

REVIEW

Imaging in gout - What can we learn from MRI, CT, DECT and US?

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Abstract

There are many exciting new applications for advanced imaging in gout. These modalities employ multiplanar imaging and allow computerized three-dimensional rendering of bone and joints (including tophi) and have the advantage of electronic data storage for later retrieval. High-resolution computed tomography has been particularly helpful in exploring the pathology of gout by investigating the relationship between bone erosions and tophi. Magnetic resonance imaging and ultrasonography can image the inflammatory nature of gouty arthropathy, revealing synovial and soft tissue inflammation, and can provide information about the composition and vascularity of tophi. Dual-energy computerized tomography is a new modality that is able to identify tophi by their chemical composition and reveal even small occult tophaceous deposits. All modalities are being investigated for their potential roles in diagnosis and could have important clinical applications in the patient for whom aspiration of monosodium urate crystals from the joint is not possible. Imaging can also provide outcome measures, such as change in tophus volume, for monitoring the response to urate-lowering therapy and this is an important application in the clinical trial setting.

Introduction

Gout is a form of inflammatory arthritis that is characterized initially by acute attacks of active synovitis related to the presence of monosodium urate (MSU) crystals in the joints and periarticular soft tissues. Chronic gouty arthropathy may supervene after a period of years, featuring ongoing synovitis in peripheral and, occasionally,

axial joints, often associated with the presence of tophi and accompanied by bone erosion. Plain radiography (XR) tends to be normal in early gout, but in chronic gout, typically after 7 to 10 years, 'punched out' extramarginal, articular, or para-articular erosions may become apparent with typical preservation of the joint space and bone density [1]. In advanced tophaceous disease, extreme bone destruction can develop with large periarticular lytic lesions associated with apparent joint space widening (Figure 1) [2], and concomitant osteoarthritis frequently accompanies these changes, especially in the feet.

In recent years, advanced imaging techniques, including magnetic resonance imaging (MRI), computed tomography (CT) using high-resolution multislice scanners, and ultrasonography (US), have led to new insights into the pathology of many forms of inflammatory arthritis [3]. Scoring systems have been developed to quantify joint inflammation and destruction by using imaging and these are now in routine use in clinical trials to provide sensitive measures of drug efficacy in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) [4,5]. In gout, the applications of advanced imaging are only now starting to be explored and are of particular relevance to the clinician assessing the impact of urate-lowering therapies [6]. These applications include (a) imaging to investigate joint pathology in gout, (b) imaging to assist in the diagnosis of gout, and (c) monitoring of joint inflammation and damage, especially in response to therapy. This review presents a critical appraisal of the current literature pertaining to advanced imaging in gout and provides specific discussion of these areas related to each modality.

1. Joint pathology in gout

Before the advent of advanced imaging, an understanding of the pathology of gout was based primarily on light microscope examination of tophi and periarticular bone, supplemented by XR to define the radiographic morphology and distribution of erosions [7]. This approach was biased toward investigating severe erosive gouty arthropathy, and specimens obtained for histopathology were usually derived from amputated digits or limbs,

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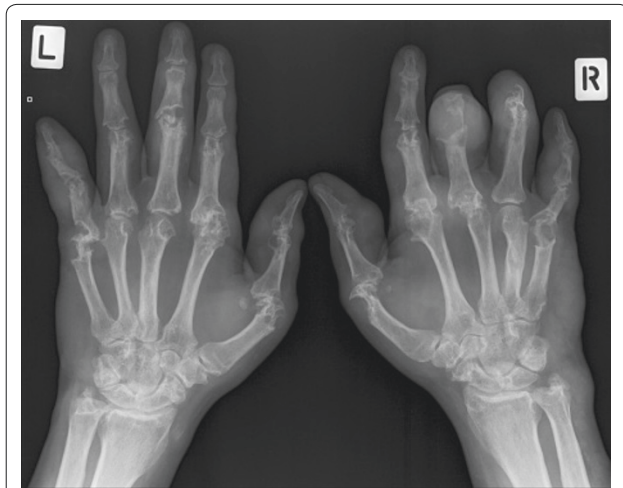


Figure 1. Plain radiograph of the hands of a Pacific islander man with longstanding tophaceous gout. Radiograph shows multiple erosions, some of which are extramarginal. Regions of bony lysis adjacent to soft tissue densities represent tophi.

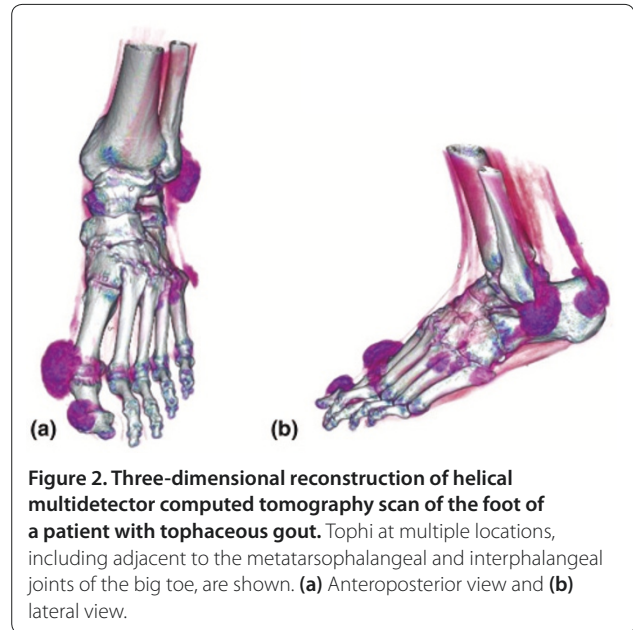


Figure 2. Three-dimensional reconstruction of helical multidetector computed tomography scan of the foot of a patient with tophaceous gout. Tophi at multiple locations, including adjacent to the metatarsophalangeal and interphalangeal joints of the big toe, are shown. (a) Anteroposterior view and (b) lateral view.

where chronically discharging tophi were often secondarily infected [8]. By contrast, advanced imaging techniques open a window into the pathology of gout at any stage of the disease process, including at presentation and in early disease, when XRs are characteristically normal and histopathological specimens are unavailable.

Computed tomography reveals tophi adjacent to erosions

Using advanced multislice CT scanning, our own group investigated the question of whether tophi were likely to be responsible for bone erosion in gout – an impression gained from XR review but not previously confirmed by using a multiplanar high-definition modality. Paired radiographs and CT scans were available for investigation in a total of 798 individual hand and wrist joints. For those bones with large radiographic erosions, 96 out of 98 (98%) had CT evidence of associated tophus. For CT erosions, 82% had visible intraosseous tophi; of the larger erosions (measuring greater than 7.5 mm in diameter), 100% (56 out of 56) contained tophi. There was also a very strong correlation between the diameters of CT erosions and intraosseous tophi ($r = 0.93$), indicating that the gouty tophus sits snugly in its pocket of bone, which may be entirely intraosseous or have a cortical breach, which, if profiled on XR, will appear as a typical gouty erosion. Figure 2 shows a three-dimensional (3D) reconstruction of a CT scan revealing discrete tophi at multiple sites adjacent to bone and within soft tissues.

The magnetic resonance imaging view of tophi

MRI scanning can also be used to image tophi, and the information this modality reveals about the inflammatory

nature of these lesions cannot be appreciated from XR or CT scanning. On MRI, tophi typically exhibit low signal on T1-weighted images and medium to high signal on T2-weighted (T2w) images, indicating the presence of cellular tissue surrounding or infiltrating the crystalline mass [9,10]. The vascularity of this tissue will influence the degree of MRI post-contrast enhancement (Figure 3), and calcification within the tophus can lead to regions of low signal on T2w images [9]. These features are consistent with the characteristics of tophi that have been excised and examined using the tools of immunohistochemistry. Palmer and colleagues [11] described the structure of a typical tophus as consisting of a mostly acellular crystalline core surrounded by a 'corona zone' and an outer, loose 'fibrovascular zone'. Dalbeth and colleagues [12] characterized the cellular architecture further in their study of 16 resected tophi. Within the corona zone, multiple cell types, including macrophages, mast cells, and lymphocytes, could be found adjacent to osteoclasts. Expression of interleukin-1 β was high in this region, providing a putative mechanism for osteoclast activation and bone resorption, and indeed evidence of enhanced osteoclastogenesis has been obtained *in vitro* and *in vivo* by these authors [13]. MRI has also provided information about the morphology of tophi, which can vary from 'discrete nodular masses' to ill-defined amorphous deposits that can spread along anatomical planes or in a 'permeative' manner without regard to compartments, as described by Popp and colleagues [14] at the wrist. Clearly, many of these lesions are not amenable to resection, leaving only imaging to inform us about their position and internal structure.

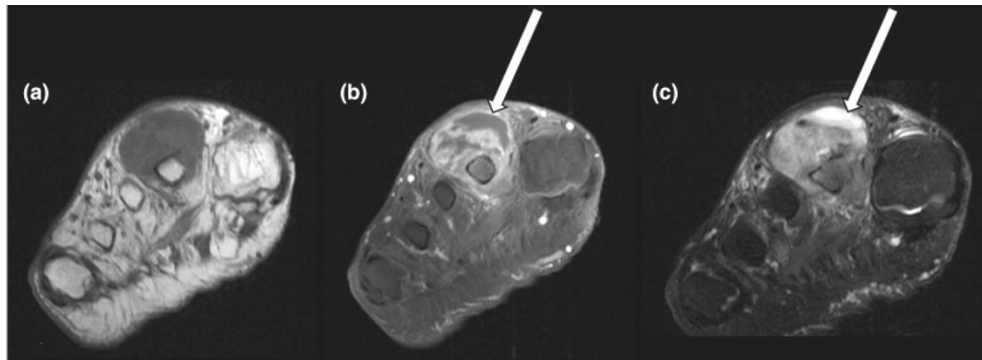


Figure 3. Axial magnetic resonance imaging scans of a large tophus adjacent to the second metatarsal head of a Pacific islander man with longstanding tophaceous gout. (a) T1-weighted (T1w) image reveals low-signal intensity tophus. **(b)** T1w post-contrast image reveals rim enhancement and a non-enhancing focus indicating fluid within the tophus (arrow). **(c)** T2-weighted image shows a crescent of fluid (white) corresponding to the non-enhancing focus on contrast-enhanced images.

Ultrasound reveals tophi and urate crystals

Ultrasound provides a different 'sonar' picture of tophi, which may appear as hypoechoic, hyperechoic, or mixed echogenicity nodules, as described by Schueller-Weidekamm and colleagues [15] (Figure 4). The commonly seen surrounding hypoechoic 'halo' probably corresponds to the outer, loose fibrovascular zone seen on histology [16]. These authors detected 'dorsal shadowing' over cartilage surfaces causing partial reflection of the US wave. This is the same entity as the 'double contour' sign (described by Thiele and Schlesinger [17]), whereby an echogenic line was detected parallel to the cortex (of, for example, a metatarsal head) with an anechoic region between, representing hyaline cartilage. MSU crystals have been proposed to form in a fine layer like icing sugar over the cartilage, but formal confirmation of this by comparison with histopathology has not been performed, because of difficulty obtaining and analyzing anatomical samples. Both ultrasound and MRI scanning can also image the inflammatory aspect of gouty arthropathy, including synovitis, tenosynovitis, and edematous soft tissue inflammation. Regions of thickened soft tissue that have moderate US echogenicity and that might represent diffuse infiltration with MSU crystals have been described [17]. Evidence of increased vascularization within the synovial membrane can be obtained on power Doppler images and contrast-enhanced MRI scans [15].

Erosions and bone marrow edema

Bone erosions in gout can be detected by MRI or US and may contain enhancing synovium as has been described in RA [18]. MRI bone marrow edema also occurs in gout and was described by Yu and colleagues [9], in 3 of their 5 patients, adjacent to intraosseous tophi. Our own recent study of the MRI features of gout in 47 patients showed bone marrow edema to be present in 36% of those with uncomplicated gout (when it was often mild) but to be

almost universal in those with gout complicated by osteomyelitis (when it was usually florid) [19]. In RA, MRI bone marrow edema is related to inflammatory osteitis [5,6]; in osteoarthritis, it is thought to indicate fibrosis and necrosis within subcortical bone [7]. In gout, the pathological correlate of MRI bone marrow edema remains unknown, and further studies are required to elucidate this.

2. Diagnosing gout by using advanced imaging

A diagnosis of gout currently rests on a demonstration of MSU crystals in synovial fluid or joint tissue or a typical clinical picture that might include acute joint swelling of abrupt onset and remission within 2 weeks, the occurrence of podagra, a raised serum urate, and, in some patients, the presence of tophi. According to 2006 European League Against Rheumatism (EULAR) evidence-based recommendations [20], 'radiographs have little role in diagnosis, though in late or severe gout radiographic changes of asymmetrical swelling and subcortical cysts without erosion may be useful to differentiate chronic gout from other joint conditions.' The contribution of advanced imaging would be to assist the diagnosis of gout at an earlier phase by revealing acute joint inflammation, bone erosion, or tophi or a combination of these. Ideally, such imaging would identify certain specific features that would confirm a diagnosis of gout without the necessity for joint aspiration. Most of the advanced imaging modalities take us some way down this path but do not deliver ultimate certainty of diagnosis. No study comparing the diagnostic accuracy of any of these techniques with the current clinical gold standard outlined above has yet been done.

Magnetic resonance imaging

In clinical practice, MRI scans have been reported as useful in diagnosing gout in unusual settings. As reported

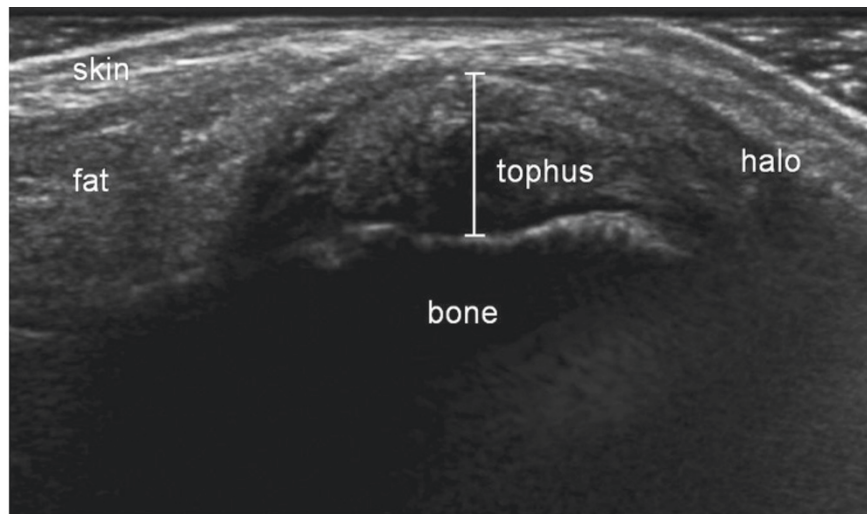


Figure 4. Ultrasound image of a subcutaneous tophus of mixed echogenicity with adjacent halo region.

by Nygaard and colleagues [21], an epidural abscess was suspected clinically in a patient with fever and low back pain, but the MRI revealed a large tophus (confirmed on aspirate) associated with vertebral destruction. In a similar vein, Gardner and McQueen [22] reported tophaceous gout of the symphysis pubis (confirmed on aspirate), in which the presentation had suggested infection or malignancy. MRI is an effective tomographic modality to image these tophaceous masses, which may not be detected clinically if deep below the skin surface. Their presence strongly suggests a diagnosis of gout, but aspirate confirmation is usually required as the differential diagnosis includes infection or other space-occupying lesions.

Ultrasound

Similarly, the US detection of tophi could be helpful in diagnosing gout, especially when these lesions are not detectable clinically. Perez-Ruiz and colleagues [23], in their study of 25 patients with crystal-proven gout, found many presumed tophi at 'hidden' sites such as under the collateral ligaments of the knee. US-guided aspiration of 12 nodules suspected to be tophi was performed; in 10 of these, MSU crystals were obtained, helping to confirm validity. A larger group of 50 nodules was detected by imaging in 22 patients; of these nodules, 37 were detected by both MRI and US, 46 were detected by US, and 41 by MRI. Thus, presumably, some false positives and false negatives were present for each modality, but defining these presents a problem. Benson and colleagues [24] have suggested that the sonographic appearances of gouty tophi may vary according to developmental state, and these features could mimic those of rheumatoid nodules, which can also evolve over time. Therefore, the

finding of a nodule on US, MRI, or CT, while suggestive of tophus in the right clinical setting, is not utterly diagnostic. Finding bone erosions may also have diagnostic relevance, and US has been shown to be more sensitive than plain XR for the detection of small erosions. In one study of 78 gouty first metatarsophalangeal joints, 52 (67%) revealed US erosion compared with only 22 (28%) where XR erosions were scored [24]. This recalls similar findings in RA, in which multiplanar imaging techniques, including US, MRI, and CT, have all been shown to be superior to two-dimensional XR for erosion detection [25]. However, the rate of US false positives is often difficult to determine from the published literature; in any case, the imaging appearance of erosive, inflammatory arthropathy is common to many conditions, including RA and PsA as well as gout [15]. The prospect that key imaging features such as the double-contour sign could confirm a diagnosis of gout remains tantalizing. Lai and Chiu [26] recently published an ultrasound study of large joints (mainly knees and ankles) in 34 patients with gout and 46 patients with non-gouty arthritis and compared sonographic findings with MSU crystal aspiration. The authors reported the double-contour sign to have a sensitivity of 36.8% and a specificity of 97.3% for the diagnosis of gout. However, Carter and colleagues [27] were not able to find US evidence of the double-contour sign in any of their 'index joints' where clinical gout attacks had occurred, and MRI erosions were present in more than half.

Computed tomography scanning

Helical multislice CT scanning has a potential role in the diagnosis of gout, largely because of the very-high-resolution 3D images that may be obtained depicting

tophi [28] (Figure 2). These tend to be higher-definition than MRI images as the slice thickness (which for CT can be as low as 0.5 mm) is considerably thinner than that of MRI (which is typically 2.5 to 4 mm) and there is no interslice gap (in fact, the slices can be reconstructed overlapping for 3D reformatting purposes). The density of tophi is usually 160 to 170 Hounsfield units and this is significantly different from that of soft tissues and bone [29]. Helical CT scanning also has the advantage of allowing imaging of larger regions than most MRI scans, so that the pattern of joint involvement can be depicted. In gout, this is typically asymmetrical, favoring the metatarsophalangeal, interphalangeal, and midtarsal joints in the feet and the proximal interphalangeal and distal interphalangeal joints in the hands. Clearly, CT would have no role in the diagnosis of acute gout, prior to the development of bone erosions or tophi, as it does not provide imaging of synovitis, tenosynovitis, or osteitis.

Dual-energy computed tomography

Dual-energy computed tomography (DECT) has established roles in cardiology as a means to image calcification within coronary artery plaques [30] and in renal medicine for the identification of uric acid calculi [31]. However, it has also recently been investigated in tophaceous gout [32,33]. DECT scanning involves the use of two x-ray tubes positioned at 90 degrees to each other (that is, a dual-source scanner) and two corresponding detectors. This allows images to be acquired simultaneously at two different energy levels, providing two datasets. These are analyzed by using a 3D material decomposition algorithm that allows characterization of uric acid (allocated a specific color) to be contrasted with calcium and soft tissue (allocated other colors) [33] (Figure 5). This means that MSU crystals can be detected with a high degree of accuracy, implying that DECT should have very high specificity for a diagnosis of gout. However, information regarding its sensitivity, especially in non-tophaceous gout, is preliminary. Choi and colleagues [32] described DECT scanning in 20 tophaceous gout patients who were all revealed to have urate deposits in contrast to the control group, in whom no deposits were detected. DECT scans detected fourfold more deposits than did physical examination, indicating the potential of the former for imaging subclinical tophi. Nicolaou and colleagues [33] described the use of DECT in the successful diagnosis of tophaceous gout in five separate cases in which patients presented with soft tissue masses or joint pain. This remains an emerging area of great interest.

3. Monitoring disease activity and damage – response to therapy

Plain XR provides a very blunt imaging instrument with which to try to track the progress of joint damage in gout

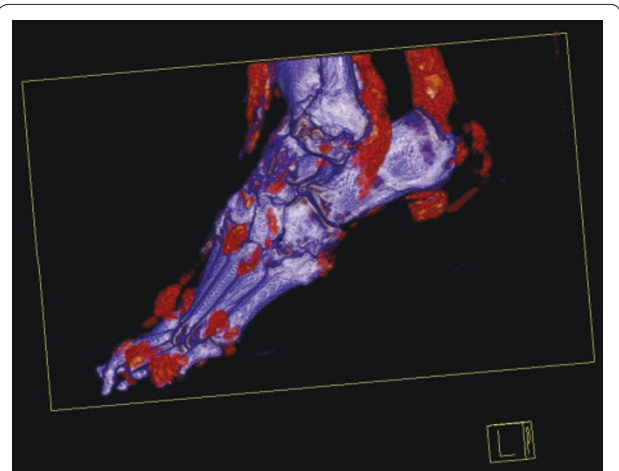


Figure 5. Dual-energy computed tomography scan of the foot of a Pacific islander man with longstanding gout. Scan reveals multiple tophaceous deposits adjacent to interphalangeal and tarsal joints as well as the calcaneal bursa, the soft tissues anterior to the ankle joint, and the peroneal tendon sheath.

and its response to therapy. McCarthy and colleagues [34] studied a group of 39 patients for 10 years and found no correlation between XR changes and serum urate concentration, and this suggests that XR may not be sufficiently sensitive to monitor change in bony damage over this time frame. More recently, a specific gout radiographic scoring method has been developed and validated and may improve sensitivity to change in longitudinal studies [2]. With the development of powerful and often costly urate-lowering therapies, the focus has shifted to the possibility that advanced imaging could be useful in this context, providing sensitivity to change over a shorter timeframe that would be clinically relevant. Of these modalities, MRI and CT have the facility to allow storage of standardized digital images and so are particularly suitable for use in longitudinal studies.

Perez-Ruiz and colleagues [23] examined the US measurement of tophi in 25 patients with gout, including change in tophus size and its association with serum urate concentrations over the course of 12 months. The authors reported excellent intraobserver (intraclass correlation coefficient (ICC) of 0.98 for volume) and good interobserver reliability (ICCs of 0.83 for maximal diameter and 0.71 for minimal diameter). They also provided data comparing US and MRI diameters of the same lesions. Interestingly, these measurements were similar but not identical, and the R^2 value for the correlation was 0.65. This suggests that definition of the outer limit of the tophus may vary according to how it is imaged. MRI diameters in this study were generally larger than US diameters, and this could be related to better imaging (by MRI) of the soft tissue component of the

tophus, which may contain regions of inflammation and hypervascularity. In 14 patients, urate-lowering therapy (with allopurinol and later benzbromarone in some) was commenced, and repeat US examination was performed at 12 months. When a reduction greater than the smallest detectable difference (SDD) was taken as indicating real change, 20 out of 38 tophi were reduced in maximal diameter at the endpoint. These patients had a significantly lower average serum urate than the group in which tophus diameter did not change. To look at this another way, in patients with an average serum urate of less than 6 mg/dL, 19 out of 28 tophi (68%) showed reduction compared with 1 out of 10 tophi (10%) in patients with urate of greater than 6 mg/dL. The authors concluded that US fulfills the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter [35,36] as a feasible, valid, and discriminative measure for evaluating changes in tophus size in gout patients on urate-lowering therapy.

Schumacher and colleagues [37] performed a multi-center study assessing the intra- and inter-reader reproducibilities of tophus volume assessment using MRI scanning. Volume measurements were made in 17 tophi from 14 subjects. These lesions ranged from very large at the elbow (mean volume of 14.1 cm³) to smaller lesions at the foot/ankle and hand/wrist (6.9 and 5.3 cm³, respectively). Reproducibility in this study was expressed as the absolute percentage difference between volume readings taken by one observer twice (intra-reader) or two observers (inter-reader). Oddly, intra-reader reproducibility in this study was slightly worse (17.2% difference between volume readings) than inter-reader reproducibility (14.2% difference between readers). These differences translated into small actual changes in volume (0.07 to 2.2 cm³). The authors felt that MRI scans without gadolinium contrast were optimal for assessing tophus volume as post-contrast scans were associated with artifact that complicated measurement. It is difficult to extrapolate from these findings whether MRI scanning would be a suitable tool for assessment of change in tophus volume in the therapeutic setting, and further studies are required.

CT has been evaluated for assessment of tophus size by our own group [28]. Forty-seven hand tophi were analyzed from 20 patients with gout, and measurements were made with a 16-slice scanner with thin (0.8 mm) slices. Two observers separately determined tophus volume with the 3D software available. Reliability was very high between and within observers (ICCs of 0.989 and 1.0, respectively). Physical measurement of subcutaneous tophi was also included in this study and, interestingly, compared well with CT in terms of reliability. For tophi that were identified by both physical measurement and CT (89%), there was good correlation between physical

measurement of the longest diameter and CT measurement of volume ($r = 0.91$), providing further validation of CT as a measurement instrument. Currently, there are no published studies evaluating change in CT tophus volume in patients on urate-lowering therapy.

Abufayyah and colleagues [38] recently reported a proof-of-concept study investigating the use of DECT in monitoring reduction of tophus volume in 12 patients on urate-lowering therapy. Scans were performed of four peripheral joint areas – elbows, wrists/hands, knees, and ankles/feet – at baseline and were repeated 11 to 29 months later. Ten patients improved on urate-lowering therapy, with a reduction in serum urate levels and lower frequency of gout attacks. Tophus volume was reduced in all of these responders; the median reduction was 64% (from 322 to 107 cm³). By contrast, the two non-responders showed a 36% increase in total tophus volume. The authors concluded that DECT scanning had potential as a sensitive, quantitative imaging tool for assessing tophus (and therefore urate) volume changes in patients with tophaceous gout.

Using advanced imaging to monitor responses to therapy in arthritic conditions has led to the development of measuring instruments by OMERACT-led international working parties in RA and PsA [4,39]. The MRI scoring systems - Rheumatoid Arthritis MRI Score (RAMRIS) and Psoriatic Arthritis MRI Score (PsAMRIS) - are now in use in clinical trials and similar systems are being evolved for studies in US [40]. The utility of these instruments lies in their ability to reproducibly measure joint inflammation and damage, incorporating characteristic pathological features including bone erosion, bone oedema and synovitis for RA, with additions now available for scoring tenosynovitis and cartilage [41,42]. For PsA, additional features such as bone proliferation and periarticular inflammation have been included in PsAMRIS to capture relevant pathology [39]. Clearly, measuring tophus volume alone in gout is incomplete as successful therapy also needs to be associated with a reduction in chronic synovitis (or acute flares) and slowing the progression of bone erosion. Thus, an all-inclusive measurement tool is needed for comprehensive assessment of gouty arthropathy and perhaps a Gouty Arthritis MRI Score or “GAMRIS” is called for. Alternatively an US or CT score could be devised for gout, keeping in mind that the different modalities have different strengths and weaknesses. For example, MRI has the advantage of revealing all components (inflammation, damage, and tophi) but probably has lower resolution and reproducibility for tophus measurement than CT scanning, whereas US can reveal all components except bone edema (and some deep tissue tophi), appears to have fair reproducibility for tophus measurement, but tends to be operator-dependent.

In summary, advanced imaging techniques are currently poised to fulfill their potential in gout. This review has summarized the great advances that have already occurred in terms of revealing pathological features in this condition. The 3D rendering of tophi is allowing computation of volume from CT and MRI, and the development of DECT means that tophaceous deposits can now be recognized not just by their morphology and tissue density characteristics but by their chemical composition. US allows a 'hands on' approach for the practicing clinician to assess tophi, erosions, and synovitis and may be particularly applicable in the longitudinal setting. It can also be used to guide aspiration of the joint or tophus to obtain material for crystal examination. Advances are being made in defining the reproducibility of imaging measurements, and ultimately the goal will be for the practicing clinician to employ these tools in the assessment of the activity and severity of gout and to determine clinically meaningful responses to therapy.

This article is part of the series *Advances in the imaging of rheumatic diseases*, edited by Mikkel Østergaard. Other articles in this series can be found at <http://arthritis-research.com/series/imaging>

Abbreviations

3D, three-dimensional; CT, computed tomography; DECT, dual-energy computed tomography; ICC, intraclass correlation coefficient; MRI, magnetic resonance imaging; MSU, monosodium urate; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; PsA, psoriatic arthritis; PsAMRIS, Psoriatic Arthritis Magnetic Resonance Imaging Score; RA, rheumatoid arthritis; T2w, T2-weighted; US, ultrasonography; XR, radiography.

Competing interests

The authors declare that they have no competing interests.

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