Assessment of Tophus Size: a Comparison Between Physical Measurement Methods and Dual Energy Computed Tomography Scanning

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Disclosures

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• Qiliang Liu was the recipient of a University of Auckland summer studentship

• I have no other relevant financial disclosures.

Background

• The tophus is a pathognomonic feature of gout

• Foreign body granulomatous response to monosodium urate (MSU) crystals
  – Innate and adaptive immune activation

Background

• Impact of tophi
  – Disfiguring
  – Discharge with secondary infection
  – Obstruct joint movement
  – Disability
  – Joint damage

• Tophus regression has been endorsed by OMERACT as a core domain for clinical trials of chronic gout

Background

• Many methods of tophus measurement described:
  – Vernier calipers (longest index tophus diameter)*
  – Tape measurement (index tophus area)
  – Counting of all visible tophi
  – Digital photography
  – Ultrasonography
  – Magnetic resonance imaging
  – Conventional computed tomography (CT)

  *OMERACT endorsed

Background

• Dual energy CT (DECT) is a sensitive and specific method to detect urate deposits in patients with gout

• DECT uses a specific display algorithm that assigns different colours to materials of different chemical composition (such as urate and hydroxyapatite)

• The reliability of DECT for tophus measurement has not been reported to date
Aim

• To compare the reliability and validity of various physical methods with DECT assessment of tophus size

Methods: patients and tophus selection

• Twenty-five patients with
  — a history of acute gout according to ACR classification criteria, and
  — at least one subcutaneous tophus

• For each patient, up to three index tophi were selected for analysis (n=64 tophi, 55 in the feet)
  — sites in the feet were preferentially selected
  — if >3 tophi present in the feet, the largest tophi were selected
  — discharging, acutely inflamed or bursal tophi were not selected

Methods: physical measurement

• Each tophus was assessed by two independent observers
  — Vernier calipers (longest diameter)
  — Tape measure (area)

• Tophus location was recorded in detail using a diagram and written description

• The total number of subcutaneous tophi was also counted

• Five patients returned within one week for repeat physical assessments

Methods: DECT

• All patients proceeded to DECT scanning of both feet (Somatom Definition Flash, Siemens Medical)

• Index tophus DECT volume was assessed by two independent observers using automated volume assessment software

• DECT scans from the returning patients were scored twice by both observers

Methods

• Each observer was blinded to the scores of the other observers and previous measures

• Intra- and inter-observer reproducibility was assessed by intraclass correlation coefficient (ICC) and limits of agreement analysis (Bland and Altman).

• For the purposes of these analyses the unit of investigation was assumed to be the tophus

Results: patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=25)</th>
<th>Patients returning for second visit (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>64 (40-85)</td>
<td>64 (40-74)</td>
</tr>
<tr>
<td>Male gender, n (%):</td>
<td>23 (92%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Ethnicity: Pacific New Zealand Maori</td>
<td>10 (40%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>New Zealand European/Other</td>
<td>14 (56%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Aspirate proven gout</td>
<td>11 (44%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Gout disease duration, years, median (range)</td>
<td>24 (3-50)</td>
<td>45 (21-49)</td>
</tr>
<tr>
<td>Serum urate, mmol/L, median (range)</td>
<td>0.39 (0.18-0.71)</td>
<td>0.37 (0.35-0.49)</td>
</tr>
<tr>
<td>On allopurinol, n (%):</td>
<td>18 (72%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Total DECT urate volume (both feet), cm$^3$, median (range)</td>
<td>1.65 (0.07-28.88)</td>
<td>8.02 (0.13-28.88)</td>
</tr>
</tbody>
</table>
Results: Intraobserver reproducibility (Assessment 1 vs. Assessment 2)

<table>
<thead>
<tr>
<th>Method</th>
<th>ICC, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernier calipers</td>
<td>0.75 (0.54-0.87)</td>
</tr>
<tr>
<td>Tape measure</td>
<td>0.91 (0.82-0.96)</td>
</tr>
<tr>
<td>Tophus count</td>
<td>0.96 (0.97-0.98)</td>
</tr>
<tr>
<td>DECT volume</td>
<td>1.00 (0.98-1.00)</td>
</tr>
</tbody>
</table>

To allow comparison between measures, the y axis value approximates twice the mean score.

Results: Interobserver reproducibility (Observer 1 vs. Observer 2)

<table>
<thead>
<tr>
<th>Method</th>
<th>ICC, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernier calipers</td>
<td>0.78 (0.66-0.86)</td>
</tr>
<tr>
<td>Tape measure</td>
<td>0.88 (0.82-0.93)</td>
</tr>
<tr>
<td>Tophus count</td>
<td>0.58 (0.25-0.79)</td>
</tr>
<tr>
<td>DECT volume</td>
<td>0.95 (0.92-0.97)</td>
</tr>
</tbody>
</table>

To allow comparison between measures, the y axis value approximates twice the mean score.

Results: Comparison of values between different methods (feet, n=55)

<table>
<thead>
<tr>
<th>Method</th>
<th>Correlation (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calipers vs Calipers</td>
<td>r=0.94</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Calipers vs Tape</td>
<td>r=0.94</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Calipers vs DECT</td>
<td>r=0.46</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Tape vs DECT</td>
<td>r=0.46</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>

Results: distribution of urate in tophi

- Large variation was observed in the amount of urate deposits documented by DECT in tophi of similar physical size
- Discrete urate collections were frequently scattered throughout the tophus, typically surrounded by soft tissue

Summary

- DECT reveals the composition of tophi which contain variable urate deposits embedded within soft tissue
- DECT scanning is a highly reproducible method of assessing urate load within tophi
  - Overall higher reproducibility than physical tophus measurement methods
  - Relatively modest relationship between physical tophus size and DECT urate volume, reflecting the composition of the tophus

Further questions/issues

- Is DECT sensitive to change?
- Is DECT feasible for use in clinical trials?
  - Cost
  - Availability
  - Radiation
- What is the relative importance of urate load compared with total tophus size on clinically relevant outcomes?

In 20% of tophi recorded on physical assessment, no urate deposits were observed in the tophus by DECT

Those tophi without urate deposits on DECT had smaller caliper diameter (p=0.02) and tape area (p=0.01)

Example of two similar sized tophi from a single patient showing large variation in urate volume. The borders of the tophi (determined from CT images) are outlined.