
Ultrasonography in gout: utility in diagnosis and monitoring

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ABSTRACT

The use of ultrasonography has a considerable potential for diagnosis and monitoring of gout due to its capacity to detect urate crystal deposits in joints, e.g. on the cartilage surface, visualised as the double contour sign, and in soft tissues, e.g. as tophi. Furthermore, ultrasonography can visualise both synovitis and bone erosion. Consensus-based definitions for ultrasonographic elementary lesions in gout were validated in 2015, and ultrasonography is already included in the 2015 ACR/EULAR classification criteria for gout. This report evaluates the current literature on the use of ultrasonography for diagnosing and monitoring gout.

Introduction

Gout is the most common inflammatory arthritic condition; the diagnosis is based on the patient's history, elevated serum urate levels and joint aspiration and subsequent microscopy verification of crystals (1). However, the diagnosis is often considerably delayed, due to both uncertainty about the actual diagnosis and postponed referral, leading to insufficient treatment of the patients (2). If treated properly, flares can be prevented, joint damage related to tophi formation can be minimised and effective reduction of serum urate levels can prevent further crystal formation and dissolve existing urate crystals (1). If serum urate levels are poorly controlled, gout may be associated with renal failure, cardiovascular disease, increased morbidity and mortality and poorer quality of life (3, 4). Therefore, timely diagnosis and appropriate management of gout is essential.

The traditional "gold standard" for diagnosing gout is based on direct microscopic visualisation of monosodium urate (MSU) crystals in the synovial fluid of affected joints (1). This assessment requires arthrocentesis which often is technically challenging and is not

always performed in patients with presumed gout. Furthermore, studies show that MSU crystals may not be identified in up to 25% of the patients showing signs of acute gout (5, 6).

Recent advances in diagnostic imaging of gout offer great potential to assist clinicians with more accurate assessment and diagnosis of gout. Ultrasonography and dual energy computed tomography (DECT) have been incorporated in the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2015 gout classification criteria (7). In these criteria, imaging modalities have an important role in patients with negative microscopy, and in patients in whom joint aspiration is not feasible or successful.

Ultrasonographic findings in gout patients

Ultrasonography visualises tissues as acoustic reflections and is excellent in the detection of bone erosions and soft tissue pathologies such as synovial hypertrophy and tenosynovitis. The ultrasound Doppler modality allows detection of hyperaemia in joints and tendons indicating active inflammation. In gout, deposits of MSU crystals reflect ultrasound beams more strongly than surrounding tissues such as unmineralised hyaline cartilage or synovial tissue. Crystalline material can therefore be detected by ultrasonography as a bright, hyperechoic signal.

Characteristic ultrasonographic findings in gout can be divided into general findings, *i.e.* pathologies that can be observed in all inflammatory arthropathies, and gout-specific findings.

The general ultrasonographic findings in gout patients include synovitis and tenosynovitis along with subcutaneous oedema which are common in patients with ongoing joint attacks.

The gout-specific findings include visualisation of the crystal deposits in both joints and tendons (8-10). Many different definitions of these deposits

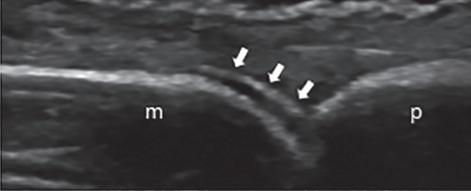
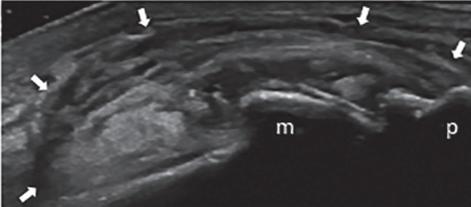
Ultrasonographic gout elementary lesions		
Ultrasonographic elementary lesion	Definition	Ultrasonographic finding
Double contour sign	Abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage (<i>arrows</i>), independent of the angle of insonation and which may be either irregular or regular, continuous, or intermittent and can be distinguished from the cartilage interface sign	 Ultrasonography of second metacarpophalangeal joint, longitudinal view. m: metacarpal head, p: phalanges base.
Tophus [independent of location (e.g., extra-articular/intra-articular/intra-tendinous)]	A circumscribed, inhomogeneous, hyperechoic and/or hypoechoic aggregation (<i>arrows</i>) (which may or may not generate posterior acoustic shadow), which may be surrounded by a small anechoic rim	 Ultrasonography of first metatarsophalangeal joint, longitudinal view. m: metatarsal head, p: phalanges base.
Aggregates [independent of location (intra-articular/intra-tendinous)]	Heterogeneous hyperechoic foci (<i>arrow</i>) that maintain their high degree of reflectivity even when the gain setting is minimized or the insonation angle is changed, and which occasionally may generate posterior acoustic shadow	 Ultrasonography of first metatarsophalangeal joint, longitudinal view. m: metatarsal head, p: phalanges base.
Erosion	An intra- and/or extra-articular discontinuity of the bone surface (<i>asterisk</i>) (visible in 2 perpendicular planes)	 Ultrasonography of first metatarsophalangeal joint, longitudinal medial view. m: metatarsal head, p: phalanges base.

Fig. 1. The OMERACT ultrasound Working Group definitions of the ultrasonographic elementary lesions in gout (12).

have been used over the years in the descriptions of the ultrasonographic lesions found in gout patients (11). In order to ensure homogeneity in gout studies, The Outcome Measures in Rheumatology (OMERACT) ultrasound Working Group in 2015 developed consensus definitions of gout lesions in a multistep process. The process began with a systematic literature review to establish previous described ultrasonographic pathologies in gout patients (11), highlighting the absence of consensus definitions. This was followed by Delphi exercises to develop consensus-based definitions of ultrasonographic elementary lesions in gout (12). Finally, the agreed-upon definitions were tested, initially in static images and then in patients (12, 13). The validation process resulted in ultra-

sonographic definitions for the four main structural lesions in gout: a. double contour sign, b. tophi, c. aggregates (all aspects of the urate burden), and d. erosions (component of structural damage) (12). The OMERACT definitions of the ultrasonographic gout elementary lesions can be seen in Figure 1. The double contour sign is believed to represent deposits of MSU crystals on the surface of the cartilage (14, 15) (Figs. 1-2). It may be differentiated from calcium pyrophosphate crystal deposits, which typically appears as crystals deposited within articular cartilage (16). A tophus represents larger collections of MSU crystals embedded in inflammatory tissue (17) (Figs. 1, 3, 5). Aggregates are believed to be deposits of crystals in joints or soft tissue not

large enough to be defined as a tophus (12) (Fig. 1). Both tophi and aggregates may be observed in joints and within soft tissue structures such as tendons and bursae (12) (Figs. 4, 6), and tophi may result in bone erosions due to their capacity to invade bone (16) (Fig. 3). Erosion in gout is perceived to be an elementary lesion. The applied ultrasonographic definition of bone erosions in gout is the same as the definition of bone erosions in rheumatoid arthritis (18), namely a cortical break seen in two perpendicular planes (Figs. 1, 3). However, bone erosions in gout patients are, in contrast to in other inflammatory arthropathies, commonly found extra-articularly (13). Therefore, the distribution of bone erosions in gout patients rather than the appearance of a single erosion, makes the erosion char-

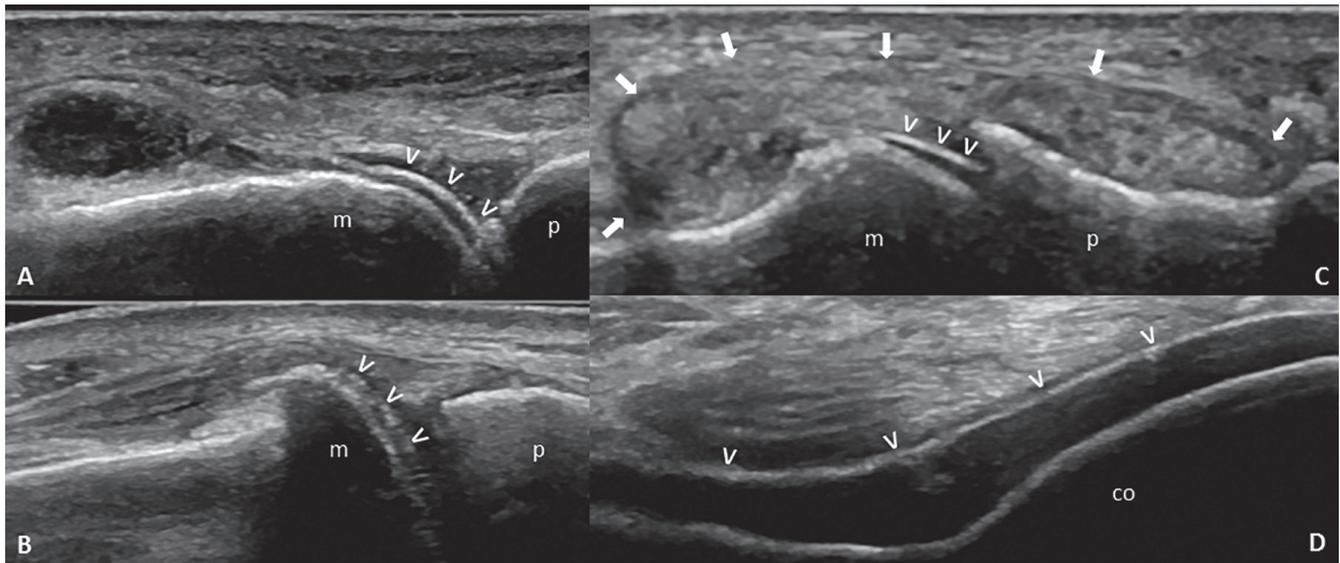


Fig. 2. Ultrasonographic double contour sign representing urate deposits on the surface of the cartilage in different joints. Note that insonation angles are less than 90 degrees to distinguish it from the cartilage interface sign. **A-B:** Ultrasonography of the third (A) and the first (B) metacarpophalangeal joint in longitudinal view. The double contour can be continuous (A) or it can be intermittent (B) (arrowheads). **C:** Ultrasonography of the first metatarsophalangeal joint in longitudinal view showing a well-defined double contour sign (arrowheads) and an intraarticular tophus (arrows). **D:** Ultrasonography of the femoral condyle of the knee in transversal view with a double contour sign (arrowheads). m: metacarpal/metatarsal head; p: phalangeal base; co: condyle.

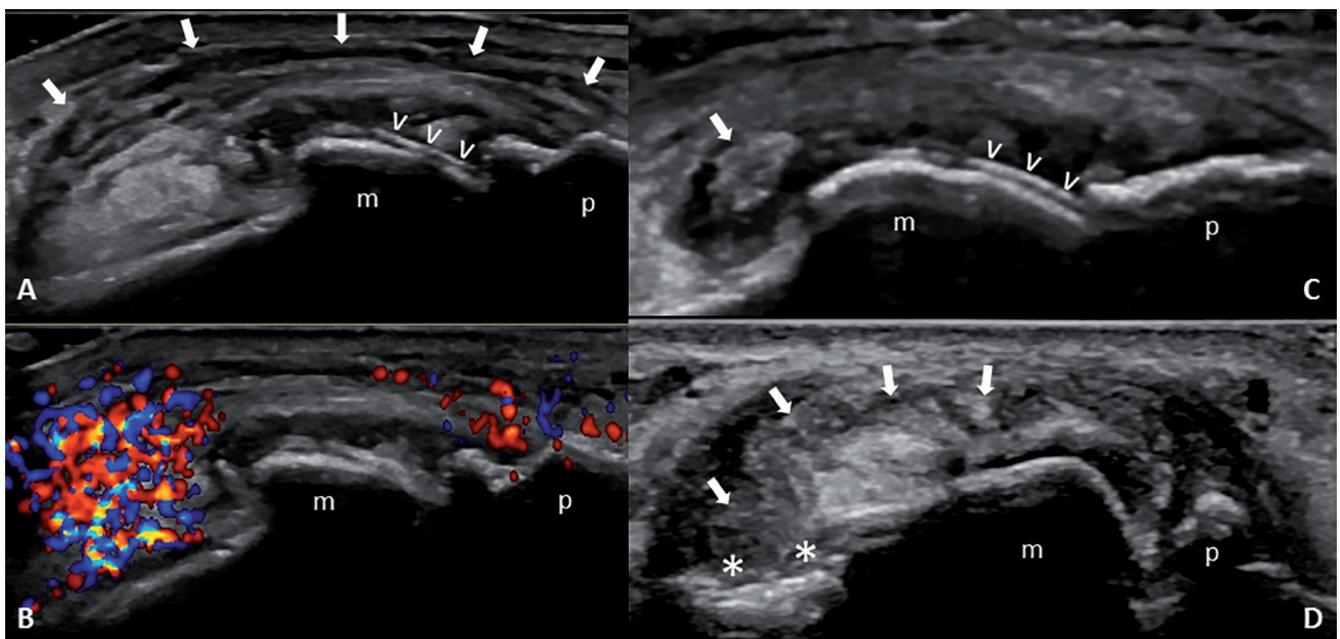


Fig. 3. Ultrasonography of the first metatarsophalangeal (MTP) joint in three different male gout patients. Longitudinal view. **A-B:** Large inhomogeneous, hyperechoic tophus surrounded by a small anechoic rim (arrows), without (A) and with (B) Doppler box. A double contour sign is also seen (arrowheads). Severe Doppler activity in the most compact part of the tophaceous deposit (B). **C:** Smaller hyperechoic tophus (arrow) in the synovial tissue accompanied by a double contour sign (arrowheads). **D:** Medial aspect of the first MTP joint. The massive tophaceous deposit in the medial aspect of the joint (arrows) has resulted in erosive changes (asterisk). m: metacarpal head; p: phalangeal base.

acteristic for gout (13). Synovitis (including Doppler activity) is not included as an elementary lesion indicative of gout, because the presence of synovitis alone is not considered specific enough to define gout (13). When synovitis and tenosynovitis are scored

in gout patients, the definitions already validated for rheumatoid arthritis by the OMERACT ultrasound group are applied (18). These definitions define synovial hypertrophy as “abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hypo-

echoic) intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal”, and tenosynovitis as “hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in 2 perpendicular planes and

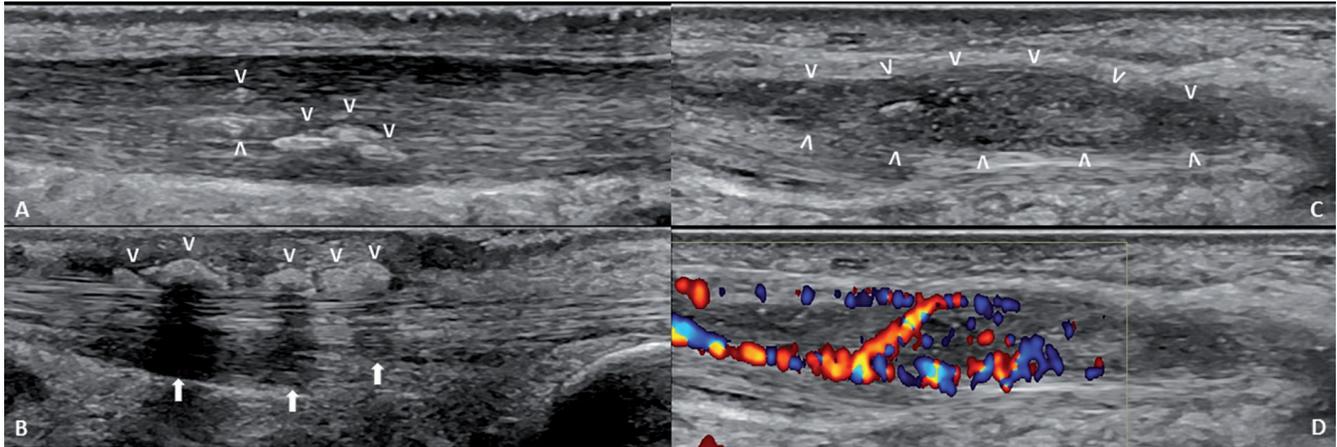


Fig. 4. Ultrasonography of tophaceous deposits in/around tendons. **A-B:** Ultrasonography of the Achilles tendon in longitudinal view. **A:** Intratendinous tophaceous deposits in an Achilles tendon (arrowheads). Note that the tendon is thickened around the tophaceous deposits. **B:** Peritendinous tophaceous deposits in an Achilles tendon (arrowheads). The massive tophaceous deposits are generating posterior acoustic shadows (arrows). **C-D:** Ultrasonography of a peroneus tendon. Longitudinal view. Massive infiltration of tophaceous material inside a peroneus tendon (arrowheads). The tendons are partially split due to the tophaceous infiltration. **D:** Severe intratendinous Doppler activity caused by the inflammation due to the tophaceous deposits.

which may exhibit Doppler signal” (18). Since the OMERACT definitions for gout elementary lesions mentioned above were first published in 2015, most studies describing specificity and sensitivity of ultrasonography in gout have not used these consensus definitions, since they were performed before the definitions. However, the various applied definitions of double contour sign were very similar.

Ultrasonography as a tool for diagnosing gout

Ultrasonography has several potential and possible important roles in the diagnosis of gout. Firstly, it can help to guide aspiration of synovial fluid for MSU crystal identification (19, 20). Secondly, in the absence of microscopically proven gout, ultrasonography can help in the detection of ultrasonographic gout elementary lesions (12).

Studies have shown double contour sign to be highly specific (specificity ≥ 0.98) to gout (21, 22), and in some studies, double contour sign is exclusively found in patients with microscopically verified gout (23, 24). Due to the utility and accuracy of ultrasonography in identifying MSU deposition in joints, ultrasonographic visualisation of double contour sign has been incorporated in the 2015 ACR/EULAR Gout classification criteria (7). These classification criteria include an entry criterion (at least one episode of peripheral joint

or bursal swelling, pain, or tenderness) and a sufficient criterion (the presence of MSU crystals in joints, bursa or tophus). If the sufficient criterion is not met, patient symptomatology is scored according to different domains which can each contribute to the total score. These domains include clinical parameters (pattern of joint/bursa involvement, characteristics and time course of symptomatic episodes), laboratory parameters (serum urate and MSU-negative synovial fluid aspirate), and imaging parameters (double contour sign on ultrasonography, urate on dual-energy CT (DECT) or radiographic gout-related erosions). According to these criteria, the presence of double contour sign can increase the score by 4 out of a possible maximum of 23, where a score ≥ 8 classifies an individual as having gout (7).

Although highly specific for gout, double contour sign is not present in all patients with gout, and studies have shown extremely varying sensitivity ranging from 0.22 to 0.92 (21-24). Furthermore, reliability of double contour sign has varied among studies. Results of an OMERACT multicentre reliability exercise showed that the reliability for double contour sign was only moderate, as assessed by both intra- and inter-observer agreement (kappa 0.53 and 0.47, respectively) (25), whereas single centre studies have found the reliability to be good (kappa 0.68-0.74

(21, 26). These data indicate that training before applying ultrasonography in clinical trials is essential.

Tophus-like changes are, like double contour sign, almost exclusively found in gout (26), and the specificity in studies are ≥ 0.90 , whereas the sensitivity, like double contour sign, varies between studies (22-24). The OMERACT reliability exercise showed both intra- and inter-observer agreement for tophus to be good (kappa 0.73 and 0.69, respectively), and tophus had the highest reliability per lesion of the four elementary lesions (25). Ultrasonography has capacity to detect tophaceous material in joints involved in the first gout attack (24).

Aggregates have been mentioned as a feature of gout in many studies, although the definitions have varied (11). The OMERACT validation process resulted in a ultrasonographic definition with better intra- than inter-observer reliability (kappa 0.61 and 0.21, respectively), indicating that different ultrasonographers do not perceive aggregates in the same way despite a common definition, and their role in the diagnosis of gout are yet to be determined (25).

Erosions are clearly visualised by ultrasonography, and with a higher sensitivity than conventional radiography, especially for small erosions (9, 23). Consequently, ultrasonography is also a method for detecting early changes

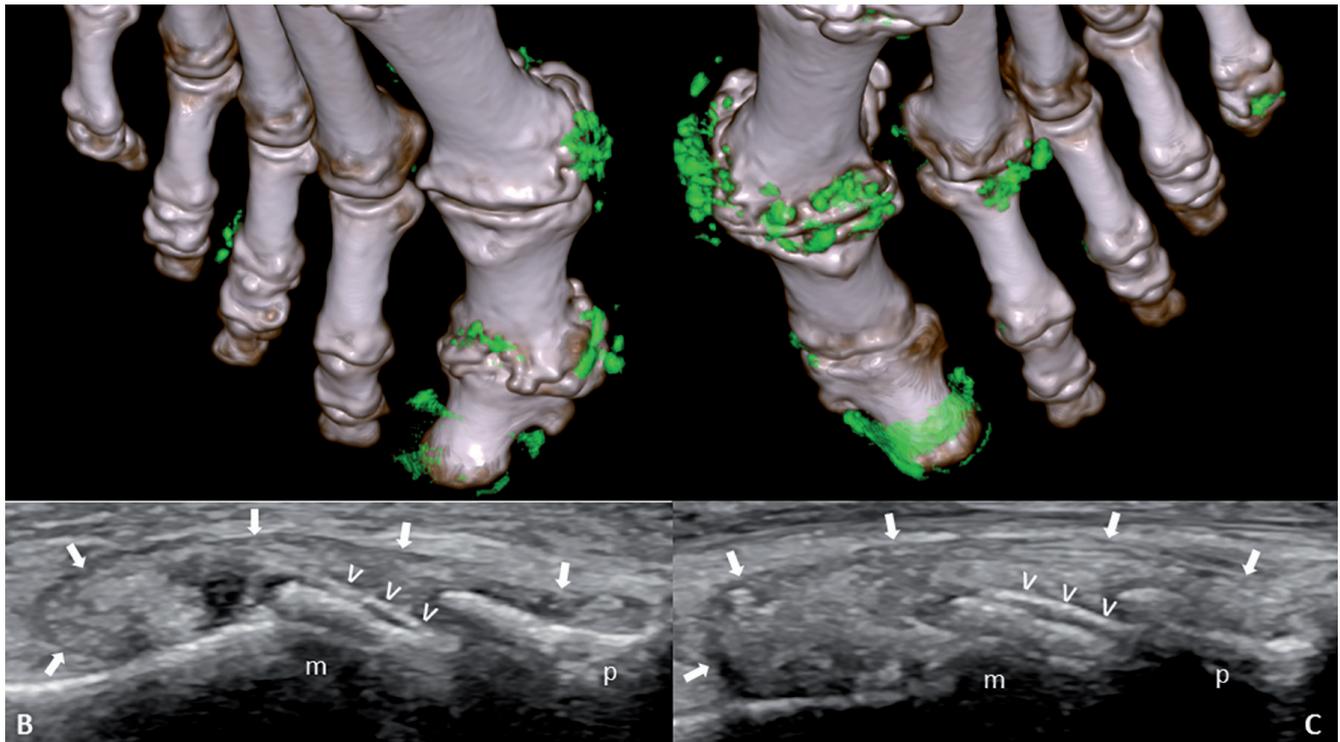


Fig. 5. Dual energy CT (DECT) of the forefeet of a male gout patient together with the corresponding ultrasonography of the bilateral first metatarsophalangeal (MTP) joints. **A:** Three-dimensional DECT with color mapping showing uric acid depositions (green) in multiple joint regions on both feet. The most pronounced deposits are seen along both first metatarsal heads, especially on the left side. Note that the green area on distal parts of the distal first phalanges represents nail bed artifacts. **B-C:** Ultrasonography of the right (B) and left (C) first MTP joint in the same patient in longitudinal view. Both sides show tophus formations (arrows) and additionally double contour sign (arrowheads). As also seen on the DECT scan the changes are most pronounced on the left side.

m: metatarsal head; p: phalangeal base.



Fig. 6. Dual energy CT (DECT) and ultrasonography showing urate deposits at the site of the attachment of the patella ligament onto the patella bone. **A:** Ultrasonography of the patella tendon in longitudinal view. Hyperechoic spots and tophaceous deposits are seen peritendinously along the proximal patella ligament attachment (arrows). **B:** Three-dimensional DECT with color mapping showing uric acid depositions (green) on the lower part of the patella corresponding to the proximal patella ligament attachment.

in the joints, that conventional radiography fails to recognise. However, both conventional computed tomography and magnetic resonance imaging have been found superior to ultrasonography in the detection of erosions in gout patients (27, 28). Erosions are not solely found in gout patients, but are also

common findings in patients with other inflammatory arthropathies, and in patients with osteoarthritis (29). Though the anatomical location of erosions may vary between different diseases, and may be located extraarticularly in gout, it is unlikely that this ultrasonographic elementary lesion *per se* will be diag-

nostic for gout. However, future studies are needed to establish its diagnostic role, possibly in combination with other lesions.

A multicentre study from 2016, in which ultrasonography was performed in 824 subjects (416 cases and 408 controls), examined the sensitivity and

specificity of ultrasonographic gout lesions using MSU visualisation by microscopy as “gold standard” reference (30). They defined gout lesions as double contour sign and tophus according to the OMERACT definitions (12), whereas hyperechoic spots were defined differently as “snowstorm type joint effusion” (16). The study showed that the overall sensitivity and specificity for the presence of any one of these ultrasonographic gout features were 76.9% and 84.3%, respectively (30). The sensitivity was higher among subjects with disease duration ≥ 2 years and among subjects with clinical suspicion of tophi. The study reported that ultrasonographic findings contribute independently to identification of gout with an odds ratio of 7.2 (30).

In general, ultrasonographic pathological findings in gout patients may occur in asymptomatic joints as well as in symptomatic joints (23). In clinically asymptomatic individuals with elevated serum urate levels, ultrasonography has been able to demonstrate signs of subclinical MSU deposit (31, 32). One study indicated that subclinical MSU deposits are common in male offspring of patients with gout (present in 30% of the participants in the study) (33). Ultrasonography may also be of value in detecting intra-articular or deep tissue tophi, since these may not be detected by physical examination.

Although DECT has also been shown to allow detection of urate deposits in gout patients, and is, along with ultrasonography, included in the 2015 ACR/EULAR classification criteria for gout (7), DECT is reported to have a slightly lower sensitivity to detect urate crystals than ultrasonography (34, 35). A report indicates that ultrasonography and DECT were discordant in assessment of tophi volume in the feet and knees, where the volume estimated by ultrasonography in general appears greater than in DECT (36).

Different study groups have reported different sets of joints and tendon regions as being sufficient for diagnosing gout. One group has suggested that bilateral scanning of one joint (radiocarpal joint) for aggregates, two tendons (patellar tendon and triceps

tendon) for aggregates and three articular cartilage surfaces (first metatarsal, talar and either second metacarpal or femoral condyle) for double contour sign is sufficient for accurate detection of urate crystal deposition (26). Other groups have suggested a four-joint assessment to be sufficient (37-39). Two groups have reported that a four-joint scan (both knees and first metatarsophalangeal joints) for aggregates and double contour sign is sufficient (37, 38). Another group argues that a four-joint investigation of both first metatarsophalangeal joints for tophi and both ankles for the double contour sign is reliable (39). Based upon a combination of ultrasonography and DECT data, yet another group argues that tendons are the most frequent anatomical location of MSU crystal deposition (40). Currently, no consensus exists on a specific reduced set of joints and/or tendons for the diagnosis of gout.

Ultrasonography as a tool for monitoring gout

Given its increasing availability in clinical practice, ultrasonography has the potential to be useful in disease monitoring. Since both tophi and double contour sign are specific to gout (21-24), these two features appear particularly relevant to assess.

Small studies have shown that lowering serum urate level can lead to disappearance of double contour sign (41-44). A few studies have also demonstrated that ultrasonographic measurements of tophi are sensitive to change in response to urate-lowering therapy (44, 45). A prospective study of patients with crystal-proven gout starting urate lowering therapy demonstrated that index tophus volume and maximal diameter measured by ultrasonography changed over a 12-month period, with a strong relationship between urate concentrations and change in measured size (45).

Although further studies are needed to determine the duration and intensity of urate-lowering therapy needed to achieve resolution of the ultrasonographic features of gout, ultrasonography would appear a strong candidate for inclusion in the definition of disease

remission and flare in the future.

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