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# Radiologic Evidence of Symmetric and Polyarticular Monosodium Urate Crystal Deposition in Gout – A Cluster Pattern Analysis of Dual-Energy CT

**Chio Yokose, MD**[1], **Nicola Dalbeth, MD, FRACP**[2], **Jie Wei, PhD**[1], **Savvas Nicolaou, MD**[3], **F. Joseph Simeone, MD**[4], **Scott Baumgartner, MD**[5], **Maple Fung**[5], **Yuqing Zhang, DSc**[1], **Hyon K. Choi, MD, DrPH**[1]

[1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA [2]Department of Medicine, University of Auckland, Auckland, New Zealand [3]Department of Radiology, Vancouver General Hospital and University of British Columbia, Vancouver, British Columbia, Canada [4]Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA [5]Formerly Ardea Biosciences Inc., San Diego, California, USA

## Abstract

**Objectives:** To determine the clustering patterns of monosodium urate (MSU) crystal deposition and bone erosions among patients with gout requiring urate-lowering therapy (ULT) using dual-energy CT (DECT).

**Methods:** DECT scans of bilateral hands/wrists, feet/ankles, and knees were obtained on 153 patients with gout on allopurinol ≥300mg daily for ≥3 months. Two radiologists assessed the images at pre-specified sites (15 in the hands/wrists, 12 in the feet/ankles, 4 in the knees). Clustering patterns of MSU crystal deposition and bone erosions were evaluated.

**Results:** Among 153 patients with gout (mean duration, 15 years) on allopurinol (mean duration, 5 years), MSU crystal deposition (67%) affected multiple sites in the hands/wrists, feet/ankles, and knees more often than would be expected by chance ($p<0.001$ for all 3 regions). In the feet/ankles, bone erosions were also observed in a clustered manner ($p<0.001$). Presence of MSU crystal deposition at a particular joint was most strongly associated with symmetric involvement of the same joint of the opposite extremity in the hands/wrists, feet/ankles, and knees (adjusted odds ratio (OR) 26.1, 46.9, and 9.9, respectively). Similarly, presence of erosions in the feet/ankles was highly symmetric (adjusted OR 91.4). Erosions were 8-fold more likely to be present in sites with MSU crystal deposition compared to those without.

Corresponding Author: Hyon K. Choi, MD, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch 165, Boston, MA 02114, USA, Tel: 617-726-7928, Fax: 617-726-2872, hchoi@mgh.harvard.edu.

**Conclusion:** Among patients with longstanding gout on ULT, MSU crystal deposition and bone erosions affect multiple joints within the hands/wrists, feet/ankles, and knees in a highly symmetric manner. These radiologic data support the notion of MSU crystal deposition in gout as a symmetric polyarthropathy.

### Keywords

Gout; Imaging; Urate; Erosions

Gout is a highly prevalent and painful inflammatory arthritis associated with hyperuricemia (1). Early gout usually manifests as episodes of self-limited acute arthritis but can evolve over time into a condition associated with chronic inflammation of multiple joints, tophi (2), and bone erosions (3, 4). This is because sustained hyperuricemia can lead to growing deposits of monosodium urate (MSU) crystals in joints and periarticular structures, which in turn can incite a chronic inflammatory response (5).

Conversely, effective urate-lowering therapy (ULT) is expected to reduce and eventually eliminate MSU crystal deposition over time (6, 7). However, data are scarce about the prevalence and clustering patterns of MSU crystal deposition and bone erosions among gout patients who are treated with ULT. Such data could shed light on underlying involvement patterns and pathophysiologic mechanisms that lead to gout. It may also inform our assessment of gout burden and treatment response to ULT, which in turn may lead to improvements in long-term gout care. To provide such data, we prospectively obtained dual-energy CT (DECT) scans of peripheral joints of 153 gout patients receiving allopurinol and evaluated the prevalence and clustering patterns of MSU crystal deposition and bone erosions.

## METHODS

### Study Design and Patients

This multicenter study was conducted in the United States and New Zealand between April 2015 and October 2016. The details of patient recruitment, enrollment, and assessment have been previously described (8). Briefly, patients were eligible for inclusion in the study if they were 18-85 years of age and fulfilled the 1977 American Rheumatism Association Criteria for the Classification of Acute Arthritis of Primary Gout (9). Study participants had to have been treated with allopurinol as the sole ULT at a stable dose of ≥300mg daily for 3 months or more prior to study initiation. Enrollment was conducted in a monitored fashion to ensure the study population included approximately 25% patients with subcutaneous tophi and 50% patients with serum urate (SU) <6 mg/dL.

### DECT Assessments

DECT scans of the hands/wrists, feet/ankles, and knees were obtained and interpreted following the protocols previously outlined (8). The presence of MSU crystal deposition and bone erosions were assessed by two radiologists familiar with DECT interpretation. If there was a discrepancy in the interpretation of the images between the two radiologists, a consensus meeting was held to resolve the discrepancy.

Presence of MSU crystal deposition was evaluated at 15 sites in the hands/wrists (1st IP joint, 2nd-5th distal interphalangeal (DIP) joints, 2nd-5th proximal interphalangeal (PIP) joints, 1st-5th metacarpophalangeal (MCP) joints, carpals), 12 sites in the feet/ankles (1st-5th interphalangeal (IP) joints, 1st-5th metatarsophalangeal (MTP) joints, tarsals, and Achilles tendon), and 4 sites in the knees (medial tibiofemoral, patellofemoral, and lateral tibiofemoral compartments, cruciate ligament). For the MSU crystal deposition prevalence analysis, in order to account for the larger number of sites assessed in the feet/ankles and hands/wrists compared to the knees, the individual sites were then grouped into four sub-regions in the feet/ankles (first MTP, other toes, tarsals, tendons) as proposed by a recent DECT scoring system (10) and three sub-regions in the hands/wrists (IP joints, MCPs, carpals). Finally, presence of bone erosions was assessed at 12 sites in the feet/ankles (1st-5th IP joints, 1st-5th MTP joints, tarsals, and Achilles tendon calcaneal insertion).

### Statistical Analysis

Continuous variables (age, duration since gout diagnosis, duration of allopurinol treatment) were summarized using mean and standard deviation. Categorical variables (sex, race, total daily allopurinol dose 300mg vs. >300mg, and SU <6 mg/dL vs. ≥6 mg/dL) were summarized using number and percentage of subjects. Prevalence of MSU crystal deposition was assessed at each anatomic site individually (n=306) as well as in pairs (n=153). Prevalence of bone erosions was evaluated at each paired anatomic site (n=153). Stratified analysis was pursued based on presence or absence of subcutaneous tophi. The prevalence of bone erosions among those with and without subcutaneous tophi were compared using Fisher's exact test.

To evaluate whether clustering of MSU crystal deposition and bone erosions are more than a random affair, we first calculated the number of subjects expected to have one or multiple sites with MSU crystal deposition or bone erosions, using a binomial distribution, as was done in evaluation of other arthritides (11, 12). This expected number was compared with the observed number of subjects with one or multiple sites with MSU crystal deposition or bone erosions using a chi-square test. We then assessed the clustering patterns of MSU crystal deposition or bone erosions using a logistic regression model to estimate the odds ratio (OR) of MSU crystal deposition or bone erosion in a particular joint according to the presence of MSU crystal deposition or bone erosion at the same joint of the contralateral extremity (i.e., symmetry), joints in the same ray (i.e., multiple joints of one digit), and joints in the same row (i.e., same joint across multiple digits) while adjusting for presence of MSU crystal deposition or bone erosion at other joints, age, sex, and race. We subsequently performed the same analyses considering jointly MSU crystal deposition or bone erosions in the feet/ankles, based on the hypothesis that MSU crystal deposition may have dissolved in response to treatment with allopurinol, leaving behind only erosions. Generalized estimating equations were used to account for the correlation among multiple joints within a subject.

## RESULTS

There were 153 patients in the study who underwent DECT imaging and were included in the analyses. Majority of the patients were male (92%) with mean age of 58.5 (SD, 11.4)

years (Table 1). Mean duration of gout was 14.9 (SD, 10.3) years and mean duration of allopurinol therapy was 5.1 (SD, 6.9) years. Most patients were on allopurinol 300mg daily (82%).

### Distribution and Prevalence of MSU Crystal Deposition in the Peripheral Joints

The region with the highest prevalence of MSU crystal deposition, defined as at least one measurable MSU crystal deposition at any anatomic site within the region assessed, was feet/ankles (61%), followed by knees (57%) and hands/wrists (23%). By sub-region, the three most commonly affected sites were in the knees, with the lateral tibiofemoral, patellofemoral, and medial tibiofemoral compartments demonstrating 42%, 39%, and 37% prevalence of MSU crystal deposition, respectively (Table 2). The first MTP joint showed 35% prevalence of MSU crystal deposition. The cruciate ligament in the knee had similar prevalence of MSU crystal deposition to that of the Achilles tendon (25% and 26%, respectively). The order of most commonly involved anatomic sites did not differ whether the sites were considered individually or in pairs, suggesting a high prevalence of bilateral involvement at any given site. Specifically in the hands/wrists where the dominant hand may be susceptible to higher joint stress and trauma which may contribute to asymmetric MSU crystal deposition, we found that there was no statistically significant difference between prevalence of MSU crystal deposition in the right vs. left hand/wrist (right hand/wrist 18.8% vs left hand/wrist 11.4%, p=0.075).

### Distribution and Prevalence of Bone Erosions in the Feet and Ankles

In the feet/ankles of these patients, bone erosions were eight-fold more likely to be present in sites with MSU crystal deposition compared to those without MSU crystal deposition, suggesting a strong association between the two findings (Table 3).

Overall, 72% of all patients had at least one bone erosion in the feet/ankles (Table 4). Patients with subcutaneous tophi had significantly higher prevalence of bone erosions than those without tophi (83% vs. 67% respectively, p=0.04). The three sites most commonly affected by bone erosions were the first MTP joint, tarsals, and first IP joint (68%, 38%, and 13%, respectively). With exception of the first IP joint, there was very low prevalence of bone erosions in the remaining IP joints or the Achilles tendon calcaneal insertion.

### Patterns of MSU Crystal Deposition or Bone Erosions

In the feet/ankles, both MSU crystal deposition and bone erosions were observed in a clustered manner at multiple sites more frequently than would be expected by chance ($p<0.001$ for both) (Supplemental Table 1). For instance, whereas only 8 patients were expected to have 4 or more areas of MSU crystal deposition in the feet/ankles, in actuality 18 patients demonstrated 4 or more areas of MSU crystal deposition. Similarly, whereas only 38 patients were expected to have 4 or more areas of bone erosions in the feet/ankles, in actuality 51 patients demonstrated 4 or more areas of bone erosions. Presence of MSU crystal deposition or bone erosions at a given joint was most strongly associated with symmetric involvement of the same joint of the opposite extremity (Table 5). The strength of this association was stronger for bone erosions than for MSU crystal deposition (adjusted OR 91.4 and 46.9, respectively). Furthermore, both MSU crystal deposition and bone

erosions tended to be observed in the same ray of joints more than in the same row (Table 5). When MSU crystal deposition or bone erosions were considered jointly in the feet/ankles, we found that they were still observed in a clustered manner at multiple sites more frequently than would be expected by chance ($p<0.001$) (Supplemental Table 1). When considered jointly, presence of MSU crystal deposition or bone erosions at a given joint was still most strongly associated with symmetric involvement of the same joint of the contralateral extremity, with an adjusted OR of 64.3 (Table 5).

Similar findings were seen in the hands/wrists and knees with MSU crystal deposition. MSU crystal deposition was observed in a clustered manner at multiple sites of the hands/wrists and knees more frequently than would be expected by chance ($p<0.001$ for both) (Supplemental Table 2). Similarly, MSU crystal deposition in the hands/wrists and knees also displayed a high degree of symmetry (Table 6). After involvement of the contralateral joint, MSU crystal deposition in the hands/wrists and knees also tended to cluster in the same ray of joints more so than in the same row of joints.

## DISCUSSION

In this study of patients with longstanding gout treated with allopurinol, we found that both MSU crystal deposition and bone erosions tended to cluster and affect multiple joints within a region more commonly than would be expected by chance. Additionally, both MSU crystal deposition and bone erosions affected joints in the hands/wrists, feet/ankles, and knees in a highly symmetric manner. The fact that MSU crystal deposition or bone erosions considered jointly, as well as bone erosions alone, demonstrated higher ORs for symmetric involvement than MSU crystal deposition alone is potentially significant and may better reflect the true burden and distribution, past and present, of gout involvement in the joints. This is because these patients had been treated with ULT for a mean of 5 years, which could have led to the dissolution of the MSU crystal deposits, leaving behind bone erosions in their wake. Together, these findings underscore the notion of gout as a symmetric polyarthropathy, especially among patients who have had the disease for multiple years.

Recognizing the pattern of joints involved by arthritis is integral to being able to distinguish different types of arthritis and can have implications in disease monitoring. To this end, systematic pattern analyses of affected joints have been carried out among patients with other types of inflammatory and non-inflammatory arthritis, such as osteoarthritis (11, 13), rheumatoid arthritis (12, 14), and psoriatic arthritis (12, 15). While gout flares do most commonly occur in an asymmetric mono- or oligoarticular manner, as observed clinically and emphasized by various classification criteria for gout (9, 16), polyarticular and symmetric gout flares and chronic gouty arthritis can occur, especially among patients with longstanding disease or high MSU crystal burden (1). Our data provide radiologic evidence that highlights the systemic nature of gout which can lead to symmetric and polyarticular MSU crystal deposition, even if they are clinically asymptomatic. The mechanisms behind the clustering of MSU crystal deposition in certain sites likely relates to factors which influence MSU crystallization in the first place, such as temperature, pH, local biochemical milieu (e.g., presence of certain proteins or other materials which promote the nucleation of

MSU crystals) (17), and mechanical stress and degenerative joint damage (18) which may similarly affect multiple joints within a region as opposed to singular joints.

To our knowledge, this study is the first of its kind to employ DECT imaging to perform such a pattern analysis of MSU crystal deposition. DECT is unique among the advanced imaging modalities in that it is currently the only one that identifies MSU crystal deposition on the basis of its chemical composition (19). The OMERACT has identified both MSU crystal burden as well as structural damage, including bone erosions, as possible areas in which imaging may have utility as an outcome measure (20). Previously, Doyle and colleagues evaluated CT scans of the feet for bone erosions in 25 patients with gout (52% with subcutaneous tophi, 88% on treatment with ULT), and found that 24 out of 25 patients demonstrated symmetric involvement (21), based on the definition of symmetry described by Helliwell and colleagues (12). Our findings are consistent with those of Doyle et al., and also provide new insight into patterns of MSU crystal deposition, including in the hands/wrists and knees, areas often underrepresented in gout imaging studies.

The recognition of gout as a symmetric polyarthropathy may have significant clinical implications. Long-term gout care remains suboptimal despite widely available treatment in the form of ULT such as allopurinol (22). One large barrier that has been identified is the widespread misconception of gout simply as an episodic disease that only requires treatment during an acute flare (23). Our findings, both of our pattern analyses as well as prevalence of MSU crystal deposition and bone erosions, lend further support to the understanding of gout as a chronic and systemic process that can affect joints in a more widespread manner than is often perceived and lead to joint damage. Furthermore, there remains a high level of interest in the role of DECT for monitoring of disease progression and response to therapy in gout (24). Our findings may suggest that in patients with longstanding gout, unilateral imaging may be sufficient to assess for gout burden and response to therapy, especially in settings where there is limited access to DECT or cost is a concern.

The strengths and potential limitations of this study warrant comments. This study prospectively and systemically scanned peripheral joints most commonly affected by gout. Centralized reading of DECT images was carried out by two trained radiologists, limiting interrater variability of the findings. Discrepant readings were adjudicated by consensus to improve accuracy of the readings. Assessment for MSU crystal deposition and bone erosions were done at the level of the individual joints and structures as well as the region as a whole, which allowed for a more detailed assessment of the extent and patterns of MSU crystal deposition and bone erosions.

Enrollment was conducted in a monitored fashion to ensure the population included approximately 25% of patients with subcutaneous tophi and approximately 50% of patients with SU <6 mg/dL, representing a realistic spectrum of patients with longstanding gout on ULT. However, this could have limited the generalizability of these findings. In particular, patients with early gout may demonstrate prevalence and patterns of MSU crystal deposition which could differ from those with longstanding disease and warrant further study. Additionally, as the study was cross-sectional, we are unable to comment on how the observations made in his study may have changed over time or in response to treatment.

Lastly, as there was no reference group in the current study, we do not have the prevalence or patterns of bone erosions in these locations in the general population. However, the strong association and consistent clustering patterns between MSU crystal deposition and bone erosions observed in this study suggest that bone erosions were indeed related to gout.

In conclusion, both MSU crystal deposition and bone erosions occur in a clustered fashion, affecting multiple joints within a region. They also exhibit a high degree of symmetry on DECT imaging, despite the common clinical manifestation of gout flares as an asymmetric mono- or oligoarticular arthritis. There is also a high prevalence of MSU crystal deposition and bone erosions among patients with longstanding gout on ULT, with patients with subcutaneous tophi exhibiting higher burden of bone erosions. These findings together emphasize the fact that the underlying pathophysiologic process leading to gout is a systemic one that requires long-term management, even during intercritical periods, especially among patients who have had gout for many years.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1:**

Characteristics of Study Patients

| Variable | N = 153 patients |
|---|---|
| Age (years), mean (SD) | 58.5 (11.4) |
| Male, n (%) | 141 (92) |
| Race, n (%) | |
| White | 99 (65) |
| Non-white | 54 (35) |
| Duration since gout diagnosis (years), mean (SD) | 14.9 (10.3) |
| Total daily allopurinol dose, n (%) | |
| 300mg | 125 (82) |
| >300mg | 28 (18) |
| Duration of allopurinol treatment (years), mean (SD) | 5.1 (6.9) |
| SU level, n (%) | |
| <6 mg/dL | 78 (51) |
| ≥6 mg/dL | 75 (49) |
| Subcutaneous tophi, n (%) | 48 (31) |

SU = serum urate; SD = standard deviation

**Table 2:**

Prevalence of Monosodium Urate Crystal Deposition According to Anatomical Location

| Anatomical Location | Prevalence by patients N = 153 patients | Prevalence by joints N = 306 joints |
|---|---|---|
| Lateral tibiofemoral compartment | 42% | 34% |
| Patellofemoral compartment | 39% | 32% |
| Medial tibiofemoral compartment | 37% | 28% |
| First MTP | 35% | 25% |
| Achilles tendon | 26% | 19% |
| Cruciate ligament | 25% | 17% |
| Other toes | 17% | 12% |
| Carpals | 14% | 9% |
| Tarsals | 13% | 11% |
| MCPs | 7% | 5% |
| Hand IPs | 5% | 3% |

MTP = metatarsophalangeal joint; MCP = metacarpophalangeal joint; IP = interphalangeal joint

**Table 3:**

Association between DECT MSU Crystal Deposition and Presence of Bone Erosions

| MSU Crystal Status | No. Joints | Erosion (%) | Crude OR | Adjusted OR* |
|---|---|---|---|---|
| **MSU Crystal Deposition (−)** | 3422 | 295 (8.6) | Reference | Reference |
| **MSU Crystal Deposition (+)** | 222 | 96 (43.2) | 8.1 (5.2, 12.6) | 8.0 (4.9, 12.9) |

*Adjusted for other joints, age, sex, and race

**Table 4:**

Prevalence of Bone Erosions on DECT of Feet and Ankles According to Anatomical Location

| Anatomical Location | All Patients N=153 | Subcutaneous Tophi N=48 | No Subcutaneous Tophi N=105 |
|---|---|---|---|
| Any site | 72% | 83% | 67% |
| MTP 1 | 68% | 75% | 65% |
| Tarsals | 38% | 46% | 34% |
| IP 1 | 13% | 17% | 12% |
| MTP 5 | 12% | 23% | 7% |
| MTP 2 | 9% | 13% | 7% |
| MTP 4 | 3% | 8% | ≤1% |
| IP 2 | 3% | 4% | 3% |
| MTP 3 | 3% | 6% | 2% |
| IP 4 | 2% | 2% | 2% |
| Achilles tendon calcaneal insertion | ≤1% | 2% | ≤1% |
| IP 3 | ≤1% | 0% | ≤1% |
| IP 5 | ≤1% | 2% | ≤1% |

MTP = metatarsophalangeal joint; IP = interphalangeal joint

**Table 5:**

Clustering Patterns of MSU Crystal Deposition or Bone Erosions in Feet/Ankles of Patients with Gout

| | MSU Crystal Deposition Adjusted Odds Ratio* (95% CI) | Bone Erosions Adjusted Odds Ratio* (95% CI) | MSU Crystal Deposition or Bone Erosions Adjusted Odds Ratio* (95% CI) |
|---|---|---|---|
| Feet/Ankles | | | |
| Same joint, other side | 46.9 (23.9, 92.2) | 91.4 (53.3, 156.6) | 64.3 (39.3, 105.3) |
| Same ray, same side | 4.6 (2.0, 10.6) | 1.8 (1.0, 3.3) | 2.0 (1.2, 3.2) |
| Same row, same side | 1.5 (0.7, 3.1) | 1.6 (1.1, 2.3) | 1.3 (1.0, 1.8) |

CI = confidence interval

*Adjusted for other joints, age, sex, and race.

**Table 6:**

Clustering Patterns of MSU Crystal Deposition in Hands/Wrists and Knees of Patients with Gout

| | MSU Crystal Deposition Adjusted Odds Ratio* (95% CI) |
|---|---|
| Hands/Wrists | |
| Same joint, other side | 26.1 (2.6, 263.6) |
| Same ray, same side | 15.0 (2.1, 107.8) |
| Same row, same side | 14.9 (1.9, 114.3) |
| Knees | |
| Same joint, other side | 9.9 (5.9, 16.5) |
| Same row, same side | 4.2 (2.5, 7.2) |

CI = confidence interval

*Adjusted for other joints, age, sex, and race.