New insights into an old disease: advanced imaging in the diagnosis and management of gout

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ABSTRACT
Advanced imaging modalities including MRI, ultrasound (US), and dual energy CT have important applications in gout. While conventional radiography (X-ray) remains the most widely used form of imaging in the clinical setting and is helpful in revealing erosions in chronic gout, these new imaging tools can reveal joint damage and tophi at a much earlier stage. As all are multiplanar techniques, they can define the position and dimensions of tophi, with startling clarity, as well as the size and extent of bone erosions. US and MRI also reveal the severity of inflammation within and adjacent to the joint and can capture information about the composite, vascular nature of many tophaceous deposits. These features can be used as imaging outcome measures, to monitor responses to anti-inflammatory and urate lowering therapies. The new possibility that gout could be diagnosed using imaging, without aspirating the joint, is on the horizon. This review discusses the clinical and research applications of advanced imaging in gout with particular focus on diagnosis and monitoring of joint inflammation and damage.

INTRODUCTION
Gout is an ancient disease, having been first identified by the Egyptians in 2640 BC and later by Hippocrates in the fifth century BC.1 It is characterised by the deposition of monosodium urate (MSU) crystals, and occurs as a consequence of hyperuricaemia. Distinct clinical phases are recognised: asymptomatic hyperuricaemia, acute monophasic gout, recurrent acute attacks with intercritical periods and chronic gout which is often tophaceous.2 As long as the serum uric acid (SUA) level remains high, crystals continue to form, urate deposits grow and new deposits continue to appear. Formation of these crystal deposits is reversible and they dissolve when SUA levels are normalised with appropriate urate lowering therapy (ULT). The disease has been deemed to be curable according to the 2006 European League Against Rheumatism (EULAR) recommendations on gout management3 but severe and tophaceous gout continues to be a major health problem within certain populations such as New Zealand Maori and Pacific peoples where gout prevalence in adult men is 10–12%.4 In some of these patients, diagnosis is delayed and management unsatisfactory with poor control of hyperuricaemia for multiple reasons including genetic factors contributing to impaired uric acid excretion,5 poor patient compliance and difficulties accessing medical care.6 Gout remains an important condition even outside these high risk groups as it is the most common form of inflammatory arthritis in men older than 40 years and has risen in terms of prevalence over the last decade.7

Research into gout has provided recent new information about the molecular mechanisms activated during acute attacks, emphasising the role of IL-1-dependent innate inflammatory pathways and the formation of the macromolecular nucleotide binding domain and leucine-rich repeat containing protein (NLRP) inflammasome complex in response to the MSU “danger signal”.8 Mechanisms of joint damage are also being explored, including the basis of bone erosion and cartilage damage.9 10 Importantly, imaging in its varying forms may offer new insights into the underlying pathology of this disease, especially when combined with studies of the immunohistology of bone and tophi.9 11 12 Some imaging studies, especially using ultrasound (US), have suggested that gout is a tissue deposit disease from the first attack, and that imaging abnormalities can be present even in the asymptomatic hyperuricaemic stage.13 In parallel, advances are being made in the management of gout and recent work has shed light on the clinical applications of traditional agents and new cytokine blockers for treating the acute attack.14 15 Of special relevance for those with erosive or tophaceous disease, ULT has also been re-examined with new emphasis on more effective dosing of allopurinol,16 alternative xanthine oxidase inhibitors and uricosuric agents as well as uricase-based therapeutics.17 18

Imaging has several important applications in the investigation of gout pathology as well as its diagnosis and clinical management. Reaching an accurate diagnosis underpins effective management and while the gold standard remains establishing the presence of MSU crystals in aspirated joint fluid or tophi,19 arthrocentesis may not always be practical or possible. Sometimes tophi can present in unusual settings, with manifestations related to compression or infiltration of involved tissues. In these situations, advanced imaging techniques, including US, MRI, CT scanning and dual energy CT (DECT) may be useful. Although most imaging research has to date been performed in patients using US and DECT, investigating those with recent-onset, pre-erosive gout. These have produced data to suggest that imaging could be more widely applied to gout diagnosis by the practicing clinician. Similarly, the successful management of gout, especially with ULT, requires outcome measures that accurately reflect therapeutic benefit. While a falling SUA is an excellent biomarker and
may be a surrogate for tophus resolution, imaging allows the direct visualisation and measurement of tophi as they resolve, even when this cannot readily be detected by clinical examination. Thus, imaging can be used to monitor the effectiveness of drug therapy in gout, at the clinical trial level and also in routine clinical practice. In this review, we discuss imaging in gout, comparing traditional radiographic methods with advanced modalities and discussing their application in the diagnosis and management of gout.

RADIOGRAPHY

Plain radiography remains the first and most readily available imaging investigation for clinicians managing patients with gout.\(^\text{20, 21}\) The inclusion of radiographic findings in the American College of Rheumatology clinical diagnostic criteria for gout (Wallace criteria\(^\text{22}\)) underscores their importance but it is notable that radiographic abnormalities frequently take 10 years or more to become apparent\(^\text{23}\) and are most marked in tophaceous disease. The more recent EULAR evidence-based recommendations for a diagnosis of gout included the presence of ‘asymmetrical joint swelling’ and ‘subcortical cysts without erosion’ in their 10 key diagnostic features (likelihood ratios of 4.13 and 6.39 respectively).\(^\text{19}\) However, the multidisciplinary guideline development group concluded that ‘radiographs play only a minor role in diagnosis in most patients with gout, though in late or severe disease characteristic radiographic features may be present’. Thus, radiographs are frequently normal in early, acute gout or may show only non-specific soft tissue swelling around the acutely inflamed joint as occurs for example in podagra. This lack of sensitivity was borne out in the study by Rettenbacher et al who used a clinical diagnosis of gout as a gold standard and found x-ray to have a sensitivity of 31% and a specificity of 93%.\(^\text{24}\)

In advanced longstanding gout, typical x-ray findings include: soft-tissue opacifications with densities between soft tissue and bone (representing subcutaneous tophi), articular and periarticular bone erosions described as ‘punched out’, often with osteophytes producing an ‘overhanging margin’. Erosions may coalesce to present a honeycomb appearance and when related to the articular surface of a joint, may be associated with subchondral collapse.\(^\text{20}\) These destructive changes are frequently associated with early degenerative osteoarthritis (OA).\(^\text{23}\) With very advanced gout, more bizarre features can occur with bone loss, described by Wright et al as ‘vanishing bones’,\(^\text{26}\) and ossification of tophi. New bone formation also seems to be a radiographic feature of longstanding tophaceous gout and regions of bone sclerosis often occur adjacent to erosions or within their overhanging margins.\(^\text{20}\) Periarticular osteopenia is not usually associated with gout. These findings contrast with the radiographic features of rheumatoid arthritis (RA) where erosions most typically involve the articular surface, do not usually have sclerotic margins (although may do in longstanding disease) and periarticular osteopenia is seen. The erosions of psoriatic arthritis can be harder to differentiate in that they may occur in ‘non-rheumatoid’ regions such as within the distal interphalangeal joints (as may also be the case for gout) and be associated with bony proliferative change. Another radiographic gout mimic in this region would be erosive OA, although the morphology of erosions and overall pattern of joint involvement differs between these conditions.\(^\text{21}\) Figure 1 shows images comparing the radiographic features of gout, RA, psoriatic arthritis and OA to illustrate these points.

**Figure 1** Hand radiographs to illustrate features of erosive arthropathies. (A) Patient with tophaceous gout, (B) detail to show erosions with overhanging margins and adjacent soft tissue opacities (arrows) with complete disc location of the first metacarpophalangeal (MCP) joint due to bone lysis and erosion (circle) (C) Patient with rheumatoid arthritis (D) detail to show marginal erosions with cartilage loss at the typical sites of second and third MCP joints (E) patient with psoriatic arthritis and predominant distal interphalangeal (DIP) joint involvement (F) detail to show erosion and bony proliferation at DIP joints (arrows) (G) patient with erosive osteoarthritis (H) detail to show subchondral erosion and ‘gull wing’ bony proliferation (circle).
ULTRASOUND
There is growing interest in the applications of US in all areas of rheumatology as this modality allows the clinician a ‘hands on’ way to supplement the standard clinical joint examination for the assessment of inflammation and damage. In addition, US allows guided joint aspiration which in some studies (but not all) has been shown to be superior to blinded joint aspiration for obtaining synovial fluid and administering local steroid injections. In gout, this application has particular relevance, as the confirmation of MSU crystals within aspirated synovial fluid, especially when identified intracellularly within neutrophils, provides the diagnostic gold standard. Studies have investigated US as a modality for detection of all features of gout including synovitis, erosion and tophi. Tophi are of particular diagnostic importance as they are unique to this condition. On US, tophi can appear as nodules that are hypoechoic, hyperechoic or of mixed echogenicity as described by Schueller-Weidekamm et al. The commonly seen surrounding hypoechoic ‘halo’ probably corresponds to the outer, loose fibrovascular zone seen on histology. US may be used to measure tophus size, and has an important role in assessing tophus resolution in patients receiving ULT. Perez-Ruiz studied tophus size in 25 patients with gout, using US. In 14 of these, paired images were available after 1 year of ULT (allopurinol and benzbromaron). Taking a reduction greater than the smallest detectable difference as indicating real change, 20/38 tophi were reduced in maximal diameter at the endpoint. In patients with an average serum urate <6 mg/dl, 68% of tophi showed reduction in size compared with 10% of tophi where the urate remained >6 mg/dl. It is important to recall that not all tophi are accessible to the US probe, especially in complex regions such as the wrist, so could remain undetected using this modality.

There is an interesting US feature known as the ‘double contour’ sign described by Thiele and Schlesinger, where an echogenic line may be detected paralleling the bony contour (of for example a metatarsal (MT) head) with an anechoic region between. This anechoic region represents hyaline cartilage over which MSU crystals have been proposed to form a hyperechoic ‘halo’ suspended in joint fluid and administered local steroid injections. Double contour sign was detected by Thiele et al in 92% of 23 patients with crystal-proven gout and in none of their controls, which would indicate 100% specificity, whereas Carter et al were unable to discern the sign on US images from any of their gout patients investigated using US and MRI. Another study assessed the reproducibility of US for detecting these signs and reported near perfect agreement between their two blinded readers, both of whom found evidence of MSU deposition in the same 13 subjects. A Mexican group extended observations to 50 patients with asymptomatic hyperuricaemia, where the double contour sign was identified in 25% of first metatarsophalangeal joints (MTPJs), compared to none of a control group of normouricemic subjects. This raises questions about using US to differentiate clinical gout from asymptomatic hyperuricaemia, which some regard as benign but others suggest is the harbinger of future disease. Another recently published US study of 26 consecutive patients with persistent asymptomatic hyperuricaemia reported MSU crystals in nine (whose joints were aspirated if US indicated effusions). There was US evidence of the double contour sign or ‘hyperechoic cloudy areas’ in 11/26 with 100% sensitivity and 88% specificity. The κ coefficient for US inter-reader reliability ranged from 0.79–0.93. Clearly further studies are warranted, especially in clinical gout, but interobserver and intercentre variability need to be carefully defined.

Bone erosions on high resolution US (HRUS) appear as breaks in hyperechoic cortical bone detectable in two perpendicular planes. HRUS has been shown to be considerably more sensitive than plain x-ray for detecting erosions in gout as it has in RA. The two modalities were compared at the first MTPJ by Wright et al. In 22 MTPJs where there had never been a clinical attack of gout, 10 erosions were detected by HRUS as compared with 3 by x-ray and agreement between the two modalities was poor (κ=0.29). The authors concluded that there were a large number of false negatives on the x-ray evaluation but the number of false positives on US could not be determined. For this to be achieved, US would need to be compared with another 3-dimensions (3D) modality that is generally regarded as an accurate gold standard, such as MRI or CT scanning. So far only one such study has been reported by Carter et al, who compared US and MRI findings in gouty joints. They examined radiographically normal ‘index’ joints where there had been clinical attacks of gout and found 56% of patients to have MRI erosions compared with only 4% (one patient) using US. More comparative studies are therefore required.

US can also image the inflammatory aspects of gouty arthropathy including synovitis, tenosynovitis and soft tissue inflammation. Regions of thickened soft tissue with moderate echogenicity have been described, which might represent diffuse infiltration with MSU crystals, and in the US study of asymptomatic hyperuricaemia referred to above, Pineda et al found evidence of Achilles and patellar enthesisopathy. Increased synovial vascularity within gouty joints has also been identified using power Doppler US, and this modality has potential for monitoring efficacy of anti-inflammatory therapies in gout, as has been achieved in RA.

CT SCANNING
Helical multislice conventional CT scanning represents x-ray in 3D and provides images of unparalleled clarity for imaging bone and tophi. The high resolution is achieved by very thin 0.5 mm slices, with a minimal interslice gap, and overlapping 3D reconstruction. Tophi may be identified as discrete nodules or masses with a density of 160–170 Hounsfield units, which differs from the density of soft tissues and bone. CT images entire joint regions such as a whole hand or whole foot, and this allows the pattern of joint involvement to be defined. Like
x-ray, CT does not image inflamed soft tissues, so is not useful for identifying or monitoring synovitis or tenosynovitis in gout. However, it is the modality par excellence for defining gouty erosions and tophi. Dalbeth et al studied CT scans of 798 hand and wrist joints from 20 patients with gout and scored erosions and tophi.49 Of those joints where erosion was present, 82% showed the presence of adjacent tophi. This implicates tophus infiltration as a dominant mechanism underlying bone erosion in gout. The same group compared CT with physical measurement of 47 surface tophi from 20 gout patients50 and found that 89% of lesions identified physically were scored as tophi on CT. There was excellent correlation between physical and CT measurements of tophus dimensions (r=0.91) and CT inter-reader reliability was very high with an intraclass correlation coefficient of 0.99. A CT scoring method for quantifying bone erosions at the feet in gout has now been developed and validated51 and includes assessments of the first MT head, second to fourth MT bases, cuboid, middle cuneiform and distal tibia. This is likely to be a reliable tool with which to monitor damage progression in gout, in the setting of longitudinal trials or observational studies.

**DUAL-ENERGY CT**

DECT is a form of imaging that was developed in the fields of urology (for determining the composition of urinary calculi) and cardiology (for investigating plaques within coronary arteries). Recently, it has been applied to gout as DECT images allow uric acid to be very specifically identified and differentiated from calcium in bone and soft tissues.52 Various different means are used to create DECT images, ranging from technology developed by Siemens, where two x-ray tubes with different voltages are aligned at 90° to one another, to dual energy scans produced on ‘single source’ machines using techniques such as rapid kV switching, being offered by other major CT vendors. The identification of specific compounds such as uric acid is possible because materials act differently at different energies depending on their chemical composition and this influences the degree to which they attenuate (block) x-rays tracking through the material during the CT scanning process. The underlying physical principle states that the attenuation of photons depends on their own energy and the atomic number of the material they are passing through. Material with a high atomic number (eg, calcium) causes a greater change in attenuation than does material with low-atomic number compounds (eg, uric acid). Materials can be differentiated by single energy CT scanning using threshold-based techniques but DECT has the advantage of utilising the ratio between high voltage (typically 140 kV) and low voltage (80 kV) attenuation, which can be depicted as x and y axes respectively. Each pixel can be plotted using these two dimensions and those with high values on both axes contain materials with high atomic number, which in biological systems often means calcium is present. Uric acid appears in a different position on this plot, and so can be very accurately defined. Therefore DECT scanning has the potential to differentiate MSU crystals from other types such as calcium pyrophosphate crystals occurring in pseudogout.52

When a new form of imaging comes onstage there is often a flurry of activity as investigators seek to define its features and clinical applications and this has certainly been the case for DECT in gout. DECT will only identify nodules as tophi if they contain MSU crystals but these are sometimes embedded within larger soft tissue masses.53 They may be peritendinous but are also frequently found adjacent to tendons and entheseal insertions54 (figure 2) and indeed DECT has produced new information about how very extensive and widely distributed urate deposits can be in gout. DECT data seems reassuringly reproducible with virtually complete agreement between observers in several studies (intraclass correlation coefficient =0.95).55 55 56 DECT also appears to be both sensitive and specific for identification of urate deposits when compared with the gold standard of positive joint aspirates. Choi et al studied 40 crystal-proven gout patients and 40 controls and found the sensitivity of DECT for gout to be 0.93 and the specificity to be 0.78. DECT-measured urate volumes of 40 index tophi ranged from 0.06 cm³ to 18.74 cm³.56 Nicolaou confirmed validity by aspirating MSU crystals from four DECT-positive sites in another small study57 and Glazebrook et al58 repeated this in a larger group of 31 patients,55 finding a sensitivity of 100% (no false negative DECT scans) and specificity of 79% (four false positives). However, we have recently validated DECT against 3T MRI (at sites concordant for two readers) and found that variation of the software algorithm used for identification of DECT deposits can have a major impact on positivity for urate.59 Thus, further validation work comparing DECT with other imaging modalities is required.

Bongartz et al investigated DECT in three patient groups; controls who underwent arthrocentesis for other joint disease, patients with aspirate-positive gout and patients where gout was suspected but joint aspiration was not possible.60 If DECT imaging suggested MSU deposits, US-guided aspiration was performed with polarising microscopy. The sensitivity and specificity of DECT for diagnosing gout were 0.93 and 0.95 respectively, based on 40 patients with confirmed gout versus 40 controls. All three DECT false negatives were observed in patients with acute podagra and the two false positive patients had advanced knee OA with a DECT signal indicating intracartilaginous uric acid deposition. DECT revealed uric acid deposition in 14 of 30 subjects with a clinical suspicion for gout but no synovial fluid aspiration. The authors concluded that DECT could have significant impact on clinical decision making when gout is suspected and aspiration is not possible. Total urate volume computed from DECT scans could also be an ideal outcome measure for application in trials of ULT. While this work is new and exciting, this modality does require specialised technology, involves ionising radiation and is relatively expensive, so it might not be widely applicable in clinical situations.

**MRI**

There is significantly less in the literature on the role of MRI in gout. This is probably because the high cost of MRI scans
Figure 3. T1 weighted coronal post contrast image of the wrist from a 51-year-old Maori male with tophaceous gout (A) coronal view reveals multiple cystic/erosive lesions with variable enhancement are present within the carpal bones (arrows to large lesions within lunate and hamate). These are likely to represent tophi. (B) axial slice at the level of the lunate shows tophus (arrow). There is also synovial enhancement indicating carpal synovitis (wide arrows).

impedes access for patients and their physicians. MRI is used most often in inpatient settings, especially when patients with severe tophaceous gout are admitted in a possibly septic state and the question of concomitant osteomyelitis is raised. Poh et al performed a retrospective review of 51 MRI scans from 47 gout patients over a 10 year period.59 The MRI finding of, ‘severe bone marrow edema’ was much more common in gout-plus-osteomyelitis (observed in 93% of scans), than in uncomplicated gout where bone oedema was mild and infrequent (8% of scans). Bone oedema is an MRI-specific imaging feature, which in RA equates to osteitis60 and predate bone erosion.61 In gout, the process of bone damage leading to erosion is quite different and further studies focussing on MRI bone oedema in this condition will be of interest.

Tophi have variable characteristics on MRI. They usually appear as discrete masses or nodules with low signal on T1 weighted (T1w) images, but signal intensity on T2 weighted (T2w) images may range from low to high, possibly influenced by the presence of calcification.62 Tophi may also enhance with contrast, implying a degree of vascularity and this is consistent with histological findings where urate deposits are often embedded in granulation tissue11 as recently demonstrated using DECT imaging.53 Because MRI images the inflammatory soft tissue component of the tophus as well as the crystal component, it can be hard to define the border (when adjacent to inflamed soft tissues) and therefore measurement of tophus size can be more variable than for example using CT scanning.63

The structure of tophi has also been shown to be variable on MRI, ranging from discrete nodules to amorphous masses that may extend through tissue planes64 and involve tendons.59 (figure 3). A recent study of 3.0 Tesla-magnetic resonance imaging (3T-MRI) has reported excellent correspondence with DECT for detecting tophi57 and it may be that this modality has great potential in gout, although it remains expensive and difficult to access for routine clinical management.

**CLINICAL POINTS: HOW CAN IMAGING AFFECT MANAGEMENT?**

The diagnosis of gout still rests on clinical history, examination, measurement of the SUA, plain radiography and where possible, joint aspiration to detect MSU crystals. The simple physical measurement of tophi can provide information for clinicians about the response to ULT over time.53 However, advanced imaging techniques have the potential to assist in certain circumstances. Where joint aspiration is not possible and other diagnostic features remain ambiguous, US, MRI and particularly DECT scanning may in some situations reveal tophi where they had not been suspected clinically. US may be useful in the early diagnosis of gout, to reveal MSU crystals coating cartilage or within synovial fluid but these findings derive from a limited number of centres of excellence and await confirmation from practicing clinicians and radiologists. Where gout damage needs to be monitored, all advanced modalities can reveal bone erosion much earlier than plain x-ray, and all have the potential to monitor the resolution of tophi following ULI. Thus, instead of imaging being a late indicator of gout in patients who have ‘missed the boat’ in terms of damage prevention, it can be a means to identify patients with early tophi and joint damage who can then be targeted for aggressive management.

**SUMMARY**

In summary, advanced imaging modalities including US, CT, DECT and MRI provide new ways to explore the pathology of gout and monitor responses to treatment. Which form of imaging to use depends on the clinical or research question being addressed. Thus, CT may be ideal to monitor tophus size in some research settings as it has the advantage of very clear delineation of the margins of erosions and tophi. MRI is already used widely to help diagnose complex clinical problems, where gout might for example be complicated by osteomyelitis. US could have a particular application in the measurement of erosions and tophi over time and its potential to assist with diagnosis of early gout has already been alluded to. DECT can provide highly site-specific information about urate deposition, and may be very helpful where there is diagnostic difficulty or the potential for dual pathology. It would not be advisable on current evidence to substitute imaging for joint aspiration in the diagnosis of gout, but this could be the case in the future and multimodality comparative studies are called for. What is indisputable is that high technology modern imaging in gout has taken a quantum leap forward in the last decade, improving our understanding of the underlying pathology of this ancient disease and allowing the development of more focused and targeted management strategies.

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<td>▶ New imaging modalities including CT, dual energy CT, MRI and ultrasound are all more sensitive than plain radiography in detecting early joint erosions in gout</td>
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<td>▶ All these imaging modalities can be used to detect tophi, and measure tophus size</td>
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<td>▶ The ultrasound double contour sign may be specific for gout but multimodality studies in patients with acute and chronic gout are required to confirm this</td>
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Review

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Multiple choice answers

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