Update on imaging in gout: contrasting and comparing the role of dual-energy computed tomography to traditional diagnostic and monitoring techniques

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ABSTRACT

In this systematic literature review, we update imaging modalities in gout, with a focus on newer technologies, particularly Dual-energy computed tomography (DECT). Conventional radiography (CR), ultrasonography (US), magnetic resonance imaging (MRI), computed tomography (CT) and dual-energy CT (DECT) have been used to evaluate different stages and clinical manifestations of gout and hyperuricaemia. We compare and contrast these modalities across the spectrum of this disease and of clinical scenarios and objectives (1).

Introduction

Gout is a common form of inflammatory arthritis with an increasing prevalence of 4% of adults in the USA and 1.4% in UK and Germany (2-4). Although crystallisation and deposition of monosodium urate (MSU) require hyperuricaemia, hyperuricaemia alone is insufficient to result in tissue deposits of urate in the absence of other factors. Further, gout flares are triggered through interactions of MSU crystals with additional co-factors.

To form crystals, the SUA concentration must exceed its solubility (usually at a pH of 7.4 with a body temperature of 37.1C). The discovery of the NLRP3 inflammasome has enhanced our understanding of the interaction between MSU crystals and macrophages in generating gouty inflammation (5). More recently the role of neutrophils in amplifying and then limiting gouty inflammation through NETosis has come to light, as well as the subsequent development of aggNETs, the rudimentary origin of tophus formation (5).

The diagnosis of gout is not always simple, because acute podagra involving the first metatarsophalangeal, the most recognisable clinical presentation of this disease, is reported in only 50% of initial presentations; therefore, many patients with gout present in an atypical fashion. Further, many other diseases can imitate gout or coexist with it (6). In the 2015 update of the classification criteria for gout, the presence of MSU crystal positivity detected by polarising microscopy (from a symptomatic joint, bursa or a tophus) remains the "gold standard" for the definitive diagnosis. However, obtaining specimens is not always practical, and polarising microscopy may not be available outside of rheumatology settings. In the absence of such "crystal proof", clinical, laboratory and/or imaging criteria must be met to establish a diagnosis (7).

Since presentations of gout are not always classical and crystal confirmation of a gout diagnosis is often not possible, other means of confirming a diagnosis often are required. Fortunately, in recent years significant progress has been made in the use of imaging for the diagnosis and monitoring of patients with gout. In this review, we update and contrast contributions that clinical parameters, conventional radiography (CR), diagnostic ultrasound (US), MRI and dual-energy CT (DECT) provide in the diagnosis and management of gout. We will focus particular attention on ultrasound and DECT.

Ultrasound in gout

Ultrasound has become widely available at the site of service in rheumatology. It is inexpensive, low risk (no ionising radiation), often portable and well tolerated by patients. It is also useful in guiding joint aspirations and therapeutic injections. Despite these benefits, limitations to ultrasound are seen, including operator dependency and also challenging in obese patients. Using ultrasound to quantify disease burden

at baseline is cumbersome and tracking disease response to therapy is limited.
Standardisation of scanning procedures is important for optimal use of this technique in clinical practice and research. The OMERACT MSUS Group created the MSUS elemental lesions in gout and tested them for reliability in still images and patients (46). In the patient-based assessment, the inter-observer reliability was good for tophus and erosions, but fair to moderate for aggregates and the double contour sign (46). An US scoring system is currently under development (46).

DECT in gout

Dual-energy CT (DECT) was introduced in 2005 and was initially applied to CT-guided angiography. The first case presentation of the use of DECT in a patient with gout was reported in 2007 by Johnson *et al*. (8, 9). DECT is a novel imaging technique based on the acquisition of images from two different x-ray beams with 80 kVp and 140 kVp. Data obtained from the images of each of these two energies can be loaded into post-processing software (Syngo Dual Energy, Siemens Healthcare) to provide the capacity to distinguish MSU deposits from connective tissue and calcium-containing structures due to their different absorptive properties (6).
Single source CT (SDECT) scanning for gout has been evaluated in a limited number of centres. This technique relies on a single x-ray source with rapid switching between two kilovoltage settings (80 and 140 kVp) at intervals of 0.5 msec during a single gantry rotation. ALternating between high- and low-energy x-ray spectra may have value for identifying crystalline deposits. Clinical data from SDECT is sparse and is therefore not a focus of this review (34).
DECT a potentially attractive diagnostic modality in gout on the basis of automated urate volume measurement, 3D reconstruction features and low radiation exposure (0.1mSV per region) (10). A recent systematic review and meta-analysis of the use of DECT in the evaluation of diagnosing gout was reported by Yu *et al*. (11). They recorded sensitivity and specificity of algorithms and they also calculated positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odd ratio (DOR), and respective confidence intervals (CI). The authors demonstrated in their meta-analysis that there is a high homogeneity in these trials with a pooled sensitivity of 88% (95% CI 84–90%) and a specificity of 90% (95% CI 85–93%) for diagnosing gout with DECT.
An important advantage of DECT is provided by automated volume evaluation software, which allows for quantification of tophaceous deposits. This measure shows high intra- and inter-reader reproducibility (32, 35). Although DECT is highly accurate in detection and quantification of tophi, multiple studies have shown that its sensitivity is lower in patients with recent onset of the disease. Bongartz *et al*. reported 30% false negative DECT results in patients with recent onset of gout (15). This is an important consideration in choosing appropriate patients to study with DECT.

DECT compared to conventional radiography

Conventional radiography (CR) is an inexpensive and widely-used imaging tool and is effective to document advanced manifestations of chronic gout, such as bone erosion, joint space narrowing and tophi. Tophi are usually identified as asymmetric, lobulated soft tissue masses with or without calcification (24). Bone erosions in gout, are classically characterised by overhanging borders. Unlike other erosive inflammatory diseases such as rheumatoid arthritis, periarticular osteopenia is not a significant feature of gout. According to Barthelemy *et al*. 86% of the patients have radiographic changes in their feet, with the 1st metatarsophalangeal joint (MTPJ) most frequently affected (25); other fruitful areas for diagnosis by plain radiography were the hands, wrists and elbows.
Dalbeth and colleagues reported in 2012 that new bone formation, mainly sclerotic and osteophytic changes, were found more frequently in joints with other radiographic features of gout, based on analysis of 798 CR and CT scans of the hands and wrists of 20 patients with gout to characterise new bone formation (NBF). They postulated a relationship between bone loss, tophus formation and new bone formation (26).
Conventional radiographs are limited as they typically do not show characteristic features of gout until relatively late stages of disease, long after the diagnosis is established. In contrast to US and DECT, synovitis, bone marrow oedema and deposition of MSU, in the absence of grossly identifiable tophi, are not detected by CR.
Dalbeth *et al*. examined the relationship between joint damage and monosodium urate (MSU) crystal deposits using both CR and DECT in 920 joints of the feet of 92 patients. The authors found that MSU deposits were most characteristically seen in joints with erosions, joint space narrowing, osteophytic changes, spurs formation, periosteal new bone and/or? Sclerosis (27). A particularly strong association was found between MSU crystalline deposits and joint erosion scores. These results, reported in 2015, support the concept of MSU crystals interacting with joint tissue to influence the development of structural joint damage in gout. In the 2015 ACR/EULAR gout classification criteria (Table I), the occurrence of gout-related erosion "cortical break with sclerotic margin and overhanging margin" in radiographs of hands or feet is a positive factor, with a score of 4 for the classification of gout, equivalent to clinical evidence of tophus or positive DECT or US findings (7).

DECT compared to joint aspiration and polarising microscopy

Although the ACR/EULAR recommendations for gout have been updated, the "gold standard" for diagnosis of gout remains detection of MSU crystals of the involved joint or tophus by aspiration and polarising. However, the false negative rate of synovial fluid crystal examination in specimens from patients with acute gout is more than >15% (12). Joint aspiration for crystal diagnosis is rarely performed (3%), particularly outside of rheumatology settings (13).
Glazerbook *et al*. reported a study, comparing the sensitivity and specificity of DECT with synovial fluid analy-

Table I. Abbreviated version of the 2015 ACR/EULAR gout classification criteria (7).

	Category	Score	
Clinic	Pattern of joint/bursa involvement during symptomatic episode(s) ever	Ankle/ midfoot	1
		MTP1 (mono-/oligo-)	2
	Characteristics of symptomatic episode(s) ever	One episod	1
	► Erythema overlying affected joint (patient-reported or physician-observed)		
	► Can't bear touch or pressure to affected joint	Two episodes	2
	► Great difficulty with walking or inability to use affected joint	Three episodes	3
	Time course of episode(s) ever		
	Presence (ever) of ≥2, irrespective of anti-inflammatory treatment:	One typical episode	1
	► Time to maximal pain <24 h		
	► Resolution of symptoms in ≤14 days		
	► Complete resolution (to baseline level) between symptomatic episodes	Recurrent episodes	2
	Clinical evidence of tophus		
	Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (*e.g.* Achilles	Present	4
LAB	Serum uric acid	<4mg/dL [<0.24mM]	-4
		6-<8mg/dL [0.36-<0.48mM]	2
		8-<10mg/dL [0.48-<0.60mM]	3
		≥10mg/dL [≥0.60mM]	4
	Arthrocentesis (polarising microscopy)	negative	-2
Imaging	Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign¶ or DECT demonstrating urate deposition**	positive	4
	Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion+++	positive	4
Max. score			23

sis in the detection of uric acid crystals (reference). Here in this study, DECT sensitivity was reported as 100 % and a specificity of 89%. These findings support DECT as a sensitive, non-invasive method for diagnosis of gout (14).

In another study of 40 patients with active gout and 41 individuals with other types of joint disease, the sensitivity and specificity of DECT for the diagnosis of gout was comparable to demonstration of MSU crystals in synovial fluid aspirates with the polarising microscope and/or electron microscopy (15). False negative results using DECT were observed only in patients with acute, recent onset gout. False positive results were primarily in patients with advanced osteoarthritis of the knee. Based on these findings, DECT offers an alternative to accurate detection of MSU crystals when polarising microscopy has failed to establish a diagnosis or when joint aspiration is either not possible or is not successful (15).

Of course, aspiration of an inflamed joint should always be performed in a patient with acute synovitis when the diagnosis is uncertain. Differentiation of gout from infection or from other forms of inflammatory arthritis is essential to appropriate patient care, and is best supported by synovial fluid aspiration and analysis (16). However, in settings in which gout may be the most likely diagnosis, aspiration may be negative due to an extra-articular locus of MSU deposits (Fig. 1) (17). DECT is well-suited to assist in diagnosis under such a circumstance (15).

DECT compared to ultrasound

ACR and EULAR recognised the value of both imaging modalities, US and DECT, within the scoring algorithm of the 2015 gout classification criteria (Table I) (7). Advantages of US include short examination times, low cost, absence of ionising radiation, immediacy of results, portability, and widespread availability, rendering it a first line imaging method in clinical practice. Moreover, US allows for evaluation of many aspects of gouty arthritis, such as synovitis manifested as synovial thickening in acute flares, power Doppler signal indicative of increased blood flow, and MSU crystals in synovial fluid providing a characteristic 'snowstorm appearance'. In chronic gout, US can detect tophaceous deposits, which may present as hyperechoic and/or inhomogeneous material with or without posterior shadowing. The double contour sign which manifests as a hyperechoic band over anechoic cartilage, is specific for gout irrespective of stage. Moreover, US can identify bony erosions, even in the early stages of disease. Thus, US findings are helpful in demonstrating the full clinical spectrum of gout, from its earliest to its most advanced characteristics (18-21).

To determine the inter-reader reproducibility of ultrasound examination of the bilateral knees and first MTP joints, Howard *et al*., studied 50 male subjects recruited during primary care visits at a Veterans Affairs hospital. Three categories of subjects were enrolled: group 1: patients with a known diagnosis of gout and group 2: patients with asymptomatic hyperuricaemia (>6.9mg/dL) or group 3: normal control subjects with no hyperuricaemia or a known diagnosis arthritis of any type. Patients were examined for the double contour sign and for tophi, as evidence urate crystal deposition. Howard reported that an almost perfect concordance was found

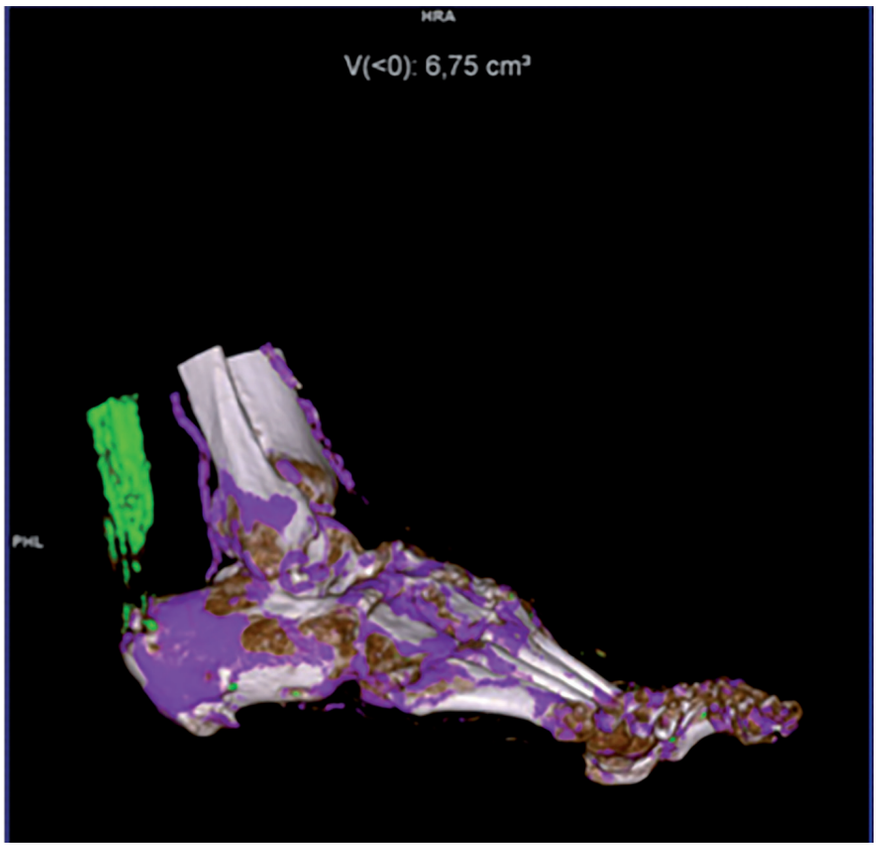

Fig. 1. Tendon involvement.

between readers for all measures at the knees and first MTP joints (18).

Comparison of the diagnostic accuracy to detect MSU crystal deposits between dual-energy CT (DECT) and ultrasound (US) has been reported in several studies. A meta-analysis by Ogdie *et al*. of 11 reports indicated that US and DECT both had high sensitivity and specificity for gout classification in established patients with a gout diagnosis of greater than 7 years (22). The authors concluded that future studies of patients with early gout and hyperuricaemia would be helpful to clarify an optimal approach for gout classification.

In a case-control study reported by Huppertz *et al*. in 2014, 60 patients clinically suspected to have gout, 39 of whom met predetermined clinical criteria for gout, underwent DECT and US. Diagnosing gout by DECT was possible in 84.6% (33/39) of the patients whereas in 100% (39/39) by US. Specificities were 85.7% (18/21) for DECT and 76.2% (16/21) for US (10).The authors concluded that DECT for the diagnosis of gout is less sensitive than US as it cannot detect small urate deposits, but positive DECT findings are very specific, differentiating urate crystal deposits from other crystals. They highlighted that DECT might be useful in those patients with ambiguous diagnostic findings, concomitant rheumatic disease, and/or with inconclusive joint aspiration.

Granger *et al*., reported that the Gout OMERACT Working Group concluded that urate deposition and structural damages could be effectively monitored by both US and DECT. Inflammation in chronic gout has been underappreciated so far. Moreover, to assess all domains (urate lowering and controlling inflammation) more then one imaging modality is needed (23).

DECT compared to MRI

MRI provides three-dimensional data on bone-structure, periarticular soft tissue and tophi, with excellent resolution compared to CR and CT. Although MSU cannot be directly visualised by MRI, tophi can be identified as node-shaped areas with low intensity on T1w and variable intensity on T2w (28). Other features of gout which can be detected by MRI include synovitis, joint effusion and soft-tissue oedema (29, 30).

Bone marrow oedema (BME) identified by MRI in gouty patients is frequent and not exclusively present in osteomyelitis (30). However, MRI findings of acute gout are not sufficiently specific to distinguish this diagnosis from other forms of inflammatory arthritis. In a study by McQueen *et al*., 40 gout patients underwent 3 Tesla MRI of the wrist and on 10 of them DECT was also performed. The MRI scans were independently scored for BME, erosions, tophi and synovitis, whereas DECT from 10 patients were only scanned for tophi. McQueen *et al*. reported that the MRI inter-reader reliability was high for erosions and tophi [intraclass correlation coefficients (ICCs) 0.77 (95% CI 0.71, 0.87) and 0.71 (95% CI 0.52, 0.83)] and moderate for bone oedema [ICC = 0.60 (95% CI 0.36, 0.77). They postulate that compared to DECT, MRI had a specificity of 0.98 (95% CI 0.93, 0.99) and a sensitivity of 0.63 (95% CI 0.48, 0.76) for tophi. Tophi were identified by MRI in 63% of the patients and were strongly associated with erosions (31).

DECT compared to CT

The radiation dose of a DECT scan lies between 0.1 - 0.5 mSv per scanned region (*e.g*. 0.5 mSv for both hands and wrists) with a total dose for all scanned peripheral joints ranged from 2 to 3 mSv, which corresponds to the average annual natural background radiation dose (2.4 mSv) (10, 32, 33).

DECT is a valuable diagnostic tool in patients with known or suspected gout, but it is not widely available. To overcome this limitation, Single-source dual-energy CT (S-DECT) with only one x-ray tube and is being studied as an appropriate alternative.

Kiefer *et al*. compared single source Dual-energy CT (SDECT) and standard CT in a retrospective analysis of 44 patients suspected of having gout,

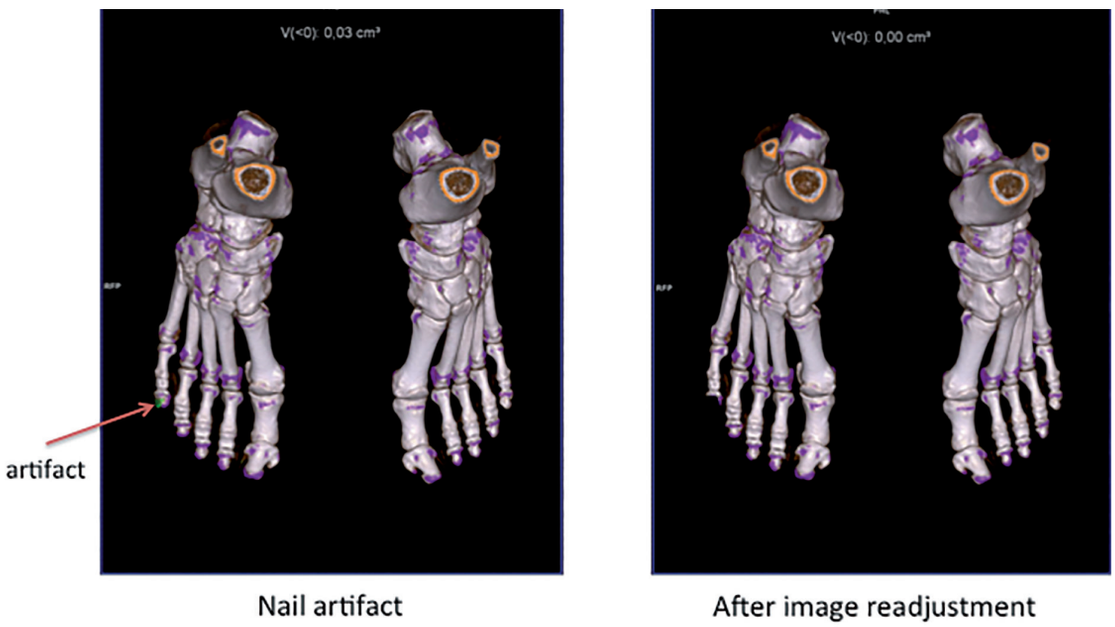

Fig. 2. Nail artifact.

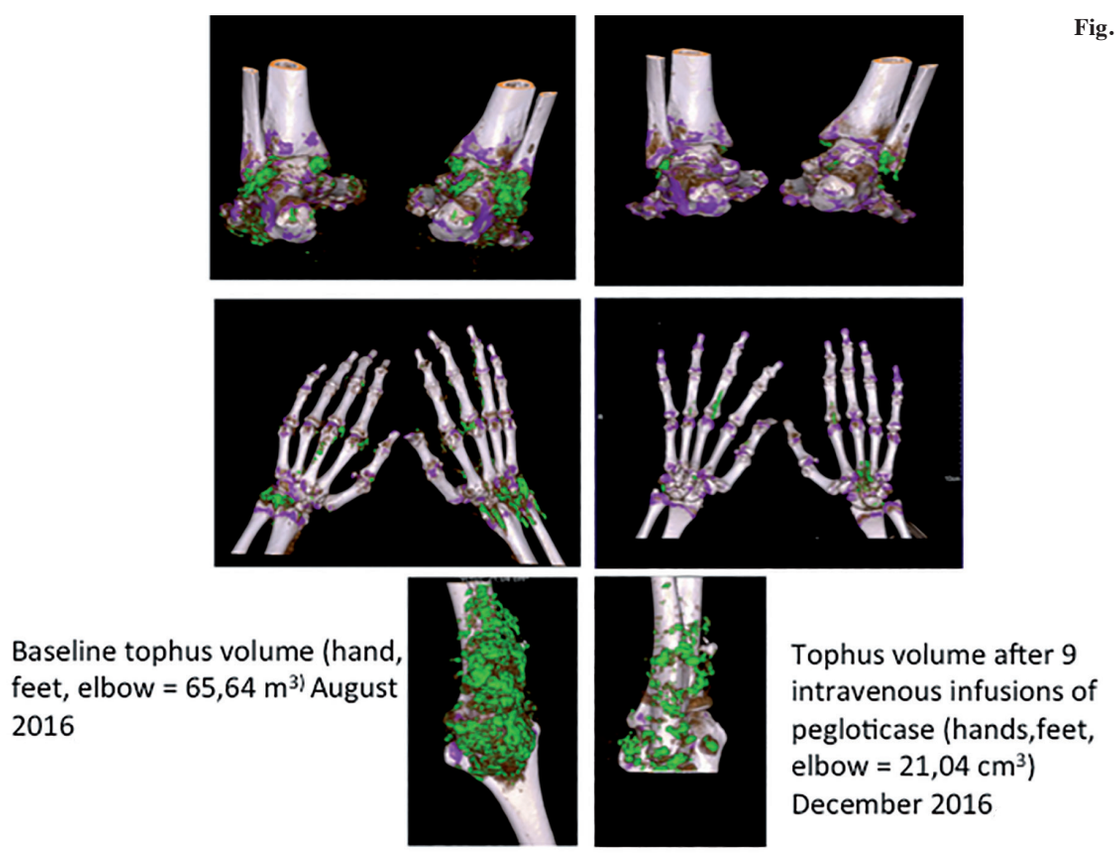

Fig. 3. Treatment follow-up.

with a hypothesis that either technology would be equivalent and capacity to detect tophi. However, SDECT has a higher specificity, higher positive predictive value (PPV), and lower negative predictive value (NPV) compared to conventional CT scanning and conventional radiography (34).

Evaluation of imaging and therapeutic response

Long-term use of uricosuric therapies to achieve subsaturating concentrations of serum urate (<6 mg/dl in gout and <5mg/dl for tophaceous gout) is the primary therapy goal in gout (36). However, control of serum urate alone is not a sufficient criterion for monitoring the efficacy of gout management. Gout flare frequency, control of chronic synovitis, patient reported outcomes, and the resolution of tophi constitute other important outcome measures in these patients (36) (Fig. 3).

These latter outcomes require careful

serial clinical examinations as well as objective measures. Imaging methods can be important not only to establish diagnosis of gout, but also to monitor treatment efficacy. It is reported that that 42% of gout patient without clinically palpable tophi and 95% with tophi have radiographic evidence of erosions and gouty arthropathy (37). These data suggest that imaging may be helpful not only to quantify disease severity at various points along the continuum, but also to monitor resolution of tophaceous deposits in patients with more extensive disease.

US and MRI also allow for the assessment of inflammation. MRI OMERACT bone marrow and synovitis scores (OMERACT RAMRIS bone marrow oedema and synovitis score [RAMRIS]) are higher in patients with an acute attack of gout than with active RA (30). Only a few MRI studies have been reported which track the response of synovitis to urate lowering therapy (ULT). A double blind, placebo-controlled study with Febuxostat on 314 subjects with early gout indicated improvement of RAMRIS score over 2 years, without notable changes in erosions (38). As previously discussed, bone oedema is not common in gout. In addition, tenosynovitis identified on MRI is reported in <20% of gout patients (39).

A study by Schumacher *et al*. demonstrated that quantitative volume measurements of palpable tophi by MRI show excellent Intra-reader reproducibility (40). Thus, both MRI and conventional CT have the capacity to measure tophus size (diameter or volume) and structural joint damage with high inter-reader reproducibility (40-42). MRI, unlike CT, can reveal signs of active inflammation. Both CT and MRI are expensive and not widely available outside rheumatology setting.

Ultrasonography is considered a sensitive and specific modality for diagnosing gout. Puig *et al*., reported that urate deposition was detectable sonographically in 34–43% of patients with asymptomatic hyperuricaemia, and in approximately 50% of patients diagnosed clinically with gout but without visible tophi (43). Grassi *et al*. reported that ultrasound distinguishes between MSU and calcium pyrophosphate (CPPD) deposition, on the basis of how these deposits are localised in and around articular structures. In their study with 36 confirmed CPPD and 24 confirmed gout patients examined with ultrasound, MSU deposition typically was visualised on surfaces of articular cartilage (double contour sign), in synovial fluid, tendons and tophi. By contrast, CPPD deposition was seen on US within articular cartilage (but not on its surface) and fibrocartilage. Focal CPPD deposition was also visualised in tendon structures (44).

To validate the applicability of tophus measurement by ultrasound, Perez-Ruiz *et al*. examined 25 patients with crystal-proven gout with US and MRI at baseline and after 12 months of uric acid lowering therapy. Five patients had no subcutaneous tophus on examination, and 3 of these 5 showed no tophus on physical and imaging examinations. In the 22 patients available for analysis, 50 nodules suspected to be tophi were detected: 46 with US, 41 with MRI, and 37 with both imaging techniques. Perez-Ruiz reported that there was good correlation between baseline and final measurements: r=0.846 and 0.852 for maximal and transversal diameters, respectively, and 0.874 for volumes. US was found to detect at least one tophus in joints in which one or more tophi was seen using MRI. The authors highlighted that there are some limitations to their study because the patients had not been randomised for the urate lowering therapy and that they did not measure tophi volume with the MRI (45).

Ottaviani *et al*., reported on a longitudinal study of US in 16 crystal-proven gout patients, treated with urate lowering therapy (n=4 with allopurinol or n=12 with febuxostat). Patients needed to exhibit proven gout by MSU crystals in synovial fluid and US-evidenced urate deposits (double contour sign and/or tophi) before starting urat lowering therapy. The authors demonstrated that 11 of 12 patients who achieved adequate urate lowering therapy (<360 μmol/l or <6mg/dl) after 6 months of treatment had either resolution or improvement of their US features, while US findings did not improve in the 4 patients whose SUA level did not reach the target. They concluded that the correlation between the whole US examination and serum uric acid level was excellent (kappa = 0.875) (47). A more recent longitudinal study by Peiteado *et al*. of 23 patients demonstrated similar results. They showed that ultrasound findings improved in gout patients who received uric acid lowering therapy and are reflective of clinical and biochemical improvement (48).

According to one prospective study by Eason *et al*., baseline radiographic damage and development of new subcutaneous tophi are correlated with progressive radiographic damage findings with a pooled sensitivity of 88% (95% CI 84-90%) and a specificity of 90% (95% CI 85-93%). The modified Sharp/van der Heijde method uses radiographs to identify and score bone erosion and joint space narrowing in rheumatoid arthritis (49). As previously noted, CR is inadequate to detecting early disease manifestations in gout, which limits its usefulness in diagnosis and monitoring of gouty arthritis.

Although DECT artifacts (Fig. 1) are often found in the nail bed, cartilage and subcutaneous deposits (about 90%) (50), they are easily identified as artifacts but should be manually excluded using the processing software prior to urate volume measurement for volume calculation. DECT can be used to evaluate both urate deposition and structural joint damage. In a study by Sun *et al*. 44 patients with gout receiving urate lowering therapy (ULT) underwent DECT at baseline and again at follow-up 6-24 months later. The authors distinguished between large (> 3mm diameter) and small (<3mm diameter) crystalline deposits. They tracked small and large deposits together and then looked at the larger deposits to measure volume: in the follow up DECT, they were able to see that both urate lowering therapy duration and serum urate levels had significant effects to decrease the measured volume of the crystalline deposits, irrespective of baseline size (51). By contrast, the study by Rajan *et al*. showed no significant correlation between serum urate levels and changes in DECT urate volume in patient with clinically stable tophaceous gout (52).

Araujo *et al*. used DECT to examine 10 pegloticase-treated patients with tophaceous gout at baseline and then repeated the DECT at the conclusion of treatment. The serum uric acid was initially suppressed to values close to zero in all patients after pegloticase therapy was initiated. The uric acid lowering effect, however, was not sustained in half of these subjects, all of whom had infusion reactions to the drug, resulting in the early termination of their treatment. Patients in whom the serum uric acid lowering was maintained until completion of therapy (10–28 weeks) became almost completely free of tophi by the conclusion of the study, with a 94.8% reduction in the volume of tophi. DECT has been described as an excellent tool to assess tophus volume and anatomical location and is thus well-suited to longitudinal monitoring (53). Bayat *et al*. developed a semi quantitative scoring system for measurement of urate deposition in gout, which fulfills many aspects of OMERACT filters. Compared to the total volume of MSU, the DECT urate scoring method had greater capacity to differentiate between pegloticase responders and non-responders (54). A longitudinal study is in progress. Dalbeth *et al*. examined 152 patients with DECT after receiving at least 3 months of allopurinol. Patients with higher sUA and clinical features of severe disease had a higher frequency and greater volume of MSU crystal deposition (55).

Summary

Although arthrocentesis remains the gold standard for diagnosing gout, newer imaging modalities, particularly DECT and US, provide improved certainty of diagnosis and monitoring of therapeutic responses. At this time, clinicians have many imaging tools to assist in gout diagnosis and management as illustrated in this report. Ultrasonography, with its wide availability, provides an excellent first-line imaging method for gout. It is low in cost, entails no ionising radiation, provides immediacy of results and is well accepted by patients and physicians alike. However, it does not lend itself to quantification of total urate stores and has the limitation of interobserver variability. By contrast, the introduction of DECT has expanded identification of small crystalline deposits even in atypical locations, which would ordinarily escape detection by ultrasound, and quantitates the extent of tophaceous disease, enabling clinicians to measure urate burden and track therapeutic responses.

It is our challenge as physicians to develop and recognise unique benefits and limitations among the newer and more traditional imaging tools in our management of patients with gout. DECT provides an important new addition to our diagnostic armamentarium.

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