knee osteoarthritis who underwent joint replacement surgery. Synovial fluid and condyles and menisci were retrieved during surgery for microscopic analysis. Twenty-five (59.5%) patients were positive for CPP crystals by MSUS, 15 (44.1%) by radiography and 14 (43.7%) by synovial fluid analysis. Sensitivity and specificity were 96% and 87% for MSUS, 75% and 93% for radiography

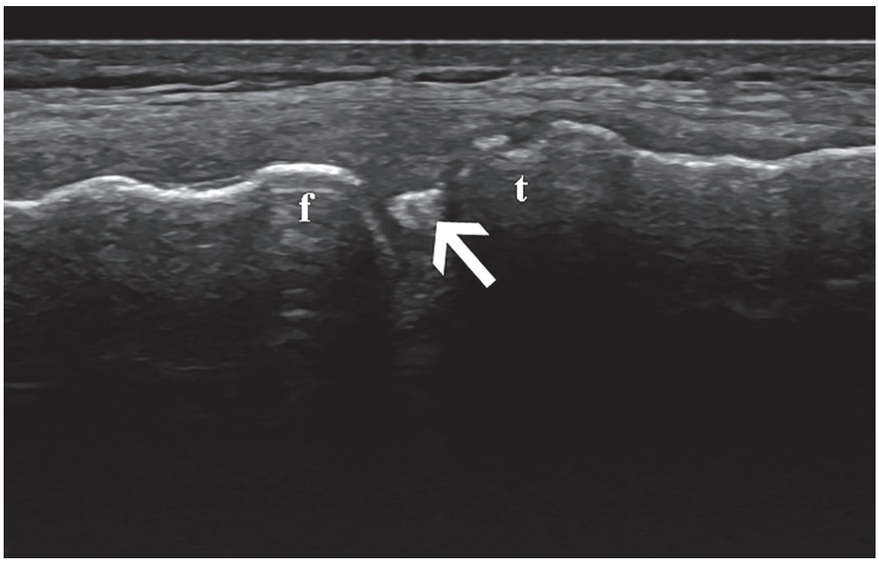

Fig. 5. Longitudinal ultrasound image of the medial femorotibial space of the knee in a patient with CPPD disease. The anterior horn of the medial meniscus shows a hyperechoic crystal deposit (arrow). **f**: femur; **t**: tibia.

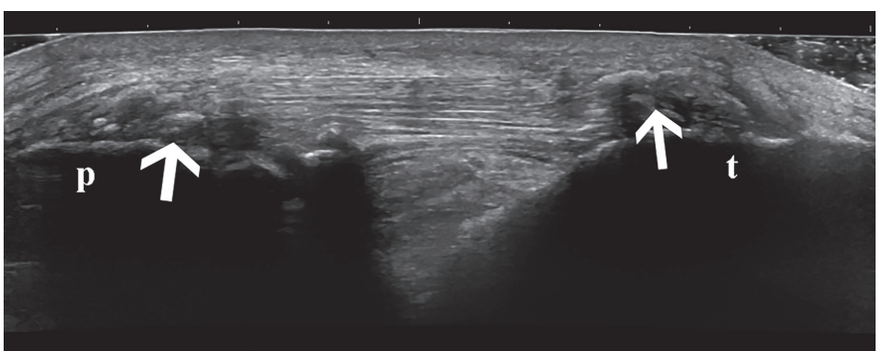

Fig. 6. Longitudinal ultrasound image of the patellar tendon of a patient with gout that shows tophi with acoustic shadowing at its proximal and distal insertions (arrows). **p**: patella; **t**: tibia.

and 77% and 100% for synovial fluid analysis, respectively. Thus, diagnostic performance of MSUS was comparable or better than that of synovial fluid analysis, which is widely considered the reference standard for diagnosing CPPPD disease.

Ogdie *et al*. (29) analysed data of 824 subjects (416 cases and 408 controls) from the Study for Updated Gout Classification Criteria (SUGAR), a large, multicentre observational cross-sectional study of consecutive patients with at least one swollen joint who conceivably may had gout. The study evaluated the performance of MSUS for the diagnosis of gout using MSU crystals confirmation in synovial fluid as gold standard. Sensitivity, specificity, PPV and NPV for MSUS features of gout (*i.e*. double contour sign, tophus, and 'snowstorm' appearance) were 76.9%, 84.3%, 83.3% and 78.1%, respectively. Sensitivity was higher among subjects with disease duration ≥2 years and among those with subcutaneous nodules detected on physical exam (*i.e*. suspected tophus). The specificity remained high in subjects with early disease and without clinical signs of tophi.

Elsaman *et al*. (30) undertook a cross-sectional study aiming to assess the relation of MSUS findings and disease duration in 100 patients with mono- or oligoarthritis (*i.e*. effusion detected on clinical examination) of the knee or the first MTP joint and no known history of gout. Patients with any known cause of arthritis were excluded. Synovial fluid analysis for detection of MSU crystals with polarising light microscopy was performed on 98 knee joints and 33 first MTP joints. The sensitivity and specificity of MSUS in diagnosing gout using as gold standard the detection by polarising light microscopy of MSU crystals in synovial fluid were 85.9% and 86.7%, respectively. Detection of echogenic foci in effusion fluid was associated with shorter disease duration (median duration 2 years) followed by double contour sign (3.5 years), erosions (4 years) and tophus (12.5 years). An interesting aspect is MSUS diagnostic capability in intercritical periods of gout and in asymptomatic hyperuricaemia (31, 32). Das *et al*. (31) studied 62 patients with gout (confirmed by demonstration of MSU crystals) in intercritical period or chronic stage and 30 control subjects (*i.e*. healthy individuals or patients with other RMD). MSUS examination of bilateral first MTP and knee joints was performed to detect features of gout. Double contour was present in 43 (69.4%) gout patients and none in the control group ($p<0.001$). Sensitivity and specificity (95% CI) of double contour were 69.4% (56.4–80.4%) and 100% (88.3–100%), respectively, and of tophi they were 66.1% (53–77.7%) and 100% (88.3–100%), respectively. The sensitivity of double contour increased to 100% in gouty patients with serum uric acid ≥7 mg/dL. Thus, MSUS seemed to perform well also in intercritical gout. Stewart *et al*. (32) carried out a study with the purpose of identifying MSUS features in the first MTP joint in subjects with gout (23 patients) and with asymptomatic hyperuricaemia (29 patients) compared with age-sex-matched normouricaemic controls (34 subjects). Subjects with gout and with asymptomatic hyperuricaemia showed significantly more frequently double contour sign than normouricaemic control [odds ratio (OR) 3.91, $p=0.011$ and OR 3.81, $p=0.009$, respectively]. More severe erosion and synovitis and less severe effusion grade were associated with gout as compared with asymptomatic hyperuricaemia ($R2 = 0.65$, $p<0.001$). The authors concluded that individuals with asymptomatic hyperuricemia had a similar frequency of urate deposition to gouty patients. Therefore, the concept of asymptomatic hyperuricaemia may be replaced with

the concept of asymptomatic gout (with subclinical MSUS-detected MSU crystal deposition) in the MSUS era.

Two studies published by the same research group dealt with the presence of tendon involvement and erosions, respectively, in patients with gout (33, 34). Ventura-Rios *et al*. (33) undertook a multicentre, multinational, transverse cross-sectional study on 80 patients with gout and a control group composed of 35 patients with osteoarthritis and 35 healthy marathon runners. All subjects underwent a MSUS examination of the quadriceps tendon, the patellar tendon at its proximal and distal insertion, and the Achilles tendon to detect intratendinous tophus or aggregates according to the OMERACT definitions. In gout patients, intratendinous tophi and hyperechoic aggregates were more frequently detected at the distal patellar insertion (41% and 35% of tendons, respectively), followed by quadriceps (26% and 23% of tendons, respectively), Achilles (22% and 26% of tendons, respectively), and proximal patellar insertion (14% and 21% of tendons, respectively). None of the osteoarthritis and healthy marathon runners showed intra-tendinous tophi. However, aggregates were also found in a variable percentage of control tendons (11%–20% of tendons). In conclusion, this study showed a great prevalence of tendon involvement in gout patients as compared to controls, particularly regarding MSUS-detected tophi. The same group (34) evaluated 40 patients with gout and 40 patients with rheumatoid arthritis (RA). Bone erosions in RA were observed most frequently at the plantar and lateral aspect of the fifth metatarsal head while in gout they were found most frequently at the plantar and lateral aspect of the fifth metatarsal head. In addition, bone erosions were larger in gout (4.0±2.3) than in RA (2.43±0.9 mm) patients.

Monitoring of therapeutic response

The responsiveness of MSUS-detected gout lesions has been of great interest in recent years. Disappearance of MSUS-detected MSU crystal deposition after serum uric acid normalisation was previously shown in a small sample size study (35). Thereafter, Ottaviani *et al*. (36) published a prospective study on 16 patients with proven gout by MSU crystal detection in synovial fluid before starting urate-lowering therapy (ULT), *i.e*. allopurinol or febuxostat. After six months of ULT, none of the 4 patients who did not achieve the targeted serum uric acid (<360 μmol/L) showed disappearance of MSUS features of gout. Among the remaining 12 patients who reached the therapy target, MSUS features (*i.e*. tophi or double contour sign) disappeared or decreased in all but one. Peiteado *et al*. (37) evaluated the responsiveness of Doppler signal in the first MTP and knee joints to ULT in 24 gout patients. At baseline, Doppler signal was detected in 95.8% of the patients. A significant parallel improvement in the serum urate level, clinical parameters and intra-articular Doppler signal was found at the follow-up assessment. However, at two years, persistence of joint Doppler signal was still found in 72.7% of the patients.

More recently, Das *et al*. (38) assessed the response of MSUS signs of MSU deposition in joints of 38 gout patients who began ULT. MSU deposition was detected by MSUS 89.74% of first MTP joints and 27.63% of knee joints. Double contour sign, tophi, and hyperechoic spots were detected in 77.63%, 43.42%, and 19.74% of first MTP joints, respectively. During the follow-up, 86.25% of double contour signs and 100% of hyperechoic spots disappeared with median time of 6 months and 5.7 months, respectively. Serum uric acid normalisation was the only significant predictor of double contour sign disappearance. Tophi disappeared completely in 4 of 33 joints (12.12%). Mean size of tophi at the eighth month was significantly smaller compared to baseline. Tophi that disappeared had significantly smaller baseline sizes compared to others which persisted.

In conclusion, 2016 has provided us with novel insights into the validity and utility of MSUS in crystal arthritis that can enhance the applicability of this imaging modality in rheumatology practice and encourage further research in this field.

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