Investigation on monosodium urate deposition in the first metatarsophalangeal joint and ankle of primary gout patients using dual-energy computed tomography

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ABSTRACT

Background: Gout is caused by deposition of monosodium urate (MSU) crystals. One of the tools of choice to identify MSU crystals is the Dual-Energy Computed Tomography (DECT). This study aims to determine MSU crystal deposition using DECT by comparing its detection in the first metatarsophalangeal joints (MTPJ) with that in the ankles, as well as to analyse the association between the crystal deposition and anthropometrics, clinical characteristics, and serum biochemical levels of a primary gout patient.

Materials and Methods: This cross-sectional study included patients (n = 94) from the Clinic Hoa Hao Medic Medical Centre in Vietnam, who were diagnosed with primary gout with pain/swelling of at least one ankle or first MTPJ. DECT of both joints was used to identify MSU. Statistical analyses were performed using the Student's t-test, Wilcoxon rank-sum, Pearson's chi-square, and Spearman's tests.

Results: Approximately 80% had MSU crystal deposition in the ankle and/or first MTPJ with no significant difference in deposition between the two joints. MSU deposition was significantly associated with disease duration (p = 0.003), flare-ups (p = 0.006), and cut-off of 6 weeks' duration (p = 0.006), bone erosion (p = 0.006), and palpable tophi (p = 0.003). There was no association between MSU deposition with age, body mass index (BMI), hypertension, serum levels of uric acid (UA), creatinine, high-sensitive C-reactive protein (hsCRP), total cholesterol (C-total), and triglyceride (TG).

Conclusions: MSU deposition occurred in both ankle and first MTP at the same rate. The deposition was associated with disease duration and flare-ups. Prevention of flare-ups seems helpful to limit MSU crystal deposition.

KEYWORDS:
ankle, Dual-Energy Computed Tomography, metatarsophalangeal joint, monosodium urate, uric acid

INTRODUCTION

Gout, which is characterised by the deposition of monosodium urate (MSU) in the synovial fluid and other tissues as a result of a chronic increase in serum uric acid (UA), is the most common form of inflammatory arthritis. The deposition of MSU crystals in-and-around the joints can lead to inflammatory reactions with clinical symptoms of swelling and pain. Microscopic identification of MSU crystals in the fluid extracted from joints is considered a gold standard in diagnosis of gout. However, this procedure involves a risk of development of complications that can cause inconvenience to patients (e.g., intra-articular infection and pain). Moreover, MSU crystals may not be detected in acute cases. In such cases, additional clinical and investigative criteria are required.[1] In asymptomatic patients, MSU crystals can be first detected by imaging techniques, such as ultrasound or Dual-Energy Computed Tomography (DECT).[2]

There are known and accepted criteria for the diagnosis of gout, in which the gout classification criteria published by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2015 is being the most commonly used criteria to diagnose this disease.[1,3,4] The usual symptoms of gout include pain, swelling, and redness of the peripheral joints, most commonly the first metatarsophalangeal (MTP) joint. In most cases, the symptoms are associated with an elevated serum UA level. Unfortunately, these presentations can also be seen in other arthropathies. Moreover, normal UA levels can occasionally be observed in some cases of acute gout. Notably, a high UA level does not necessarily lead to MSU crystal deposition.[5,6]

DECT, also known as spectral imaging, was initially designed to detect UA deposition in kidneys (i.e., kidney stones), which has been validated both by *in vitro* and *in vivo* studies. DECT has since been successfully modified for use in musculoskeletal imaging with unique applications.[7]

In a dual-source, two X-ray sources run simultaneously at two kilovolt levels (80 kV and 140 kV), with two corresponding detectors. These provide two spiral data sets that are acquired simultaneously in a single scan.[8] A specific display algorithm assigns different colours to materials of different chemical composition. This includes detection of the elementary chemical composition of urate, allowing visualisation of MSU crystal deposition.[9]

A dual-source DECT scanner enables superior spectral contrast differentiation between urate and non-urate

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depositions. Compared to conventional single-energy scans, high-resolution images with excellent material separation may be obtained using dual-source DECT without increasing the radiation dose.[10] Dual-energy imaging easily allows for the separation and characterisation of calcium, a high-molecular-weight compound, from UA, a low-molecular-weight compound, thus making DECT an important non-invasive tool in the diagnosis of gout.[7,8,11]

MATERIALS AND METHODS

Patients and Control Subjects

This cross-sectional study was performed from April 2018 to July 2019. The protocol was approved by the respective ethics committees of the Hue University of Medicine and Pharmacy, the Hue Central Hospital, and the Clinic Hoa Hao, Medic Medical Centre. All participants provided informed consent.

Ninety-four adults were diagnosed with gout based on the ACR/EULAR gout classification criteria.[1] They presented with an acute attack of pain, swelling, redness, and tenderness in their ankle joint or their first MTPJ. Their condition was confirmed by clinical evaluation, ultrasound, X-ray, and haemato-biological investigations in order to exclude other arthropathies and related diseases. Patients with known malignancy, infectious disease, undergoing immunosuppressive therapy, or having a history of ankle or foot trauma were excluded from this study. All anthropometric indices, clinical signs, and characteristics of the disease, such as flare amount, disease duration, and tophi presentation, were recorded.

Blood samples were collected, after an overnight fast of at least 12 h, for routine blood chemistry and for measurement of haemoglobin (Hb), serum UA, high-sensitive C-reactive protein (hsCRP) and serum lipoprotein cholesterol levels. Patients with a blood pressure (BP) of >140/90 mmHg and/or on anti-hypertensive medication were considered as hypertensive.[12] Anaemia was defined according to the World Health Organisation criteria.[13]

Measurements and Calculations

The ankle joint and the first MTPJ of all patients were subjected to DECT for MSU crystal detection using a Toshiba Aquilion ONE 640 (Japan).

This dual-energy CT system is equipped with two x-ray tubes allowing simultaneous acquisition at two different energy levels and creation of two different data sets that are loaded into the post processing software on a multi-technique CT workspace. An image-based two-material decomposition algorithm of the datasets is subsequently performed to separate calcium from monosodium urate, using soft tissue as the baseline. The material-specific differences in attenuation between the high- and low-tube voltage acquisitions enable easy classification of the chemical composition of scanned tissue, thus allowing accurate and specific characterisation and separation of monosodium urate (color-coded in red) from calcium (color-coded in blue). These images then were interpreted by a senior imaging diagnostic physician to identify signs of MSU crystal deposition, erosion, and soft tissue inflammation.

Statistical Analysis

Continuous variables between group comparisons were analysed using an unpaired Student's t-test or the non-parametric Wilcoxon rank-sum test, as applicable. Dichotomised variables were compared using the Pearson's chi-square test. The null hypothesis was rejected at $p < 0.05$. Data are presented as mean ± standard deviation (SD) for variables with normal distribution, or as numbers and percentages wherever appropriate. A correlation analysis using Spearman's correlation was performed for continuous variables, while Fisher's exact test was used to analyse categorical variables. Statistical analysis was performed using SPSS software 18.0 for Windows.

RESULTS

Patient Characteristics

Patients (Table I) had a mean age of 48.1 ± 10.8 years, a BMI of 24.4 ± 2.8 kg/m^2, and a disease duration of 41.8 ± 31.8 months (minimum–maximum: 1–180 months). A tophus was detected in 23.4% of the patients. The proportion of patients that were subjected to DECT of the joints was 20.2% for the ankle, 21.3% for the first MTP, and 58.5% for both joints. The average serum UA concentration was 9.0 ± 2.2 mmol/L, which was considerably higher than the serum urate level defined by the ACR/EULAR 2015 criteria (0.36 mmol/L).1 In addition, the hsCRP concentration was higher (17.9 ± 25.5 mg/L) than the normal range (≤10 mg/L).[14]

DECT Data

The results from DECT showed that 79.8% of the patients had MSU crystal deposition in at least one of the ankles or the first MTPJ (Table II). There was no significant difference in MSU crystal deposition between the two joints ($p = 0.249$) and in the amount of simultaneous MSU crystal deposition in both the joints. Among the patients with positive DECT, 62.7% showed simultaneous sedimentation in both the joints, with a significant difference compared to patients that were negative ($p < 0.001$).

The relationship between the presence of MSU crystal deposition and demographics, clinical characteristics, gout features, and biochemical levels (Table III) showed that flare-ups ($p = 0.006$), disease duration ($p = 0.003$) with cut-off at 6 weeks ($p = 0.006$), bone erosion ($p = 0.006$), and tophi presence ($p = 0.003$) were associated with a positive DECT.

DISCUSSION

DECT was validated as a tool to confirm the presence of MSU crystal deposits in the assessment of gout because of its non-invasive nature and high specificity.[2,7]

In our study, the proportion of patients that were subjected to DECT of the joints was 20.2% for the ankle, 21.3% for the first MTP, and 58.5% for both joints. A study by Bongartz et al. (2015) including 40 patients with active gout and 41 patients with other types of joint disease surveyed gout patients using DECT in one of four groups of joints – wrist, elbow, pillow, or ankle/foot.[2] In a study by Ahmad et al. with 90 patients suspected of having gout, DECT was performed on two groups of ankle joints and two lateral knees.[15]

Table I: Clinical data of patients with gout disease

Parameter		Patients with gout
No.patients		94
Age (years)		48.08±10.77
BMI (kg/m^2)		24.41±2.83
Minimum/maximum duration (months)		1/180
Number of flare-ups		7.68±4.80
Systolic blood pressure (mmHg)		107.28±20.61
Diastolic blood pressure (mmHg)		74.24±17.42
Tophi n (%)		22 (23.40)
Joint n (%)	Ankle	19 (20.21)
	First MTPJ	20 (21.27)
	Both	55 (58.51)
UA (mmol/l)		9.04±2.23
Creatinine (μmol/l)		98.65±28.62
Total cholesterol (mmol/l)		5.52±1.22
Triglyceride (mmol/l)		3.36±2.37
hsCRP (mg/l)		17.86±25.52

BMI, body mass index; DECT, Dual-Energy Computed Tomography; hsCRP, high-sensitivity C-reactive protein; MTPJ, metatarsophalangeal joint; UA, uric acid

Table II: Monosodium urate (MSU) deposition in joints

Joint	DECT				p-value
	Negative		Positive		
	n	%	n	%	
Ankle	5	26.3	14	18.7	0.249†
First MTPJ	6	31.6	14	18.7	
Both	8	42.1	47	62.7	
All	19	20.2	75	79.8	<0.001

† Fisher's exact test

DECT, Dual-Energy Computed Tomography; MTPJ, metatarsophalangeal joint

Table III: Relationship between monosodium urate (MSU) deposition, demographics, clinical characteristics and biochemical levels

Variable	DECT positive (n=75)	DECT negative (n-19)	p-value
Age (years)	49.01±10.707	44.42±10.543	0.097
BMI (kg/m2)	24.31±2.884	24.74±2.725	0.571
Flare-ups (n)	8.36±4.884	5.00±3.999	0.006
Flare-up duration, n (%)			
<6 weeks	1(1.30)	4(21.10)	0.006*†
≥6 weeks	74(98.70)	15(78.90)	
Disease duration (weeks)	188.37±145.359	84.21±64.999	0.003
Hypertension, n (%)	14(18.70)	2(10.50)	0.512
Bone erosion, n (%)	20(26.70)	0(0.0)	0.010†
Tophi, n (%)	22(23.4)	0(0.0)	0.003†
Serum UA (mmol/L)	8.93±2.268	9.47±2.091	0.349
Creatinine (μmol/L)	102.52±62.958	78.47±39.448	0.117
Total cholesterol (mmol/L)	5.43±1.243	5.89±1.100	0.138
Triglyceride (mmol/L)	3.21±2.303	3.95±2.614	0.230
hsCRP (mg/L)	19.36±27.681	11.95±12.981	0.260

* Between <6 weeks and ≥6 weeks

† Fisher's exact test

BMI, body mass index; DECT, Dual-Energy Computed Tomography; hsCRP, high-sensitivity C-reactive protein; UA, uric acid

In our study, 79.8% of the joints analysed by DECT were positive for MSU crystal deposition, with no significant differences of MSU crystal deposition rate between the two examined joints. This indicates that neither joint had a priority in MSU disposition (Table II).

Although all of the patients in the current study had different regimes for gout, they had high serum UA concentration (9.0 ± 2.2 mmol/L) and inflammatory responses were significant as indicated by hsCRP levels (Table I). It may be explained that these patients did not follow up strictly therapy for gout leading to changes in UA level and hsCRP level.

A positive correlation was observed between duration of gout and MSU deposition (p = 0.003). This association was recorded at a cut-off of 6 weeks (p = 0.006). Number of positive DECT was more at patients with 8.36 ± 4.884 of flares to those with 5.00 ± 3.999 (Table III). This result is in line with current clinical concepts that gout is characterised by deposition of MSU in synovial fluid and other tissues as a result of a long-term increase in serum UA levels.[16] Flares of gout caused by inflammatory responses are associated with the deposition of MSU in joints and periarticular tissues.[17] Therapies controlling flares should aim to decrease deposition of MSU at that sites.

Our study included 5 patients with gout <6 weeks, wherein deposition of MSU was not detected in 4 patients (80%) subjected to DECT. In patients with gout of 6 weeks or more, 81.3% had MSU crystal deposition. Our study was unable to evaluate the sensitivity and specificity of DECT in detecting MSU deposition in gout patients. However, the study by Bongartz et al. determined the sensitivity and specificity of DECT to be 0.90 (95% CI: 0.76–0.97) and 0.83 (95% CI: 0.68–0.93), respectively. A recent meta-analysis by Ogdie et al. demonstrated a pooled sensitivity of 0.87 (0.79–0.93) and specificity of 0.84 (0.75–0.90).18 It was concluded that, in fact, DECT was capable of detecting UA deposition with good sensitivity and high specificity.[11]

Our study showed no correlation between detection of MSU crystals on DECT and UA concentration. This may be due to the possible effect of treatment regimens on UA levels, and changes in the patient's clinical presentation of gout as a result. This was consistent with the results showing that DECT correlated with the presence of bone erosion markers and tophi particles (p < 0.01 for both) (Table III).

Similarly, the study of Svensson et al. on 55 patients with new or established gout, as well as the study of Dalbeth et al. on 152 gout patients treated with allopurinol also revealed an association between positive DECT with bone erosion and presence of tophi.[19,20] However, in the latter study, UA concentration was >35.69 mmol/L, which was much higher than the concentration estimated in our study.

The study by Ahmad et al. on 90 gout patients to evaluate the sensitivity and specificity of DECT for diagnosing gout compared to a composite gold standard including joint aspiration and/or the American College of Rheumatology clinico-radiographic criteria showed that DECT had a sensitivity and specificity of 82 and 89%, respectively. Compared to radiographs and non-contrast computed tomography (NCCT), the sensitivity and specificity with aspiration as a reference (n = 55) was not significantly different than the CGS. However, DECT showed a higher sensitivity of 100% (95% CI: 86–100%) and a lower specificity of 48% (95% CI: 28–68%) with aspiration alone. Thus, DECT was able to diagnose several cases of gout which would have been missed by radiographs and NCCT.[15]

Our study found no association between positive DECT and BMI, serum creatinine concentration, or serum total cholesterol (C-total) and triglyceride (TG) concentration.

Various studies have reported obesity as a risk factor for gout. A recently published meta-analysis data showed that obese people had a relative risk (RR) of 2.06–4.30 for gout, depending on each study. This analysis also showed that the association of hypertension to gout varied in terms of RR in different studies. However, there was no data regarding the association of obesity and hypertension with MSU deposition in this meta-analysis.[21] A meta-analysis of Evans et al. showed that subjects with a BMI ≥ 30 kg/m^2 had a risk of gout that was 2.14 higher than the rest of the study population.[11] However, in our study, most of the patients were not obese (BMI < 30 kg/m^2), and this index was probably negatively impacted by its association with MSU deposition in the joints.

CONCLUSION

MSU crystal deposition between the ankles and first MTPJ did not show differences in the patients analysed in the current study. The longer the duration of gout in the patients, greater was the likelihood of MSU deposition in the joints as detected by DECT. Such deposition was also related to the number of flares. Therefore, prevention from flare-ups seems one of ways to limit MSU deposition. There was no association between detection of MSU deposition and age, BMI, and serum concentrations of UA, creatinine, C-total, and TG.

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