Dual-energy computed tomography: a valid tool in the assessment of gout?

Gout is the most common inflammatory arthropathy worldwide and the most prevalent inflammatory arthropathy in males. One of the risk factors implicated in the rising prevalence of gout is metabolic syndrome. Gout itself is an independent risk factor for cardiovascular morbidity and mortality. Current imaging modalities for gout lack specificity and sensitivity, especially with atypical presentations. Dual-energy computed tomography (DECT) is a promising new tool for imaging monosodium urate deposits with a high degree of specificity and sensitivity. DECT has the ability to detect subclinical gout, potentially allowing early detection of urate tophi in asymptomatic hyperuricemic patients. DECT could potentially serve as a primary imaging modality in the diagnosis of gout and monitoring response to urate-lowering therapy.

KEYWORDS: crystal deposition arthropathy ■ dual-energy computed tomography ■ gout imaging

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Gout is the most common inflammatory arthropathy worldwide and arises from the crystallization of monosodium uric acid (MSU) within the joints. Currently in the USA alone, more than 8 million individuals over the age of 20 years are suffering from this disease [1]. Burden of disease for individuals suffering from gout continues to expand with the prevalence in the USA increasing by nearly 150% in the last decade [1]. Lifestyle factors, dietary choices and socioeconomic parameters have been proposed to explain these epidemiological observations [2]. Arguably, unhealthy dietary habits and sedentary lifestyle appear to be a major factor for the rise of gout in western countries. Choi *et al.* reported a 1.85 relative risk factor for incidence of gout in males consuming two or more sugar-sweetened soft drinks per day [3]. This is attributed to an increased production of uric acid in the liver as well as an attenuated renal uric acid clearance, both secondary to excessive fructose consumption. Sugar-sweetened soft drinks represent the single largest food source of calories in the US population [4,5], and their consumption have consistently increased over the last decades [4]. Moreover, obesity, hypertension and insulin resistance, which are all associated with the metabolic syndrome, are well-established independent risk factors for the incidence of gout. Hence, the increased prevalence of gout is partially a consequence of the rapidly increasing incidence of these comorbid conditions [2]. Moreover, hyperuricemia, often present in gout, is an alternate independent risk factor for stroke [6]. Lastly, gout itself has been recognized as an independent risk factor for cardiovascular morbidity and mortality [7]. Therefore, along with pharmacological and lifestyle changes, new techniques for early detection and treatment of gout will be necessary in managing this rising epidemic.

Many physicians rely on clinical presentation and elevated serum urate levels for the diagnosis of gout; this dependence may lead to misdiagnosis or a late diagnosis associated with irreversible anatomical damage. Elevated serum uric acid levels are present in 5–8% of the population but only 5–20% of individuals with hyperuricemia develop gout. Patients with hyperuricemia may not necessarily develop gout, and those with gout may have normal serum uric acid levels, particularly during acute gout attacks [8–10]. Higher degrees and longer durations of elevated urate levels can lead to greater severity of disease which is the impetus behind lowering urate levels in the treatment of gout.

Current standards of diagnosis

The gold standard for the diagnosis of gout is aspiration of the involved joint followed by polarized light microscopy of the aspirate demonstrating needle-shaped negatively birefringent MSU crystal [11]. Arthrocentesis may be technically challenging in a number of scenarios, including anatomically difficult-to-access joints such as the spine and sacroiliac joint, immunodeficient

Future Medicine part of fsg

patients with inadequate fluid volumes and severely inflamed joints. In addition, arthrocentesis is painful and carries risks of infection, hemorrhage and damage to involved tissues. Furthermore, samples retrieved by arthrocentesis require immediate analysis to conserve the technique's sensitivity and specificity, introducing practical limitations. Many nonspecialty healthcare professionals mainly rely on clinical assessment and the patient's response to treatment. As such, a noninvasive test to confirm the presence of MSU crystals would highly desirable.

Current imaging techniques used in the detection of gout include radiography, ultrasound, computed tomography and MRI [11–13]. Unfortunately, these techniques lack the specificity to facilitate and confirm the diagnosis of gout [12,14–16]. Classic osseous radiographic findings demonstrate well-defined 'punched out' periarticular erosions with overhanging edges, normal mineralization, relative preservation of the joint spaces and asymmetric eventual polyarticular distribution [11]. Such findings take several years to manifest after an acute attack implying these findings without urate deposits indicate osseous changes due to remote, currently inactive gout [17]. The presence of urate crystals with underlying bone erosions may indicate the presence of chronic gout.

Ultrasound identifies tophi as echogenic nodules that cast posterior acoustic shadowing, but such findings are nonspecific as rheumatoid, heberdens, bouchard and amyloid nodules have similar appearances [18]. Single-energy or single-source computed tomography is a nonspecific technique for identifying urate deposits. Gouty tophus can appear as round oval opacities that range from 150 to 200 Hounsfield unit (HU), and may overlap with the attenuation of calcium mineralization, making differentiation between the two difficult [19]. Calcium may present over a range of attenuations depending on density and composition of the deposit. In addition, dual-energy computed tomography (DECT) is able to differentiate between tophi of different composition, such as gout (MSU) and pseudogout (calcium). MRI is useful in assessing synovial inflammation during the early stages of the disease [20]. However, even though MRI may reveal additional information on the damage produced by tophi in adjacent tissues [21], urate tophi deposits are nonspecific on MRI and are shown as intermediate intensities on T1 and low-to-intermediate intensities on T2 and can enhance on post-gadolinium T1-weighted sequences [12].

Conventional imaging is only capable of visualizing late stages of the disease and findings often correspond with the presence of irreversible tissue damage. Subclinical or untreated recurrent gout attacks can lead to permanent joint destruction as well as tendon and ligament rupture. A cross-sectional, controlled study looked at ultrasound to detect structural changes in the joints and has shown evidence of uric acid deposits suggestive of gout in individuals with asymptomatic hyperuricemia [22]. Thus, early detection of subclinical disease could have implications in patients with asymptomatic hyperuricemia given the high frequency in the general population.

DECT: technical aspects

DECT, also known as spectral imaging, is a promising new imaging technique offering potential new applications in a number of clinical areas. DECT has been utilized in the characterization of urinary calculi and renal masses, myocardial perfusion for ischemia, vessel/bone separation and virtual noncontrast imaging. Spectral imaging relies on the concept that tissues with large differences in atomic weights will attenuate the spectral x-ray beam by different degrees. This differential change in attenuation of the kV spectrum allows one to separate molecular compounds based on their chemical composition, thereby directly visualizing the substrate of disease and confirming the presence of urate deposits in the assessment of gout. DECT has significant advantages over other modalities in that it has high sensitivity and potentially high specificity in confirming the presence of MSU deposits [23,24].

DECT scanners are equipped with two x-ray tubes to allow for simultaneous acquisition at two different energy levels (e.g., 80 and 140 kVp) [25]. The two-material decomposition algorithm applied after data acquisition is based on material-specific differences in attenuation between the high- and low-tube-voltage acquisition and allows for differentiation of the chemical composition of scanned tissues [26,27]. Material-specific differences depend on atomic number, electron density and absorption of the x-ray beam by different degrees with each compound having an assigned dual-energy index value. Dual-energy index values capture the difference in attenuation of materials between the low- and high-voltage levels. The greater the difference between dual-energy indices of materials, the better the separation and characterization. The advantage of DECT over single-energy threshold techniques for material separation is that the dual-energy index is independent of

density or concentration of the tissue. Therefore materials with a higher atomic number, such as calcium, will be easily distinguishable from materials, such as uric acid, formed from component elements of lower atomic numbers; moreover, the algorithm's performance can be improved by defining the energy index range of interest, eliminating computed tomography values outside of this range. Postprocessing software on a multimodality computed tomography workspace and the postprocessing of DECT data yields color-coded cross-sectional (Figure 1A) and 3D volumetric rendered technique (VRT) images (Figure 1B). At our institution, the scanning parameters for the dual-energy protocol in the assessment of gout are as follows [9]: 140 kV and 55 mAs for tube A, and 80 kV and 243 mAs for tube B. Collimation of 0.6 mm is reconstructed to 0.75 mm thickness. The base material is soft tissue and base values were chosen to be at 80 kV (50 HU) and at 140 kV (50 HU). Setting the parameter ratio to 1.36 and assigning the range of values between 150 and 500 HU have provided the best results.

DECT is unlike other existing imaging modalities with its ability to specifically identify urate depositions based on chemical composition [24]. DECT scans carry several other potential benefits over MRI including lower costs (approximately one-sixth), shorter scan time (approximately 15 min for all peripheral joints), simultaneous scanning of multiple joints, obvious color-differential display of crystals, and minimal influence of positioning [28] and higher inter-observer agreement [23].

Role of DECT in the diagnosis of gout

As DECT becomes increasingly available across institutions, it gains the potential to serve as a diagnostic and problem-solving tool capable of specific and accurate diagnosis of gout [29]. DECT can play a role in distinguishing gout from its close clinical 'mimickers'. In addition, DECT can detect asymptomatic as well as subclinical gout in patients without elevated serum urate levels, proving beneficial in the early diagnosis and management of gout [24]. Software processing of images obtained via DECT can undergo quantitative volumetric analysis to estimate the total urate burden. Early work has shown the potential of DECT in monitoring disease regression in response to treatment [30].

The use of DECT in detecting uric acid depositions in gout is one of the latest applications of spectral imaging in routine clinical practice. The application of DECT has extended into a noninvasive means for visualizing urate deposition around and within joints, in ligaments, tendons and bursas. In a study of 20 consecutive patients with aspiration-proven tophaceous gout, all had obvious color-coded evidence of urate deposition by DECT, while ten controls with other types of arthritis had no signs of urate deposition on volumetric analysis [28]. This study was expanded to 83 patients with clinically diagnosed gout, of

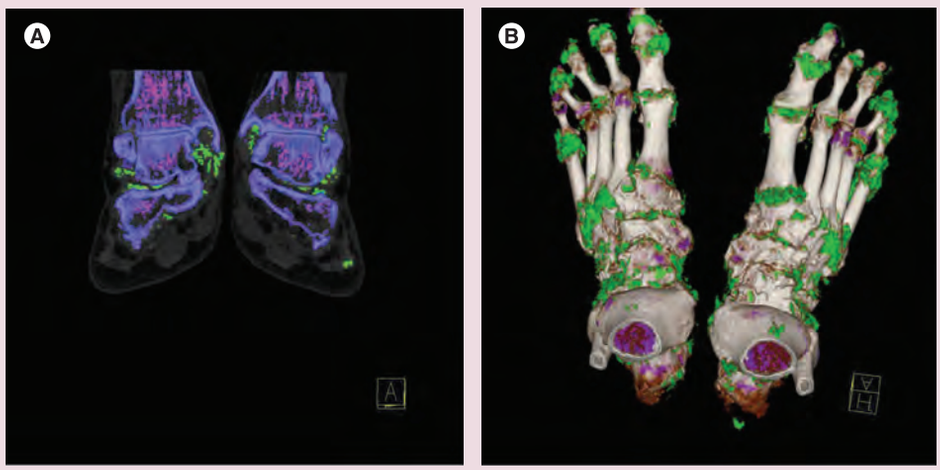

Figure 1. Gout of the ankle joints and feet demonstrated on dual-energy computed tomography. (A) Coronal multiplanar color-coded image of the ankle joints as viewed on the dual energy viewer. Green areas represent focal monosodium urate deposits, indicating extensive gout and consequent regional erosion in this 73-year-old male. **(B)** Volume rendering technique image of the feet in a 73-year-old male with extensive gout. Green color-coded regions represent focal monosodium urate deposits.

which 26 patients had aspiration-proven gout and 48 patients had clinically detectable tophi, with 19 control patients with clinically diagnosed nongouty arthritis (e.g., erosive osteoarthritis, rheumatoid arthritis and rheumatologic arthropathy) [31]. This study demonstrated 96.4% sensitivity in detecting urate deposits and 100% specificity; in other words, no erroneous urate deposits were identified in all 19 control patients. A recent retrospective study investigated the sensitivity and specificity of DECT in 94 patients suspected of having gout or presenting with arthralgia, using joint aspiration as a gold standard [23]; this study reported a sensitivity of 100% with a near perfect interobserver reliability, as well as a specificity of 79 and 89% for the two independent reading radiologists [23].

Our initial experiences revealed that DECT was four-times more efficacious in accurately delineating uric acid deposits when compared with a full rheumatologic assessment [9]. Subclinical gout was identified by DECT in many locations, with a strong affinity to the cruciate ligaments of the knee, which is difficult to examine clinically. Urate deposits accumulating in the knee can cause locking and simulate a torn meniscus and loose body. Spinal gout is also difficult to diagnose due to nonspecific appearance on conventional imaging and anatomical challenges making aspiration difficult [32]. A study at our institution looked at patients with clinically detectable tophi who underwent a DECT scan of the thoracolumbar spine [33]. Of the 17 patients they examined, 47% had axial MSU deposits and 23% had erosive changes in the spine. The most common location of MSU deposits was the lumbar spine, especially within disc spaces. It has been shown that radiological findings of axial gout are 14% more common than recognized on clinical exam [34]. Gout may initially be overlooked if it presents in unusual locations such as proximal appendicular or axial skeleton [34].

Illustrative clinical examples

The classical presentation of acute gout in males is a monoarthropathy in the distal appendicular skeleton and most commonly with involvement of the first metatarsophalangeal joint (podagra) [11]. Atypical presentations of gout may be mistaken for malignancy or infection. As a clinical example, a 74-year-old man with chronic lymphocytic leukemia presented at our emergency department with a 24 h history of progressively increasing pain and swelling of the second toe proximal interphalangeal joint with no history of fever [9]. Upon reviewing the radiographs, the differential diagnosis consisted of septic arthritis, osteomyelitis or malignant infiltrate. However, elevated serum uric acid levels raised the possibility of gout; DECT revealed gouty tophus at the site of interest and was later confirmed by joint aspiration. Another case illustrating the challenge of differentiating septic arthritis from gout was a 55-year-old patient presenting

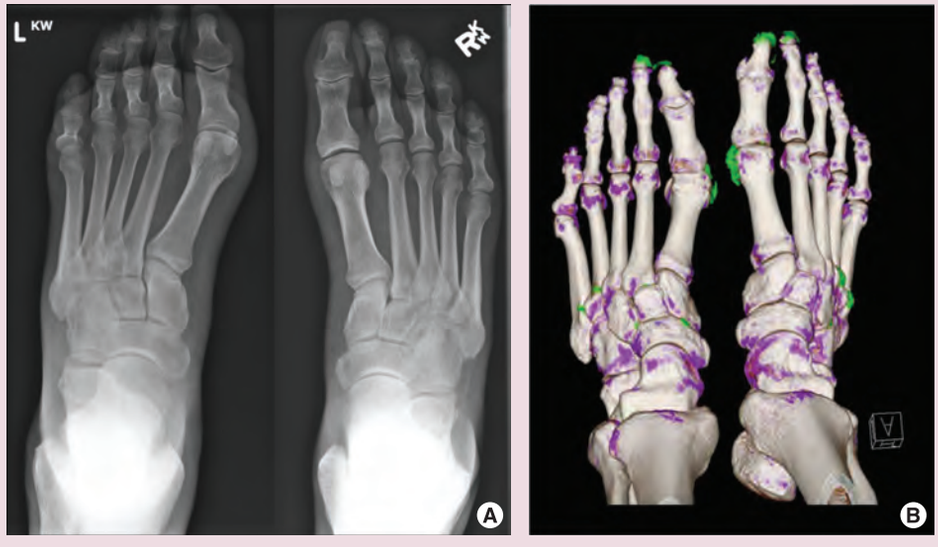

Figure 2. Gout of the ankle joints demonstrated on radiograph and dual-energy computed tomography. (A) A normal feet radiograph of a 30-year-old hyperuricemic female with a previous episode of inflammatory gout. **(B)** Dual-energy computed tomography volume rendered image of both feet in a 30-year-old female patient. Green regions are in keeping with prominent monosodium urate deposits along the metatarsophalangeal joints.

with a red inflamed swollen elbow and sudden onset of pain. The patient was on warfarin and aspiration of the joint was relatively contraindicated. Radiographs showed elbow effusion and computed tomography revealed slightly hyperattenuating foci in the joint. DECT imaging however illustrated urate deposits within the joint confirming the diagnosis. An illustrative case of subclinical gout is of a hyperuricemic 30-year-old female patient with a previous episode of inflammatory gout. This was supported with a normal radiograph of the feet which did not reveal any erosions, hyperattenuation or soft tissue swelling (Figure 2A). However, DECT examination showed prominent areas of MSU deposits along the metatarsophalangeal joints (Figure 2B), midfoot and knee.

Polyarthropathy form of gout is recognized as an unusual clinical presentation, most common among the elderly and women. DECT is useful in excluding urate depositions in nongouty arthropathy and has been used to distinguish gout from inflammatory gout mimics such as psoriasis, rheumatoid arthritis, pseudogout and pigmented villonodular synovitis [28]. As an example, a 48-year-old female presented with pain and locking of the left knee and was suspected to have pigmented villonodular synovitis. As illustrated in Figure 3A, MRI showed nonspecific low-signal material at the anterior aspects of the knee joint. Further investigations of the same patient with DECT confirmed the presence of urate deposits along the anterior aspect of the knee joint (Figure 3B).

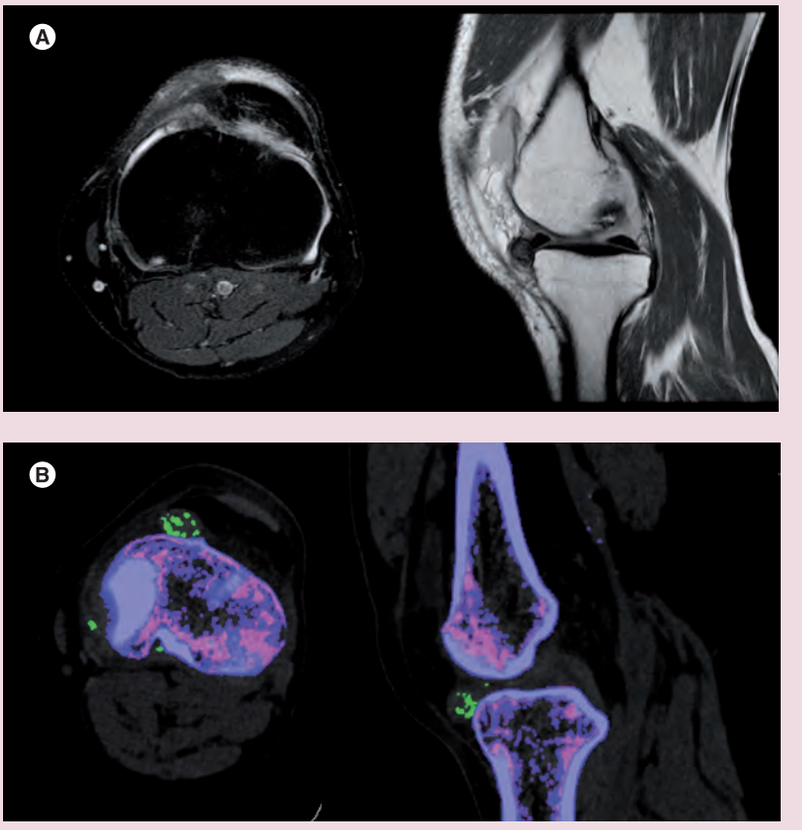

Figure 3. Correlation of gout of the knee on MRI and dual-energy computed tomography. A 48-year-old female presents with locking and pain in the left knee, query pigmented villonodular synovitis. **(A)** Axial fat-saturated proton density and sagittal T1-weighted MRI sequences of the left knee display nonspecific low-signal material at the anterior aspect of the knee joint. **(B)** Axial and sagittal two-material decomposition dual-energy computed tomography images of the left knee confirms the presence of monosodium uric acid tophi deposits along the anterior aspect of the knee joint.

Volumetric analysis of tophi

Volumetric quantification of urate volumes in patients with gout provides tophus quantification, and documentation of regression is an important outcome measure for disease monitoring and prevention of joint destruction. Conventional computed tomography and MRI can identify and quantify tophi, but require manual delineation of tophus margins for volumetric calculations [11,12]. Ultrasound detects both subcutaneous and intra-articular tophi but is operator-dependent and tophus measurements are usually limited to a few index lesions [16]. Automated volumetric quantification by DECT are sensitive and specific and without user variability [23,24]. This may potentially allow for DECT to evaluate small changes in tophus burden and document response to treatment for purposes of daily practice or clinical trials.

The potential for DECT to document changes in tophus volume in gout patients on urate-lowering therapy is shown in a study of 12 patients with tophaceous gout receiving urate-lowering therapy [30]. Initial and follow-up DECT scans were performed and demonstrated 67% reduction in tophus volume in ten responders to therapy. DECT volumetric quantification monitors urate burden of disease and may prove to be one of the most clinically efficacious applications of this tool in the management of gout. Outcome Measures in Rheumatology has proposed that tophus regression is validated as a core domain for outcome measures in chronic gout and since DECT-automated urate volume estimation allows for periodic quantification of tophi, it has the potential to be the primary assessment tool in the long-term management of chronic gout. The 3D volume-rendered color-coded images of urate deposits can visualize the extent of MSU deposits in tissues and could be motivational for patient compliance to therapy [24].

Limitations

Radiation is the primary risk of DECT and total radiation dose per patient ranges between 2 and 3 mSv [9]; this is similar to annual global per caput average dose due to natural radiation sources (2.4 mSv) and the regions examined are radioinsensitive to the deleterious effects from radiation [28]. Further, technical limitations of DECT in the assessment of gout are factors to be considered. Arguably, the application of DECT in gout is a newly evolving technique and despite the presence of a few ongoing clinical trials on the topic, most of the DECT literature published to date consists of yet to be validated case series. Due to the recent application of DECT for the investigation of gout, more work is needed to further validate this technique. In order for this imaging to be routinely implemented, specific reproducible protocols need to be established. Such protocols necessitate a discussion on optimized imaging settings selected to maximize the resolution of the software in identifying urate crystals and minimizing erroneous display of urate deposits, while maintaining high sensitivity and specificity. Artifacts can be seen in erroneous urate deposits along nail beds, calluses, streak/beam attenuating artifacts from increased noise, prosthesis and along the edge of bones. Artifacts need to be recognized as such, and be minimized by modifying the advanced parameters in the analytical software and choosing a dedicated reconstruction kernel at reducing beam attenuation artifacts. Last, DECT is still early in implementation and lacks a large worldwide installation base [35], further limiting its current application in the setting of gout.

Conclusion

DECT is a unique noninvasive imaging technique to accurately detect uric acid deposition. Its ability to visualize uric acid deposits may challenge the way we image and understand gout. DECT's ability to display the pathology of gout may be a tool to understand the pathophysiology of this disease. Early studies have shown a high sensitivity and specificity with DECT in detecting subclinical gout. Although further investigation is warranted, DECT may have a role in the early detection and management of gout. DECT facilitates diagnosing challenging cases of gout with atypical presentations or disease mimics and reduces unnecessary delay in diagnosis. Automated volumetric quantification has the potential to monitor disease progression and response to gout therapy.

Future perspective

DECT is a promising new modality that has the potential to innovate musculoskeletal imaging including imaging of the tendon/ligament meniscus, bone marrow edema, tumor iodine quantification, tumor angiogenesis and reducing artifacts from orthopedic prosthesis.

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Executive summary

- Gout is the most common inflammatory arthropathy worldwide and the prevalence is rising along with associated metabolic syndrome.
- Current imaging techniques used to confirm and monitor gout lack the specificity to facilitate the diagnosis of gout. Arthrocentesis can be technically challenging and impractical.
- Dual-energy computed tomography (DECT) is a unique noninvasive imaging technique to accurately detect uric acid deposition and may have a potentially high degree of specificity, sensitivity and inter-user agreement.

Perspectives

- DECT can be used to determine the degree of subclinical disease burden, accurately delineating the anatomic distribution of urate deposits.
- DECT as a problem-solving tool in identifying gout in clinically challenging cases.
- Automated volumetric quantification by DECT are sensitive and specific and without user variability and can be used to evaluate small changes in tophus burden and document response to treatment for purposes of daily practice or clinical trials.
- 3D volume-rendered color-coded images of urate deposits obtained with DECT can possibly improve communication for physicians and patients and potentially be motivational in maintaining compliance with their treatment.

Conclusion

- DECT is promising as a primary modality in the diagnosis and management of gout and demonstrates potential in new applications in the field of musculoskeletal imaging.

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