Development of a dual energy computed tomography scoring system for measurement of urate deposition in gout

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ABSTRACT

Objective: To develop a semi-quantitative dual energy CT (DECT) scoring system for measurement of urate deposition in gout.

Methods: Following a structured review of images, a semi-quantitative DECT urate scoring method for foot/ankle scans was developed for testing. This method included four regions, each scored from 0-3, with a maximum total DECT urate score of 12. DECT scans from 224 patients (182 with gout, 42 without gout) were scored by two independent readers. Automated urate volumes were also measured. Paired scans from eight patients receiving pegloticase were analysed. A timing exercise was undertaken. The properties of the DECT urate score were analysed according to the Outcomes in Rheumatology Clinical Trials (OMERACT) filter.

Results: The inter-reader intraclass correlation coefficient (95%CI) for the DECT urate score was 0.98 (0.97-0.98). All scored regions contributed to the total DECT urate score. DECT urate scores and volumes were highly correlated (r=0.91, p<0.0001). Both DECT urate scores and volumes discriminated between gout and non-gout control participants, and between the tophaceous gout, non-tophaceous gout and control groups. Compared with urate volume, the DECT urate score had greater ability to discriminate between responders and non-responders to pegloticase therapy (p<0.001 for DECT urate score and >0.05 for volume). The mean (SD) time required for the DECT urate score was 121 (2) seconds and for urate volume was 240 (2) seconds (p=2x10^{-31}).

Conclusion: We have developed a novel semi-quantitative DECT scoring method for measurement of urate deposition in the feet/ankles. This method fulfils many aspects of the OMERACT filter.
SIGNIFICANCE AND INNOVATIONS

- Dual energy CT (DECT) allows visualisation and measurement of urate deposition in gout.
- DECT urate deposition is currently measured using volume assessment, but this system is time consuming and does not easily allow for volume measurement of specific sites of deposition.
- We describe a semi-quantitative DECT urate scoring method that allows measurement of urate deposits at specific sites.
- We demonstrate in a large sample set that the DECT urate scoring method is a feasible and reliable scoring system with high discrimination.
Gout is a chronic disease of monosodium urate (MSU) crystal deposition (1). Symptoms of gout result from the individual’s inflammatory response to these crystals, either as acute inflammatory flares, or tophi resulting from densely packed MSU deposits in the joint, tendons and other soft tissues (2). The cornerstone of effective gout treatment is long-term serum urate lowering to a target <6mg/dL, which ultimately leads to dissolution of MSU crystals and prevention of symptomatic disease (3).

Dual energy computed tomography (DECT) can visualize monosodium urate (MSU) crystal deposits in patients with tophaceous gout (4), and also at an earlier stage before tophi can be detected by clinical examination (5). Due to its non-invasive nature, and high sensitivity and specificity (6). DECT is an attractive tool for the diagnosis and assessment of gout (4, 7-12).

In addition, DECT has a potential role as an outcome measure to assess MSU crystal deposition in patients undergoing studies of urate-lowering therapy (13). The burden of urate crystal deposition can be assessed using automated volume assessment software, with excellent inter-reader agreement (8, 14). Although this software is automated, urate volume assessment is time-consuming, due to the need to identify regions of interest and exclude areas of artefact (15). Frequently the urate volume in an entire scan is recorded, which means that differential changes at separate regions cannot be appreciated. Although it is possible to measure urate volume at specific regions using DECT, such detailed analysis further increases the time required for data generation. To date, the sensitivity to change of DECT urate volume assessment has not been reported.

Given these limitations of automated urate volume assessment, we developed a semi-quantitative DECT scoring system for urate deposition in gout. Here we report the properties
of this scoring including construct and content validity, inter-reader reliability, ability to discriminate between different disease states, sensitivity to change in response to treatment, and feasibility.

PATIENTS AND METHODS

Patients

DECT scans of the feet and ankles obtained from 224 patients were analysed. The scans had been obtained as part of routine clinical care or for clinical research studies in gout and hyperuricemia in Erlangen, Germany and Auckland, New Zealand. There were 182 participants with gout, all of whom fulfilled the 1977 preliminary American Rheumatism Association classification criteria for gout (16). There were 42 control participants without gout (7 with other forms of arthritis (rheumatoid arthritis, psoriatic arthritis, and osteoarthritis), 25 individuals with asymptomatic hyperuricemia and no history of arthritis, 10 healthy normouricemic volunteers with serum urate <6.8mg/dL). Clinical data were recorded including demographic information, gout disease duration, medications, presence of subcutaneous tophi, and serum urate concentration at the time of DECT scanning. Ethical approval was provided by the ethics committees of the University of Erlangen-Nuremberg and the New Zealand Health and Disability Ethics Committee.

DECT scanning

Images were obtained on a dual X-ray tube 128 detector row scanner (Somatom Definition Flash, Siemens Medical, Erlangen, Germany). The patients were positioned feet-first in a supine position with the feet in a plantar flexion position. The scan was acquired in a craniocaudal direction, starting proximally 5 cm from the ankle joint to the toe tips. Both ankles and feet were scanned axially in one acquisition. All scans are performed with the
same image protocol; acquisition at 128x0.6mm and pitch of 0.7. X-ray tube 1 was operated at 80kV/260mA and tube 2 at 140kV/130mA.

Automated urate volume analysis

A proprietary workstation (MultiModality Workspace, Siemens Medical) was used with proprietary gout software (syngo DE Gout #MM, Siemens Medical) for analysis. For the 80kV images, fluid was set at 50 Hounsfield units (HU), the ratio for urate at 1.36, minimum HU 150 and smoothing range 4. For the 140 kV images, fluid was set at 50HU and maximum HU at 500.

Definition of DECT urate scoring system for testing

After an initial structured review of both positive and negative DECT scans by a group of musculoskeletal radiologists and rheumatologists (JR, GS, BM, AC, ML), a preliminary DECT urate score was derived for further testing. The initial review process considered the scans to be scored, identifying regions most frequently affected, and the method of scoring. Review of available images indicated that the vast majority of scans were of the feet and ankles. Given the high frequency of foot and ankle involvement in gout (17) and to allow for consistent scoring, the DECT urate score was developed for foot and ankle scans only. The initial review of DECT scans by the panel of radiologists and rheumatologists identified that the 1st metatarsophalangeal joint (MTPJ) was frequently affected, and required separate scoring. The high frequency of tendon involvement was also noted throughout the foot, and therefore, tendons were selected for specific scoring. The foot was then separated into the other joints of the toes (2nd-5th MTPJ and interphalangeal joints), and the joints of the ankles/midfeet.
In the scoring system, each scan (including both feet and ankles) is divided in the following regions: 1st MTPJs, other joints of the toes (joints), ankles/midfeet (joints), and tendons (all visible tendons in the feet/ankles). All images are viewed by scrolling in the axial, coronal and sagittal planes to identify the highest score through the region. Each region is then scored according to the maximum amount of urate deposition observed on visual inspection (scored as 0=no deposit, 1=dots, 2=single deposit, 3=more than one deposit). Representative images for each region are shown in Figure 1. The total DECT urate score is derived by adding all values from the four regions (minimum score=0 and maximum score=12).

For further assessment of the scoring system, single joint scores for the 1st MTPJs were compared with the urate volumes measured by a separate reader (MS) in the same joints in 64 patients with tophaceous gout. In these joints, dots (score 1) were visible but measured below 0.01cm$^3$ in volume (i.e. below the level of measurement). The single deposits (score 2) were measurable at low volume (0.01-0.03 cm$^3$), and the score of 3 (more than one deposit) measured above 0.03cm$^3$.

**DECT scoring procedure**

All DECT scans were scored by two independent readers, a rheumatology fellow without prior experience in DECT scoring (reader 1, SB) and a rheumatologist with four years of experience in DECT scoring (reader 2, ND). The rheumatology fellow received training from a musculoskeletal radiologist prior to commencing the scoring. Both readers were blinded to all clinical details and each other’s scores. One reader (SB) also re-scored 32 scans more than 6 months after the original scoring (blinded to all clinical details and her previous scores).
For each scan, the urate volume was assessed by one of the readers using automated volume assessment software (syngo Volume Calculation). Nail bed, skin, motion and beam hardening artefacts were excluded from the analysis and urate volume measurement (15). Urate volume was assessed in 73 scans by both readers (each blinded to the other’s results), yielding an inter-reader intraclass correlation coefficient (95% confidence interval) of 1.00 (1.00-1.00).

Paired DECT scans were also available for eight patients with tophaceous gout who received pegloticase treatment. Change in mean DECT urate score and urate volumes were compared between responders (those who achieved a serum urate concentration <0.6mg/dL during treatment) and non-responders (those who did not achieve a serum urate concentration 6mg/dL during treatment) (18). Both readers were blinded to gout diagnosis, treatments and serum urate results for these patients.

Each reader completed a timing exercise for both DECT urate score and automated urate volume assessment for at least 30 scans. Timing commenced at time of loading images onto the workstation and was completed at the time of data entry. The DECT urate score was assessed prior to the urate volume assessment in this exercise.

**Assessment according to the OMERACT filter**

The development of the DECT urate score instrument was undertaken according to the framework of the Outcomes Measures in Rheumatology Clinical Trials (OMERACT) filter (19, 20). Assessment of truth included construct validity by comparing DECT urate score values with automated urate volume measurements, and content validity by analysing the contribution of various sites to the total DECT urate score. Assessment of discrimination
included inter-reader reliability, ability to differentiate between tophaceous and non-tophaceous gout, differentiation between gout and non-gout (including hyperuricemic control participants), and sensitivity to change in response to treatment. Assessment of feasibility included the timing assessment.

**Statistical analysis**

Data were analysed using SPSS (v21, SPSS Inc., Chicago, IL) and GraphPad Prism (v6, GraphPad Software Inc, La Jolla, CA). Inter-reader and intra-reader reproducibility for the DECT urate score was assessed by intraclass correlation coefficient and limits of agreement (Bland and Altman) analysis. The relationships between different measurements were analysed using Spearman correlations. Differences between groups were analysed by t-tests and where relevant, analysis of variance (ANOVA) with post tests for multiple comparisons. All tests were two tailed and p<0.05 was considered statistically significant.

**RESULTS**

**Participants**

Clinical features of the participants are shown in Table 1. Briefly, foot and ankles DECT scans were available from 224 patients, including 182 with gout. The majority of the individuals were male with a mean age over 60 years. Two thirds of the patients with gout (n=120; 65.9%) received urate lowering therapy at the time of DECT scanning, half of the patients with gout (n=89; 48.9%) had clinical evidence of tophi and one third (n=63; 35%) had microscopically proven gout.

**DECT urate scores and urate volumes**
The mean DECT scores and urate volumes are shown in Table 2. The mean (SD) DECT urate score for all scans was 5.67 (4.23) units on a scale from 0 to 12. All four regions contributed to the DECT score. Urate deposits were most pronounced in the tendons, followed by the MTPJ1, the ankle and midfoot regions, while the toes showed the lowest extent of urate deposits. The mean (SD) urate volume for all scans was 1.96 (5.78) cm$^3$. The DECT urate scores and urate volumes were highly correlated; $r=0.91$, $p<0.0001$.

**Inter-reader and intra-reader reliability of DECT urate scores**

For all scans, the mean (SD) DECT urate score for reader 1 was 5.79 (4.25) and for reader 2 was 5.55 (4.28). The inter-reader intraclass correlation coefficient (95% confidence interval) for the DECT urate score was 0.98 (0.97-0.98). In limits of agreement analysis, the inter-reader bias (SD) for the DECT urate score was -0.24 (0.95).

For reader 1, the intra-reader intraclass correlation coefficient (95% confidence interval) for the DECT urate score was 0.99 (0.98-1.00). In limits of agreement analysis, the intra-reader bias (SD) for the DECT urate score was -0.13 (0.49).

**Discrimination between groups**

Both DECT urate scores and urate volumes were higher in those with gout (mean DECT urate score 6.75) compared with control (mean DECT urate score 1.02) participants (Table 2, $p<0.0001$ for both DECT urate scores and urate volumes). When groups were separated into tophaceous gout, non-tophaceous gout, hyperuricemic controls and normouricemic controls, both the DECT urate score and the urate volume measurement differentiated between non-tophaceous gout and both control groups (Dunn’s multiple comparisons test $p<0.0001$ for both methods, Figure 2). In this analysis, both DECT urate scores and urate volumes were
higher in the tophaceous gout group compared with all other groups, including patients with non-tophaceous gout (Dunn’s multiple comparisons test < 0.001 for all comparisons).

**Sensitivity to change analysis**

The paired scans of eight patients with tophaceous gout who received pegloticase were analysed for both the DECT urate score and urate volume. The mean time between baseline and follow-up scan was 9.5 (6.2) months. There were five pegloticase responders and three non-responders. The mean serum urate of the responders during treatment was 2.3 (1.8) mg/dL, and of the non-responders was 11.7 (2.8) mg/dL. The baseline and post-treatment DECT urate scores and urate volumes are shown in Table 3. Compared with baseline, pegloticase responders had a significant reduction in the DECT urate score in the post-treatment scans (Sidak’s multiple comparison test p < 0.001). A similar, but non-significant, trend was observed using the DECT urate volume measurement (Sidak’s multiple comparison test p > 0.05). No significant change was observed in the non-responders using either method of measurement (Sidak’s multiple comparison test p > 0.05 for both the DECT urate score and urate volume). There was a significant difference in the change scores between responders and non-responders using the DECT urate score, but no significant difference using the urate volume measurement (Figure 3).

**Timing exercise**

Each reader completed an exercise in which the time from loading the images onto the workstation to the time of data entry. The exercise was completed for 33 scans by reader 1 and 44 scans by reader 2. For the 77 scans included in the timing analysis, the mean (SD) time required for the DECT urate scoring was 121 (2) seconds and the mean (SD) time required for the urate volume assessments was 240 (2) seconds (p = 2x10^{-31}).
DISCUSSION

Here, we describe a novel semi-quantitative dual energy CT scoring method for assessment of urate deposition. This method fulfils many principles of the OMERACT filter. The method has high concordance with total scan urate volume and is able to differentially and comprehensively capture deposition at the most frequently affected sites. The method has high inter-reader reproducibility and is able to discriminate between individuals with and without gout. Compared with total scan urate volume, this method has greater ability to discriminate between responders and non-responders to intensive urate-lowering therapy. This method is feasible, with significantly shorter scoring times required compared with total scan urate volume measurement.

The DECT urate scoring method is able to capture urate crystal deposition at a number of regions within the feet and ankles. Although tendon involvement is less clinically apparent, previous DECT and ultrasound studies have shown that tendon involvement is as frequent as joint involvement in patients with gout (9, 21). Although our current project did not specifically address changes at different regions of urate deposition, the regional sub-scales of the DECT urate score may also allow future analysis of whether urate crystal dissolution occurs at a similar rate at different regions in patients receiving urate-lowering therapy.

Our analysis did identify some evidence of urate deposition in control participants (mean score 1.02). The majority of these control participants had asymptomatic hyperuricaemia, consistent with recent imaging studies demonstrating that urate deposition is frequently present in such individuals (5, 22-24). It is also possible that some of the very small
‘deposits’ represent artefact (15). Further analysis of changes in these very small lesions in response to urate-lowering therapy will be of interest.

This analysis showed that the DECT urate scoring method had greater ability to differentiate between pegloticase responders and non-responders. A key reason for this difference between methods may be the large variation in urate volumes in patients with tophaceous gout. Such wide variation in urate volumes makes analysis of change more complex and may lead to reduced power to detect differences over time. The lower variation in the DECT urate scoring system may have particular advantages in studies examining changes in urate burden in response to therapy.

We recognise that analysis of pegloticase responses alone is a limitation of our current study. Pegloticase is an intensive intervention typically reserved for patients with severe disease characterised by high urate burden (18). The marked reduction in serum urate concentrations in pegloticase responders make this agent an excellent model for assessing sensitivity to change of the instrument with small patient numbers, but may not entirely reflect sensitivity to change using less intensive therapy or in patients with lower baseline urate crystal burden (eg. conventional oral urate-lowering in patients with non-tophaceous gout). At present, longitudinal datasets examining the effects of urate-lowering therapies that reduce serum urate to less intensive levels are not available. Additional studies examining sensitivity to change of the DECT urate score in this context are planned as these datasets become available; this work is required to fully validate this scoring system.

The proposed DECT urate scoring system includes bilateral feet and ankles, but not other joints. The vast majority of patients with gout present with foot and ankle symptoms during
the course of their disease (17). Consistent with this clinical observation, on our initial review of DECT scans, most of the available scans were of the feet and ankles. It is possible that inclusion of other joint areas, such as knees, hands and elbows, may provide some additional value for both the urate volume assessment and the DECT urate score (21).

However, limiting the scans to bilateral feet and ankles has a number of advantages, particularly in the context of an instrument for use in clinical trials. This protocol is likely to efficiently capture clinically important disease with reduced time and cost of scanning and scoring. Importantly, by limiting to a single peripheral joint area, this protocol substantially reduces medical radiation exposure, allowing for safer and more feasible repeat assessments, a key issue for outcome measurement in gout.
CONFLICT OF INTEREST STATEMENT

Ardea Biosciences funded the study but had no influence over development of the study design, conduct of the study, data analysis or manuscript preparation.

Sara Bayat: no conflicts disclosed
Opetaia Aati: no conflicts disclosed
Jürgen Rech: no conflicts disclosed
Mark Sapsford: no conflicts disclosed
Alexander Cavallaro: no conflicts disclosed
Michael Lell: no conflicts disclosed
Elizabeth Araujo: no conflicts disclosed
Christina Petsch: no conflicts disclosed

Lisa K. Stamp: discloses consulting fees (<$10,000) from AstraZeneca
Georg Schett: no conflicts disclosed
Bernhard Manger: no conflicts disclosed

Nicola Dalbeth: discloses consulting fees (<$10,000) from Takeda, Pfizer, Ardea, AstraZeneca, Crealta, and Cymabay, and speaker fees (<$10,000) from Menarini, Teijin and AstraZeneca.

AUTHOR CONTRIBUTIONS

Sara Bayat: 1b, 1c, 2, 3
Opetaia Aati: 1b, 2, 3
Jürgen Rech: 1a, 1b, 1c, 2, 3
Mark Sapsford: 1b, 2, 3
Alexander Cavallaro: 1c, 2, 3
Michael Lell: 1c, 2, 3
Elizabeth Araujo: 1b, 2, 3
Christina Petsch: 1b, 2, 3
Lisa K. Stamp: 1b, 2, 3
Georg Schett: 1a, 2, 3
Bernhard Manger: 1a, 2, 3
Nicola Dalbeth: 1a, 1b, 1c, 2, 3
REFERENCES


Table 1. Patient characteristics at the time of DECT scanning. Unless specified, data are presented as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>Gout (n=182)</th>
<th>Controls (n=42)</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>157 (86.3%)</td>
<td>38 (91%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61 (12)</td>
<td>63 (15)</td>
</tr>
<tr>
<td>Gout disease duration, years</td>
<td>9 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>Number (%) on urate-lowering therapy</td>
<td>120 (65.9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Number (%) with microscopically proven gout</td>
<td>63 (35%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number (%) with tophi</td>
<td>89 (48.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Serum urate, mg/dL</td>
<td>7.2 (2.2)</td>
<td>8.3 (2.2)</td>
</tr>
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</table>
Table 2: DECT urate scores and urate volumes. Data are presented as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>All scans</th>
<th>All gout</th>
<th>All controls</th>
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<tbody>
<tr>
<td>DECT urate volume, cm$^3$</td>
<td>1.96 (5.78)</td>
<td>2.41 (6.33)</td>
<td>0.02 (0.06)</td>
</tr>
<tr>
<td>Mean DECT urate score (range 0-12)</td>
<td>5.67 (4.23)</td>
<td>6.75 (3.95)</td>
<td>1.02 (1.21)</td>
</tr>
<tr>
<td>Mean DECT sub-score at MTP1 (range 0-3)</td>
<td>1.47 (1.33)</td>
<td>1.77 (1.27)</td>
<td>0.14 (0.52)</td>
</tr>
<tr>
<td>Mean DECT sub-score at toes (range 0-3)</td>
<td>1.09 (1.25)</td>
<td>1.31 (1.27)</td>
<td>0.08 (0.27)</td>
</tr>
<tr>
<td>Mean DECT sub-score at ankle/midfoot (range 0-3)</td>
<td>1.34 (1.34)</td>
<td>1.60 (1.33)</td>
<td>0.21 (0.64)</td>
</tr>
<tr>
<td>Mean DECT sub-score at tendons (range 0-3)</td>
<td>1.78 (1.06)</td>
<td>2.05 (0.96)</td>
<td>0.58 (0.51)</td>
</tr>
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</table>
Table 3. DECT urate scores and urate volumes in patients treated with pegloticase.

Pegloticase responders achieved a serum urate concentration <6mg/dL during treatment and non-responders did not achieve a serum urate concentration <6mg/dL during treatment. Data are presented as mean (SD). *** Sidak’s multiple comparison test p<0.001.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>Two way ANOVA P for interaction</th>
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<tbody>
<tr>
<td>Baseline DECT urate score</td>
<td>11.9 (0.22)</td>
<td>10.0 (3.46)</td>
<td></td>
</tr>
<tr>
<td>Post-treatment DECT urate score</td>
<td>5.4 (2.7)***</td>
<td>10.0 (3.46)</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline urate volume, cm³</td>
<td>17.8 (20.0)</td>
<td>5.63 (4.77)</td>
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<tr>
<td>Post-treatment urate volume, cm³</td>
<td>0.22 (0.20)</td>
<td>4.25 (3.56)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1. **Representative scores for each region.** The figure show 2-dimensional DECT images with urate colour-coded as green. The score of 3 in the toes refers to the urate deposition in the 3rd metatarsophalangeal joint.

Figure 2. **Box and whisker plot showing discrimination between groups.** A. DECT urate scores and B. urate volumes for the following groups: tophaceous gout (tophus, n=89), non-tophaceous gout (no tophus, n=93), hyperuricemic (HU) controls (n=28) and normouricemic (NU) controls (n=14). Kruskall-Wallis p<0.0001 for both methods, ****Dunn’s multiple comparisons test p<0.0001.

Figure 3. **Box and whisker plot showing change values in patients treated with pegloticase.** A. DECT urate scores and B. urate volumes. Pegloticase responders achieved a serum urate concentration <6mg/dL during treatment and non-responders did not achieve a serum urate concentration <6mg/dL during treatment.
Figure 1. Representative tendon scores. The figure show sagital 2-dimensional DECT images of the Achilles tendons with urate colour-coded as green.

209x138mm (300 x 300 DPI)
Figure 2. Box and whisker plot showing discrimination between groups. A. DECT urate scores and B. urate volumes for the following groups: tophaceous gout (tophus, n=89), non-tophaceous gout (no tophus, n=93), hyperuricemic (HU) controls (n=28) and normouricemic (NU) controls (n=14). Kruskall-Wallis p<0.0001 for both methods, ****Dunn’s multiple comparisons test p<0.0001.
Figure 3. Box and whisker plot showing change values in patients treated with pegloticase. A. DECT urate scores and B. urate volumes. Pegloticase responders achieved a serum urate concentration <6mg/dL during treatment and non-responders did not achieve a serum urate concentration <6mg/dL during treatment.
Supplementary figure 1. Representative scores for each region. The figure shows 2-dimensional DECT images with urate colour-coded as green. The score of 3 in the toes refers to the urate deposition in the 3rd metatarsophalangeal joint.