

# Identification of monosodium urate crystal deposits in patients with asymptomatic hyperuricemia using dual-energy CT

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## ABSTRACT

**Objectives** Dual-energy CT (DECT) scan is a sensitive and specific tool used to visualise and quantify monosodium urate (MSU) crystal deposits in the joints. Few studies have examined MSU crystal deposits in patients with asymptomatic hyperuricemia (ie, hyperuricemia in the absence of gout) using DECT.

**Methods** We conducted a prospective, non-interventional cross-sectional study to detect MSU crystal deposits on DECT scans among patients with asymptomatic hyperuricemia. We also examined patient factors associated with subclinical MSU crystal deposits. Out of 130 subjects aged  $\geq 40$  years with metabolic syndrome screened for serum uric acid (sUA) levels  $\geq 6.5$  mg/dL, 46 underwent a foot/ankle DECT scan.

**Results** The mean age of the study participants was 62 ( $\pm 8$ ) years, 41% were men and the mean sUA level was 7.8 ( $\pm 1.0$ ) mg/dL. Seven (15%) of 46 patients had MSU crystal deposits on DECT with a mean total volume of 0.13 ( $\pm 0.14$ ) cm<sup>3</sup>. In the univariable logistic regression analysis, older age had a significant association with presence of MSU crystal deposits (OR 1.20, 95% CI 1.03 to 1.39), but sUA did not (OR 1.36, 95% CI 0.63 to 2.95). In the univariable analysis, sUA levels showed a trend towards a modest linear association ( $\beta=0.11$ ,  $P=0.09$ ) with total volume of MSU crystal deposits.

**Conclusions** Fifteen per cent of patients with asymptomatic hyperuricemia had subclinical MSU crystal deposits on foot/ankle DECT scans. Older age, but not sUA, was significantly associated with presence of subclinical MSU crystal deposits among patients with asymptomatic hyperuricemia. Clinical significance of these subclinical MSU crystal deposits needs to be determined.

## INTRODUCTION

Hyperuricemia is common affecting over 21% of adults in the USA between 2007 and 2008.<sup>1</sup> Elevated levels of serum uric acid (sUA) greater than 6.8 mg/dL (410  $\mu$ mol/L) can cause crystallisation of monosodium urate (MSU) crystal deposits and eventually trigger gout in some patients.<sup>2,3</sup> While hyperuricemia

## Key messages

### What is already known about this subject?

- Dual-energy CT (DECT) is a reliable imaging tool to detect monosodium urate (MSU) crystal deposits in patients with gout.

### What does this study add?

- In this study of patients with asymptomatic hyperuricemia, we found 15% with MSU crystal deposits identified with a DECT scan of the foot.

### How might this impact on clinical practice?

- Some patients with asymptomatic hyperuricemia may already have MSU crystal deposits in their joints. Clinical significance of subclinical MSU crystal deposits needs to be further studied.

is a known cause of gout, many patients with hyperuricemia do not develop gout. To date, it is not fully understood why and when some patients with asymptomatic hyperuricemia (ie, hyperuricemia in the absence of gout) develop gout.

For many decades, the gold standard for the diagnosis of gout has been the identification of MSU crystal deposits in the synovial fluid of the affected joint using polarised light microscopy.<sup>4,5</sup> Given the limitations of joint aspiration and use of polarised microscopy, alternative strategies for diagnosing gout have been developed, including dual-energy CT (DECT).<sup>6</sup> Non-contrast DECT is an imaging tool with high sensitivity and specificity for detecting MSU crystal deposits in patients with suspected gout compared with synovial fluid analysis for MSU crystal deposits under a polarised microscope.<sup>6-11</sup> DECT scanning is quick, non-invasive and allows for the imaging of more than one joint in a single scan.<sup>12</sup> Furthermore, the DECT



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post-processing software program can quantify the total MSU crystal deposit volume identified within the entire region of interest, whereas polarised light microscopy is dependent on the skills and experience of the clinician performing the aspiration as well as the quality and availability of the microscopy equipment.<sup>5 11</sup>

Several studies have reported that some patients with asymptomatic hyperuricemia have subclinical MSU crystal deposits.<sup>7 13</sup> In a study of 25 patients with asymptomatic hyperuricemia (sUA  $\geq 9$  mg/dL or 540  $\mu$ mol/L), 24% had DECT-identified MSU crystal deposits in joints and tendons.<sup>7</sup> However, it remains unclear what factors affect the presence of subclinical MSU crystal deposits in patients with asymptomatic hyperuricemia. The objective of this prospective, non-interventional, cross-sectional study was to examine the presence of MSU crystal deposits on foot/ankle DECT scans among patients with asymptomatic hyperuricemia and to determine clinical factors associated with MSU crystal deposits.

## METHODS

### Study cohort

We conducted a prospective, non-interventional, cross-sectional study to determine the presence of MSU crystal deposits in the foot/ankle using DECT technology among patients with asymptomatic hyperuricemia. The inclusion criteria were (1) adults aged  $\geq 40$  years, (2) sUA levels  $\geq 6.5$  mg/dL and (3) presence of metabolic syndrome. We required patients to have metabolic syndrome as patients with metabolic syndrome tend to have high sUA levels.<sup>14</sup> We defined metabolic syndrome based on the National Cholesterol Education Program—Adult Treatment Panel III criteria, which required to have three out of the following criteria: abdominal obesity, triglycerides  $>150$  mg/dL, high-density lipoprotein  $<40$  mg/dL, hypertension or taking antihypertensive medications, and fasting blood glucose  $>100$  mg/dL.<sup>15 16</sup> In this study, we used body mass index (BMI)  $>29.4$  kg/m<sup>2</sup> instead of waist circumference for abdominal obesity because BMI values were readily available as vitals taken from routine visits in the medical records. Prior research showed that a waist circumference of 102 cm corresponded with a BMI of 29.4 kg/m<sup>2</sup>, thus allowing us to use BMI as one of the criteria to determine metabolic syndrome.<sup>17</sup> We excluded patients with gout, nephrolithiasis, urolithiasis, HIV, hepatitis B or C, malignancy, chemotherapy, end-stage renal disease, renal replacement therapy (dialysis/transplant), type 1 diabetes or weight  $\geq 450$  lbs. We also excluded patients who used xanthine oxidase inhibitors, colchicine or probenecid. Pregnant women or women of childbearing potential who were not willing to use effective birth control methods were not eligible for the study. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital.

### Patient recruitment

Patients were primarily recruited from the Partners Healthcare Biobank (<https://biobank.partners.org>), the Brigham and Women's Hospital (BWH) Arthritis Centre or the BWH Endocrinology clinic. With the permission of several participating physicians, we reviewed medical records of potentially eligible patients for the inclusion and exclusion criteria. Patients who met study criteria via reviewing their medical records were contacted via letter and then via phone or in person while waiting for their scheduled clinic visits. After obtaining an informed consent for the participation in this study, patients further confirmed their study eligibility through a structured pre-screening visit reviewing the aforementioned inclusion and exclusion criteria in person. Those who met all the inclusion and exclusion criteria had a screening visit in which their sUA was measured by enzymatic colorimetric assay, unless they had a sUA value  $\geq 6.5$  mg/dL in their medical record from within the last year. We chose this threshold to maximise the likelihood of finding patients with a wide range of asymptomatic hyperuricemia. A board-certified rheumatologist (SCK or DHS) examined both feet/ankles for any sign of undiagnosed gout.

### Study visit for DECT imaging

We collected information on patients' demographics, current medication use and comorbidities. These patients underwent a non-contrast DECT scan of their right foot and ankle (unless the right foot had any surgical hardware), using a dual-source CT scanner (SOMATOM Definition Flash; Siemens Medical Systems, Forchheim, Germany) using both 80 kV and 140 kV tube potentials simultaneously. Technical features included slice thickness of 0.6 mm, field of view 120 and slice interval of 0.3 mm. Dual-energy analysis technical factors included a dual-energy ratio of 1.36 and resolution range of 3. Bone and soft tissue window algorithm images were obtained in the axial plane with additional sagittal and coronal reconstructed images. The raw CT images allowed for evaluation of the presence of abnormal erosions, soft tissue mineralisation or soft-tissue swelling (online supplementary figure 1A). The use of a different kilovoltage for each tube exploited the kilovoltage-dependent nature of CT numbers, allowing spectral differentiation of materials having differing atomic numbers to be visible on the post-processed images. Post-processing of the CT images was performed by the musculoskeletal radiologist using a commercial software program (*syngo.via*, CT Workplace; Siemens Medical Systems) using the gout platform to create both 2D (axial, sagittal and coronal) and 3D volume rendered images, where MSU crystal deposits were colour-coded as green (online supplementary figure 1B,C). This software is known to have high specificity and sensitivity  $\geq 89\%$ .<sup>11 18 19</sup> The settings for the tissue decomposition algorithm in *syngo.via* (Multi-Modality Workspace; Siemens Medical) are as follows: The gout protocol included the following material/

tissue definitions: for the low energy (80 kV), soft tissue was set at 50 HU with soft tissue at the high energy (140 kV) set at 50 HU with the ratio for urate set at 1.36. The minimum HU was set at 150 and maximum at 500 HU, with a resolution of 3, an air distance ratio of 5 and bone distance of 10.

Green colour-coded deposition within toenails (due to keratin), a known artefact on DECT using the gout platform, was noted if present and excluded. The overall volume of green colour-coded gout deposition within the foot was automatically calculated and displayed on the final post-processed 3D volume rendered images (online supplementary figure 1C). Through this process, only sufficient aggregates of MSU crystal deposits were detected in the images collected. In addition to sUA level, patients also had high-sensitivity C reactive protein (CRP) and serum creatinine levels measured.

### Statistical analysis

We used descriptive statistics to characterise the study cohort. We used univariable logistic regression to assess the association between sUA levels, other clinical factors and the presence of MSU crystal deposits (yes/no). We further examined the association between clinical factors and the presence of MSU crystal deposits after adjusting for sUA levels. We performed univariable linear regression to examine the association between sUA and total volume of MSU crystal deposits. Due to the small number of patients with MSU crystal deposits, no further multivariable analyses were performed. We used SAS V.9.4 Statistical Software (SAS Institute, Cary, North Carolina, USA) for all analyses.

### RESULTS

A total of 131 patients were consented into the study and one patient did not complete the screening blood draw. Among the 130 patients aged  $\geq 40$  years screened for asymptomatic hyperuricemia, 46 (35.4%) had sUA levels  $\geq 6.5$  mg/dL and underwent a foot/ankle DECT scan. The range of sUA levels was 6.5 mg/dL to 14.4 mg/dL for these 46 patients. The mean age was 62 ( $\pm 8$ ) years, 41% were men and the mean sUA level was 7.8 ( $\pm 1.0$ )

mg/dL (table 1). The mean high-sensitivity CRP level was 8.7 ( $\pm 14.7$ ) mg/L. Seven (15%) of 46 patients had positive DECT results with MSU crystal deposits in the first metatarsophalangeal joint as well as other parts of the feet. Their sUA levels range from 6.6 mg/dL to 9.1 mg/dL. Among patients with MSU crystal deposits, the mean total volume of MSU crystal deposits was 0.13 ( $\pm 0.14$ )  $\text{cm}^3$ .

Seven patients (15%) had abnormal green colour-coded material on DECT evaluation with 6/7 (85%) demonstrating MSU crystal deposits adjacent to the first metatarsal head or neck as follows: two patients with deposition volar to the metatarsal head with additional deposition at the adjacent first intermetatarsal interspace, two patients with deposits at the medial aspect of the first metatarsal head and two patients with minimal deposition along the first and second metatarsal head/neck junctions. The last patient demonstrated a small foci at the plantar fascial attachment on the calcaneus.

Univariable analysis showed that elevated sUA levels had numerically, not statistically significantly, elevated odds of having DECT-positive MSU crystal deposits (OR 1.36, 95% CI 0.63 to 2.95). Older age was positively associated with the presence of MSU crystal deposits on DECT. However, other patient characteristics including sex, body mass index, presence of diabetes and renal function were not (table 1). Even after adjusting for sUA level, older age remained significantly associated with the presence of MSU crystal deposits (OR 1.21, 95% CI 1.03 to 1.41). Among the seven patients with DECT-positive MSU crystal deposits, their sUA levels had a modest linear association ( $\beta$  coefficient=0.11,  $P=0.09$ ), although statistically not significant, with total volume of MSU crystal deposits (figure 1).

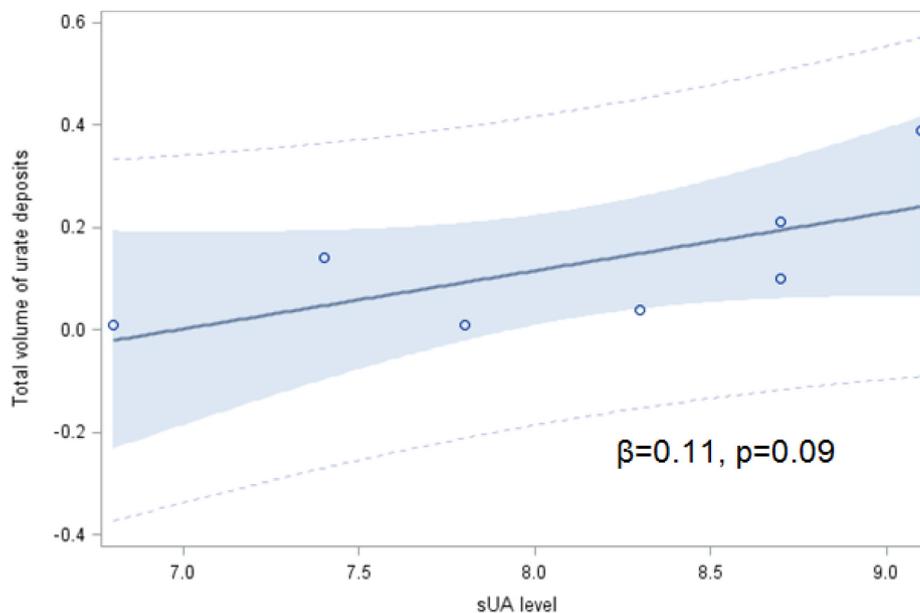
### DISCUSSION

In this cross-sectional study of 46 patients with asymptomatic hyperuricemia (sUA levels  $\geq 6.5$  mg/dL), 7 (15%) patients were noted to have MSU crystal deposits in the foot/ankle DECT scan. In line with previous research, our study supports that some patients with

**Table 1** Association between patient characteristics and presence or absence of MSU crystal deposits on DECT scans among patients with asymptomatic hyperuricemia (n=46)

Patient characteristics	Mean $\pm$ SD or %	Univariable OR (95% CI)	sUA-adjusted OR (95% CI)
sUA, mg/dL	7.8 $\pm$ 1.0	1.36 (0.63 to 2.95)	–
Age, years	62 $\pm$ 8	1.20 (1.03 to 1.39)	1.21 (1.03 to 1.41)
Male sex	41%	1.08 (0.21 to 5.49)	1.06 (0.21 to 5.47)
Body mass index, $\text{kg}/\text{m}^2$	36.4 $\pm$ 6.3	0.97 (0.85 to 1.11)	0.94 (0.81 to 1.10)
Type 2 diabetes	54%	0.97 (0.19 to 4.93)	0.87 (0.16 to 4.62)
Serum creatinine, mg/dL	1.04 $\pm$ 0.3	0.92 (0.08 to 11.19)	0.62 (0.05 to 8.53)
hs-CRP, mg/L	8.7 $\pm$ 14.7	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)

DECT, dual-energy CT; hs-CRP, high-sensitivity C reactive protein; MSU, monosodium urate; sUA, serum uric acid.



**Figure 1** Linear regression to examine the association between serum uric acid (sUA) level (mg/dL) and total volume of monosodium urate crystal deposits (cm<sup>3</sup>) measured with dual-energy CT (n=7).

asymptomatic hyperuricemia (ie, in the absence of gout) have MSU crystal deposits on the DECT scan.<sup>7</sup> While high sUA level is a strong risk factor for gout, our study did not find a significant association between sUA level and subclinical MSU crystal deposits among patients with mild-to-moderate asymptomatic hyperuricemia. However, we noted that age was significantly associated with presence of MSU crystal deposits on DECT in these patients. Furthermore, among patients with MSU crystal deposits on DECT scans, there was a trend towards a modest linear association between sUA levels and total volumes of MSU crystal deposits.

To date, it remains unclear why some patients with high sUA levels develop MSU crystal deposits and subsequent gout while others with the same sUA levels do not. There is no doubt that high sUA levels are required to form MSU crystal deposits that can lead to the development of gout. However, sUA levels alone do not fully predict the presence of MSU crystal deposits or the risk of developing gout. Among the male subjects enrolled in the Normative Ageing Study, the 5-year cumulative incidence rate for gout was 22% of the population with sUA levels above 9.0 mg/dL (540  $\mu$ mol/L) while it was only 3% among those with sUA levels between 7.0 and 8.9 mg/dL.<sup>3</sup> In a previous DECT study, only 24% within a population of 25 patients with asymptomatic hyperuricemia (mean sUA of 9.8 mg/dL) had any MSU crystal deposits, whereas 82% of 33 patients with gout with a lower mean sUA level (7.2 mg/dL) had MSU crystal deposits.<sup>7</sup> These results suggested that sUA levels were not the only cause of MSU crystal deposition that eventually leads to the onset of gout.

These studies of patients with asymptomatic hyperuricemia including our study strongly support that there are other factors that cause MSU crystallisation

in the body besides high sUA levels, such as a change in the body's pH or temperature or a genetic predisposition.<sup>20</sup> In this study, older age in a univariable analysis and a bivariable analysis adjusting for sUA level remained significantly associated with presence of DECT MSU crystal deposits. It is possible that older individuals have had asymptomatic hyperuricemia for a longer period of time than younger patients with asymptomatic hyperuricemia. While we do not have information on the duration of asymptomatic hyperuricemia in our study cohort, it is possible that MSU crystal deposit formation might be related to the length of time subjects had high sUA levels in their bodies. Findings from a previous study also supported this hypothesis.<sup>7</sup>

This study had several strengths. First, we prospectively enrolled the study subjects and assessed sUA level and MSU crystal deposits of the foot/ankle using DECT scan. We asked a series of questions to exclude any patients with remote history of gout or undiagnosed gout, and the study rheumatologists (SCK and DHS) performed a joint examination for both feet prior to undergoing a DECT scan. Second, we minimised potential variations in the quality and interpretations of DECT images as our study was based on a single centre using the same imaging protocol for DECT scans and a single senior musculoskeletal radiologist (SS) reviewed all the images of 46 patients. Lastly, gout is known to most frequently affect the first metatarsophalangeal joint, but it can involve other parts of the body.<sup>10 11</sup> With the advantage of DECT scans allowing to analyse multiple joint sites within the entire foot in a single scan, we were able to find MSU crystal deposits outside the metatarsophalangeal joints.

Our study has several limitations. First, while patients with long-term exposure to high sUA levels may be predisposed to having subclinical MSU crystal deposits, we were unable to examine such association given its cross-sectional study design.<sup>9</sup> Second, this study was based on a cohort of 46 patients with mild-to-moderately elevated levels of sUA. Although, to the best of our knowledge, this study is the largest study that evaluated DECT MSU crystal deposits among patients with asymptomatic hyperuricemia, evaluating a larger number of patients with MSU crystal deposits on DECT may further characterise factors associated with subclinical deposition of MSU crystals. Third, the upper quartile level of sUA in our study cohort was 8.4 mg/dL, with that a large portion having sUA levels below 8 mg/dL. Future research with longitudinal follow-up on patients with moderate-to-severe asymptomatic hyperuricemia may help elucidate risk factors for developing gout in relation to subclinical MSU crystal deposits on DECT as there is a higher probability of developing gout in higher sUA levels.<sup>3, 20</sup> Fourth, our study used *syngo.via* software for automated urate volume analysis. However, it would be interesting to implement the newer semiquantitative DECT urate scoring method in future research.<sup>21</sup>

In conclusion, in this cross-sectional study of 46 patients with mild-to-moderate asymptomatic hyperuricemia, 15% had MSU crystal deposition as noted on the foot/ankle DECT scans. Older age, but not sUA levels and other measured patient characteristics, was associated with the presence of MSU crystal deposits on DECT scans. We also noted a potential, modest linear relationship between sUA levels and the total MSU volume on DECT scans. While the clinical significance of these subclinical MSU crystal deposit was unclear, it is possible that these patients may go on to develop gout, or they may have 'resistance' by reacting against MSU crystal deposits. Further research on why certain patients with hyperuricemia develop gout may present important clues for gout prevention.

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