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Review

Clinical utility of dual energy computed tomography in gout: current concepts and applications

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Summary. Gout is the most common inflammatory arthritis and is increasing in prevalence and incidence in many countries worldwide. Dual Energy Computed Tomography (DECT) has a high diagnostic accuracy in established gout, but its diagnostic sensitivity is low in subjects with recent-onset gout. A meta-analysis of 17 studies showed a pooled sensitivity and specificity of 0.85 and 0.88, respectively. DECT is a useful diagnostic tool for patients with contraindications for joint aspiration or for those who refuse joint aspiration. This article aims to give an up to date review and summary of existing literature on the role and accuracy of DECT in the imaging of gout. (www.actabiomedica.it)

Keywords: gout, dual-energy computed tomography, ultrasonography, imaging, diagnosis, tophaceous gout, non-tophaceous gout

Introduction

Gout is a common inflammatory form of arthritis that develops after a history of hyperuricemia and subsequent deposition of monosodium urate (MSU) crystals in joints and soft tissues (1). Overall, the prevalence in the Italian general population increased from 6.7 per 1000 inhabitants in 2005 to 9.1 per 1000 inhabitants in 2009, while the incidence was stable (respectively, 0.93 and 0.95 per 1000 person-years) (2). Clinical manifestations include acute arthritis (typically, first affecting the foot or the ankle), recurrent and chronic arthritis, tophi, bursitis, urolithiasis and renal disease. Tophaceous gout has been associated with relevant structural damage of joints and peri-articular tissues. In a recent international survey of more than 600 patients with gout, the presence of gouty tophi was associated with impairments to quality of life, productivity, and increased healthcare resource use (3). Gout is also associated with increased cardiovascular (CV) morbidity and mortality (4). Demonstrating MSU crystals in the joint fluid or an in tophus is the gold standard for gout diagnosis. However, many health care providers do not perform arthrocentesis and the identification of MSU crystals can be challenging, especially in early disease, since the treatment is distinctly different from that of other types of inflammatory arthritis. However, characteristic radiographic findings are only seen late

in the disease, including "punched-out" erosions with overhanging edges and sclerotic margins, often in association with asymmetric soft tissue masses (5). Various advanced imaging techniques are being utilized, including ultrasonography (US) with power Doppler, magnetic resonance imaging (MRI), and conventional computed tomography (CT).

CT, US and MRI are valuable diagnostic tools for the diagnosis and the guidance of interventional procedures in a wide range of organs (6-28).

Each has its unique advantages and disadvantages. However, none are specific enough to confirm a diagnosis of gout. Dual Energy Computed Tomography (DECT) is a relatively new imaging modality which shows great promise in the diagnosis of gout. It has been considered a good noninvasive alternative to the synovial fluid aspiration to detect MSU crystals. DECT has been reported to have higher sensitivity and specificity than the other techniques for gout diagnosis (29, 30), and is incorporated in the 2015 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria (31). In this article, we will review techniques in image acquisition, processing and interpretation, diagnostic value and clinical significance, pitfalls and artifacts of DECT, as a valuable and accurate imaging modality in patients with gout.

Basic principles of DECT

DECT or spectral imaging is a revolutionary imaging method, and its use has had an increase in the last decade in many clinical applications, such as in the field of neuroradiology and chest, cardiovascular, abdominal and musculoskeletal systems. Dual-source scanners are equipped with two independent X-ray tubes, coupled with two independent detectors; each set is mounted within the same gantry with an angular offset of about 90°. DECT data are acquired by the two tubes which operate at different voltages (70 kV and 150 kVp), allowing simultaneous acquisition of images at these two different energy levels. The use of two X-ray tubes makes it possible to extract information and characterizes the chemical composition of material, based on the different degrees of the X-ray beam, absorption and attenuation, according to the atomic weight electron density of the compounds. High atomic number materials, such as calcium, have a greater difference in attenuation when exposed to X-rays of two different energy levels.

In comparison, materials of lower atomic number such as MSU have a smaller difference in attenuation at different X-ray energy levels. This characteristic allows differentiating some substances such as iodine, calcium, uric acid crystals, gadolinium, and xenon. These compounds are then color-coded and displayed as an overlay on a standard DECT grayscale image, for a simultaneous display of anatomy and localization of urate deposits. Although color coding can vary between manufacturers, green is the most common color assigned to MSU crystals, lavender to cortical bone, and pink to trabecular bone (29). Dedicated software allows automated volume evaluation of urate deposition.

Clinical characteristics and DECT findings - a structural approach

Deposits of MSU crystals and tophi have been identified both adjacent to and within tendons and also at the tendon-bone interface using histology (32), US (33), CT (34), and DECT (35). Tophus infiltration into tendons has also been observed during surgery (36). A recent DECT analysis in the feet of patients with tophaceous gout has demonstrated that tendon involvement in gout is much more common than previously thought (Figure 1). In this study, 10.8 % of the tendon/ligament sites analyzed had MSU crystals present (35).

Diagnosing gout by DECT

ACR-EULAR gout classification criteria

In an attempt to achieve a more uniform system for reporting and comparing studies on gout, the ACR and the EULAR formulated criteria in 2015 for the classification of gout (31). The entry criterion for the new classification criteria is the occurrence of at least

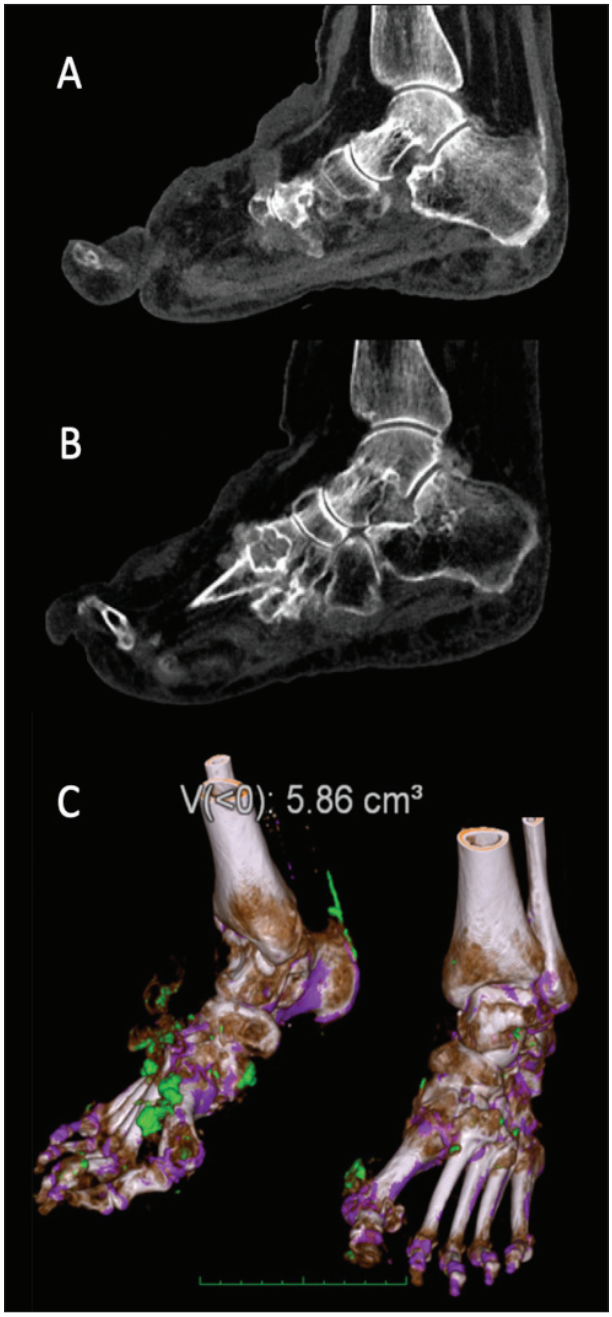

Figure 1. Dual-energy CT. A-B: sagittal multiplanar reformatted grayscale images of ankles/feet showing large bone erosions and severe joint damage at the tarso-metatarsal joints of both feet, with high-attenuating material adjacent to the erosions and along the distal end of the right Achilles tendon (A) representing monosodium urate deposition. C: corresponding volume-rendered color-coded dual-energy image of ankles/feet showing urate deposits (depicted in green) at the tarsometatarsal, metatarsophalangeal and interphalangeal joints and along the distal end of the right Achilles tendon. Automated quantification of urate volume is displayed at the top of the image.

one episode of peripheral joint or bursal swelling, pain, or tenderness. The presence of MSU crystals in synovial fluid (SF) of symptomatic joint/bursa or in a tophus is a sufficient criterion for classification of the subject as having gout and does not require further assessment. The new classification criteria include 4 clinical, 2 laboratories (serum urate and SF analysis) and 2 imaging (DECT OR US, and conventional radiography) criteria (31). The maximum possible score of the criteria is 23. A score of ≥8 classifies an individual as having gout.

Diagnostic accuracy of DECT in gout

The Outcomes Measures in Rheumatology (OMERACT) gout working group suggested that DECT is superior in the quantification of urate burden when compared to other modalities (37). A meta-analysis of 11 studies by Ogdie et al. (38) showed a pooled sensitivity of 0.87 (95% CI 0.79–0.93) and specificity of 0.84 (95% CI 0.75–0.90), compared with the reference standard of crystal identification by means of polarised light microscopy. More recently, Lee and Song performed a meta-analysis on the diagnostic accuracy of DECT in gout diagnosis. Of the eight studies analyzed, which included 510 patients and 268 controls, the pooled specificity and sensitivity of DECT were 93.7% and 84.7%, respectively. The authors concluded that DECT is highly accurate in the diagnosis of gout (30). In a prospective study by Choi et al. (39) investigating 40 crystal proven gout patients (17 tophaceous) and 40 controls with other arthritic conditions, the specificity and sensitivity of DECT for gout were 0.93 (95% CI 0.80– 0.98) and 0.78 (95% CI 0.62–0.89), respectively, with near-perfect inter- and intra-observer intraclass correlation coefficients for DECT volume measurements. In the present review, we pooled data from 17 studies and performed analyses to provide clinically more applicable data for clinicians; in person-based evaluations, the pooled (95% CI) sensitivity and specificity were 0.85 (0.70 to 0.90) and 0.88 (0.77 to 0.94), respectively. Details of the performance of the 17 included studies are presented in Figure 2.

DECT, generally, has good diagnostic accuracy in established gout and is regarded as a critical appliance to diagnose gout patients. However, DECT has lower

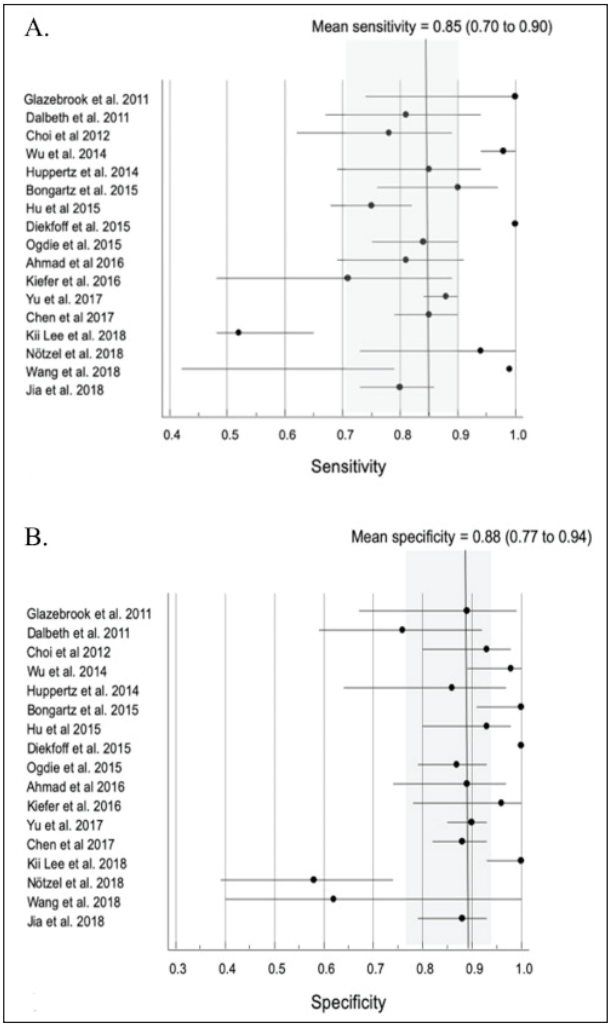

Figure 2. Sensitivity (A) and specificity (B) estimates for dual-energy computed tomography for the diagnosis of gout. Circles and lines represent point estimates and 95% confidence intervals, respectively.

sensitivity when restricted to individual crystal-proven gouty joints in non-tophaceous disease or in individual with short disease duration, especially in the first onset patients (40). The detection of MSU deposits by DECT depends on their size and density and the detection parameters of the DECT scanner (41). Several studies have reported that some patients with asymptomatic hyperuricemia have subclinical MSU crystal deposits. In a study of 25 patients with asymptomatic hyperuricemia (sUA ≥9 mg/dL), 24% had DECT-identified MSU crystal deposits in joints and tendons (42). In a cross-sectional study of 46 patients with asymptomatic hyperuricemia (sUA levels ≥6.5 mg/dL), 15% of patients with asymptomatic hyperuricemia had subclinical MSU crystal deposits on foot/ankle DECT scans (43).

Comparison between DECT and ultrasound in the diagnosis of gout

According to a recent systematic review, DECT and US have similar sensitivity and specificity in diagnosing gout in patients with crystal proven disease, being US more sensitive and DECT more specific (44). However, a comprehensive analysis aiming at comparing DECT with US in the diagnosis of gout should include not only their diagnostic accuracy in the detection of MSU crystal deposits, but also the main intrinsic properties and characteristics of these imaging techniques. Different diagnostic performances reported in the literature should be interpreted in the light of the following key aspects: standard reference for diagnosing gout (i.e., definitive diagnosis of gout fulfilling international criteria, MSU crystals identified using synovial fluid analysis); disease duration; and anatomic sites to scan (i.e., the clinically involved joints, a defined core set of the most frequently involved structures) (45, 46). In 2015, the OMERACT US working group finalized a process to obtain international consensus-based definitions on US elementary abnormalities indicative of MSU crystal deposition (i.e., double contour sign, tophi and aggregates) (47). Of note, double contour sign was included in the imaging domain of the ACR/EULAR gout classification criteria as sonographic evidence of urate deposition (31).

Moreover, US allows for the detection of not specific abnormalities, including synovial effusion, and helps to obtain synovial fluid to be assessed by polarized microscopy, improving the rate of successful aspirations guiding the needle to reach difficult targets such as small or deep fluid collections (48). These issues together with the US characteristics of being safe, not invasive, well accepted by patients, with low running costs, and increasingly available and portable, explain why several authors agree in considering US as a first-line imaging technique to screen the presence of MSU crystal deposition, especially in the early stages of the disease, and a suitable tool for monitoring changes in-

duced by urate-lowering therapy. However, despite the efforts of the OMERACT US working group a scoring system for the assessment of MSU crystal deposits is currently not available yet (49). Hence, US potential is underused in follow-up assessments and mainly based on the presence/absence of US findings.

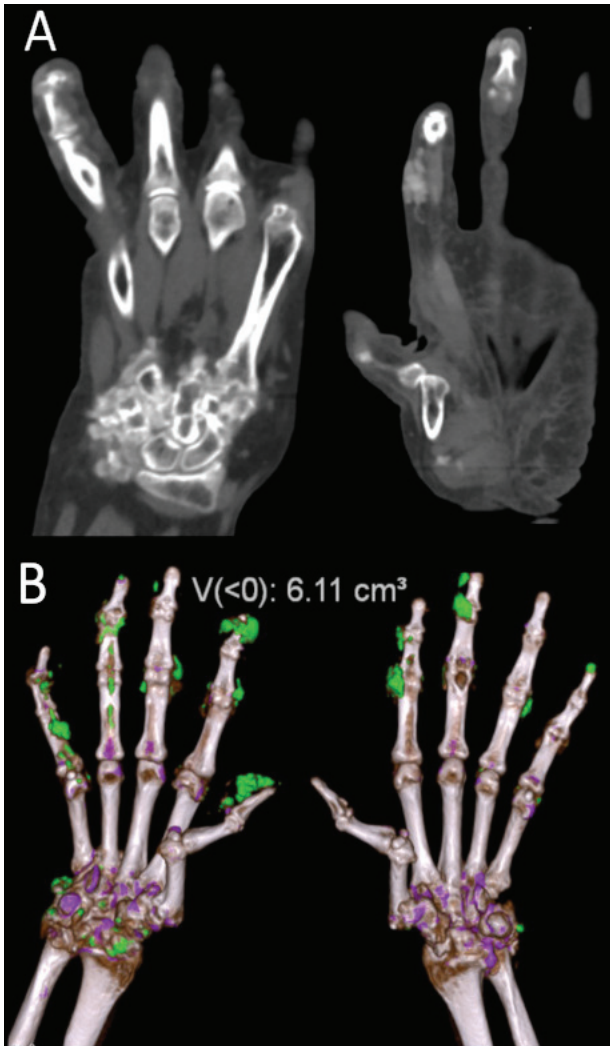

Figure 3. Dual-energy CT. A: coronal multiplanar reformatted grayscale images of hands/wrists showing bone erosions at left wrist and fingers of both hands, with high-attenuating material adjacent to the erosions and along the metacarpophalangeal and proximal and distal interphalangeal joints, indicative of monosodium urate deposits. B: corresponding volume-rendered color-coded dual-energy image of wrists/hands showing numerous urate deposits (depicted in green) along the metacarpophalangeal and proximal and distal interphalangeal joints and in the both wrists. Bilateral dislocation of first metacarpophalangeal joints can also be observed. Automated quantification of urate volume is displayed at the top of the image.

On the other hand, one of the advantages of DECT is to display the extent of the MSU crystal deposits in a single 3D image, which facilitates the estimation of their amount (Figure 3). Taking into account its high specificity, DECT should be used especially in cases with no clear diagnosis and in patients with high clinical suspicion and negative US findings (45).

Role of DECT in monitoring disease activity and damage – response to treatment

Beyond the clinical evaluation essential for all rheumatic diseases (50-58), imaging plays a fundamental role in the initial assessment and follow up of many pathologies in the musculoskeletal field and other organs (59-65).

DECT has shown to be of value in burden quantification and treatment monitoring and continues to be actively investigated in these roles. DECT also allows for the accurate and reproducible quantification of MSU deposits using automated software techniques (Figure 4), which calculates the volume of MSU deposits independent of the volume of hyperdense or calcified soft tissue. Furthermore, the quantitative software automation of DECT is valuable because visual analysis of

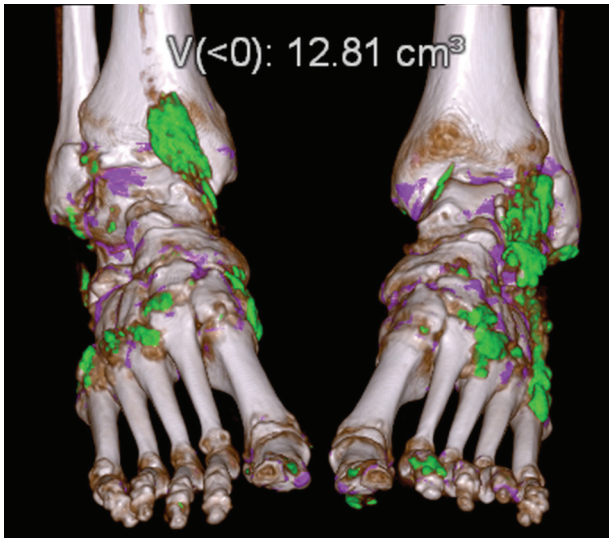

Figure 4. Dual-energy CT. Volume-rendered color-coded dual-energy image of ankles/feet showing urate deposits (depicted in green). Automated quantification of urate volume is displayed at the top of the image.

the gout burden after treatment may not discern small decreases in MSU crystal volume. This is helpful for follow-up imaging for assessing the reduction in volume of MSU deposits as a marker of treatment response in serial DECT scans without dependence on operator-defined margins of perceived tophi used in other methods of assessment. Overall, the level of evidence was low with one report of two randomized controlled trials, two non-randomized studies and 69 case series and reports. The review concluded that treatment with urate-lowering therapy including allopurinol and/or benzbromarone, febuxostat or pegloticase, can lead to a reduction in tophi. Finkenstaedt et al. (66) evaluated the diagnostic impact of DECT in patients with known hyperdense soft-tissue deposits on radiographs or conventional CT images, so patients with high suspicion for gout. This study showed that the therapy was changed in 23/43 (53%) of the patients, with a low incidence of gouty attacks in the following year. Dalbeth et al. (51) examined whether dose escalation of allopurinol to achieve serum urate target can influence bone erosion or MSU crystal deposition as measured by DECT in patients with gout. It provides evidence that long-term urate-lowering therapy using a treat to serum urate target strategy can influence structural damage and reduce urate crystal deposition. These findings are consistent with prospective studies conducted in gouty patients receiving urate-lowering therapy (31). Araujo et al. (67) investigated the effect of intensive lowering of serum uric acid (SUA) levels by pegloticase on the resolution of tophi in patients with refractory gout. In this paper, Araujo et al. described the ability of DECT to show the reduction of MSU deposits in responders. While DECT was superior for identifying total (including occult) urate deposition and assessing the volume of deposits, other modalities, such as Vernier calipers, photographs and musculoskeletal ultrasound, may permit better assessment of non-urate tophus components.

Pitfalls and problems in DECT

Interpretation of DECT in patients with suspicion of gout, particularly non-tophaceous gout, can be complicated by artifacts that are color-coded similar to MSU crystals, leading to false-positive results. False-positive color coding can be seen in nails, nailbeds, skin, callus, and vasculature. The most frequently reported artifact by far, is the nail bed artifact, which can be seen in 76% of imaged feet. Nail bed artifact may be due to the overlap of DECT values of MSU crystals and the keratinous nail bed. Skin artifacts may also be present in callused or thickened skin of the feet, such as the heel or toes, due to keratin content within these regions. Increased noise can also give rise to artifacts in the dual-energy data set. Urate-like pixellations in vascular calcification has also been described, although it remains unclear if this is due to real MSU deposition or an artifact. Urate deposition has been implicated as a factor in endothelial dysfunction in patients with gout and cardiovascular disease, but this has not been corroborated in necropsied cases so far. The sources of image noise are numerous, but two of the most common are using too low of an x-ray tube current or an inappropriate reconstruction algorithm. Patient motion during the scan can also result in image distortion and artifacts. Ensuring patient comfort and immobilization of the target anatomic site (e.g., via the use of taping or cradling devices) can help limit the occurrence of this artifact.

Conclusion

In conclusion, gout is becoming increasingly more relevant to properly identify and treat due to its association with metabolic syndrome. Various inflammatory arthritides such as pseudogout, rheumatoid arthritis, psoriatic arthritis, septic arthritis can mimic gout. DECT allows for highly accurate detection and quantification of MSU crystal deposits and should be implemented on a larger scale. This is especially true in all those situations where synovial fluid analysis is not feasible. However, several common artifacts can occur with DECT imaging. Knowledge of these artifacts is crucial for accurate qualitative and quantitative assessment of MSU crystals using DECT in patients with gout.

Conflict of interest: Authors declare that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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