Dual-energy computed tomography in the diagnosis and treatment monitoring of gout

Dual-energy Computertomographie in der Diagnostik und im Behandlungsverlauf von Gicht

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Abstract

Objectives

The purpose of this study was to show the capabilities of dual-energy computed tomography (DECT) in the diagnosis and treatment monitoring of gout and to define the threshold (in g/ml) of a reliable detection of monosodium urate (MSU) crystals and calcium deposits in DECT.

Materials and Methods

Sodium ascorbate and potassium citrate were used as substitutes for MSU and calcium deposits, as these materials have similar characteristics in DECT and were more easily available than the original substances. Phantoms with different sizes (10 cm, 20 cm, 30 cm and 10 + 10 cm, 20 + 20 cm diameter) were scanned with different concentrations of sodium ascorbate (0.2 - 0.5 g/ml, 0.05 g/ml increment) and potassium citrate (0.1 - 0.5 g/ml, 0.1 g/ml increment) using clinical DECT protocols. In order to assess the influence of different scan protocols, additional examinations for sodium ascorbate 0.35 g/ml and potassium citrate 0.2 g/ml were performed.

To simulate tophus formation, sodium ascorbate (0.5 g/ml) mixed with agarose-gel was injected into a pig leg (intramuscularly, subcutaneously, the knee joint capsule). The leg was then examined with different DECT-protocols.

Furthermore 150 DECT examinations of the foot and hand (43 women, 107 men, mean age 61 ± 12 years) and the DECT examinations of a follow-up group of 17 patients (3 women, 14 men, mean age 56 ± 10 years), all of which were made using the same DECT system, were reviewed. Data was acquired operating at a tube voltage of 80 kV and Sn 140 kV. After determining the region of interest, MSU volume was calculated.
Results

The experiments showed that sodium ascorbate (MSU substitute) can be reliably detected in DECT above a concentration of ≥ 0.35 g/ml with an accuracy ≥ 65 %. Accuracy was related to phantom size (96 % for small phantoms) and x-ray exposure. Potassium citrate (calcium deposit substitute) was reliably detected and differentiated in DECT above a concentration of ≥ 0.2 g/ml (accuracy ≥ 99 %).

The test object with injected sodium ascorbate agarose gel solution showed adequate HU numbers for MSU.

Treatment response could be objectively measured using DECT and automated urate volume analysis.

Conclusions

DECT should be performed with anatomically adapted protocols. DECT reliably differentiates MSU in concentrations ≥ 0.35 g/ml and calcium deposits in concentrations ≥ 0.2 g/ml.

DECT is an instrument to non-invasively diagnose MSU deposition and seems to be able to monitor treatment effects. MSU tophi do not always correlate with high serum uric acid concentrations. The same scan-protocols should be used for follow-up examinations to get reliable results.
Zusammenfassung

Hintergrund und Ziele

Ziel dieser Studie war es, die Möglichkeiten der Dual-energy Computertomographie in der Diagnostik und Verlaufskontrolle bei Gichtpatienten aufzuzeigen und die Bestimmung von Schwellenwerten für Mononatriumurat und Kalkaineinlagerungen zu definieren ab denen es möglich ist MSU und Kalzium mit Hilfe der DECT zu erkennen und zu unterscheiden.

Material und Methoden

Phantome unterschiedlicher Größe (10 cm, 20 cm, 30 cm, 10 + 10 cm, 20 + 20 cm) mit unterschiedlichen Konzentrationen von Natriumascorbat (0.2 g/ml - 0.5 g/ml, in 0.05 g/ml Schritten) und Kaliumcitrat (0.1 g/ml - 0.5 g/ml, in 0.1 g/ml Schritten) wurden mit DECT untersucht. Natriumascorbat wurde als Äquivalent für Mononatriumurat und Kaliumcitrat als Äquivalent für Kalkaineinlagerungen benutzt, da diese leichter verfügbar waren und in Tests die gleichen Eigenschaften wie Mononatriumurat und Kalk zeigen. Zusätzliche Untersuchungen für Natriumascorbat mit einer Konzentration von 0,35 g/ml und Kaliumcitrat mit einer Konzentration von 0,2 g/ml wurden mit unterschiedlichen Protokollen durchgeführt.

Zur Simulation von Gichttophi wurde Natriumascorbat (0,5 g/ml) mit Agarosegel gemischt und in das Bein (intramuskulär, subcutan, in die Capsula articularis des Knies) eines Hausschweins injiziert. Das Bein wurde danach mit unterschiedlichen DECT-Protokollen gescannt und ausgewertet.

Des Weiteren wurden 150 Bilder von DECT Untersuchungen von Händen und Füßen (43 Frauen, 107 Männer, Durchschnittsalter 61 ± 12 Jahre) und die DECT Untersuchungen einer Verlaufsgruppe aus 17 Patienten (3 Frauen, 14 Männer, Durchschnittsalter 56 ± 10 Jahre), welche alle auf dem gleichen DECT System entstanden sind, berücksichtigt. DECT wurde mit einer Röhrenspannung von 80 kV und Sn 140 kV durchgeführt und die Mononatriumurat-Ansammlungen volumetriert.
**Ergebnisse und Beobachtungen**

Natriumascorbat, als Ersatz für MSU, konnte gesichert ab einer Konzentration von $\geq 0.35$ g/ml mit einer Genauigkeit von mindestens 65 % mit DECT nachgewiesen werden. Bei kleineren Phantomdurchmessern konnte diese auf 96 % gesteigert werden. Bei größeren Phantomen musste die Röntgendosis angespasst werden.

Kaliumcitrat, als Ersatz für Kalkeinlagerung, konnte bei einer Konzentration von $\geq 0.2$ g/ml mit mindestens 99 % im DE Verfahren erkannt werden.

Die Untersuchungen mit Natriumascorbat-Agarosegel in einem Testobjekt zeigten passende HU Werte für MSU.

In den Patientenuntersuchungen (DECT der Hände und Füße) konnte das MSU-Volumen volumetriert und ein Ansprechen auf die Therapie im Verlauf quantifiziert werden.

**Praktische Schlussfolgerung**

DECT kann MSU-Konzentrationen von $\geq 0.35$ g/ml und Kalk-Konzentrationen von $\geq 0.2$ g/ml zuverlässig nachweisen. Da der Nachweis durch erhöhtes Bildrauschen beeinträchtigt wird, sind anatomisch adaptierte Protokolle erforderlich. Um für longitudinale Vergleichsstudien valide Daten zu erhalten müssen die Untersuchungen mit dem gleichen Protokoll durchgeführt werden.

1. Introduction

Monosodium urate (MSU) crystal deposition is the hallmark of gout. The gold standard to diagnose gout is the microscopic identification of MSU crystals under polarizing light (1). However, in up to 25% the clinical suspicion of gout is low (2) and crystal identification may be hampered (3). A variety of imaging techniques are used to diagnose gout noninvasively, including plain radiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and dual-energy computed tomography (DECT) (4, 5).

DECT has recently become popular in the detection of MSU crystals in patients with tophaceous gout (6). MSU is identified on the basis of its atomic number and separated from calcium in bone and soft tissues (6). This method showed to be very specific and moderately sensitive in the identification of MSU tophi after positive joint aspirates (7).

The deposition of MSU crystals is the pathological feature of gout. It leads to acute flares, chronic synovitis and tophaceous disease with associated cartilage and bone destruction (8). Chronic inflammation, bone erosion and tophi formation are the result of joint and tissue damage in gout (9).

Gout is a chronic inflammatory disease affecting more than 1% of the adult population, being the most prevalent of all inflammatory diseases with rising incidence in industrially developed countries (longer life expectancy, genetic and environmental risk factors such as male gender, alcohol, purine-rich products, metabolic syndrome, obesity, hypertension, use of diuretics and chronic renal disease) (10-19). The highest incidence of gout attacks is reported to occur during spring (20, 21). Men are four times more likely to develop gout than women at a younger age (< 65 years). Above the age of 65 the men/women-ratio becomes 3 / 1 (10, 22).

Patients with gout have a poorer health-related quality of life and on average five more absence days from work per year (23, 24). Besides clinical assessment, imaging might establish a central role in the diagnosis and monitoring treatment (25) and may help to improve outcome (26-29).
The aim of this study is to systematically evaluate the range of MSU concentration detectable in DECT, and to demonstrate the effectiveness of DECT in diagnosis and treatment monitoring of gout.
2. Material and Methods

2.1 Experimental study

2.1.1 Phantom

To simulate different sizes of extremities, concentric plastic tanks (10 cm, 20 cm, 30 cm and 10 + 10 cm, 20 + 20 cm diameter) were used. Vials with different sodium ascorbate or potassium citrate concentrations were inserted and the tanks were filled with water. Sodium ascorbate was used as a substitute for MSU crystals and potassium citrate as a substitute for calcium deposits because of similar DECT properties (30), better availability and easier handling. Different tanks were used to simulate different body parts (10 cm diameter: single hand; 20 cm: single foot; 30 cm: body regions, e.g. hip or shoulder joints; 10 + 10 cm: both hands; 20 + 20 cm: both feet).

2.1.2 Concentrations

Seven different concentrations of sodium ascorbate (0.2 g/ml, 0.25 g/ml, 0.3 g/ml, 0.35 g/ml, 0.4 g/ml, 0.45 g/ml and 0.5 g/ml) and 5 concentrations of potassium citrate (0.1 g/ml, 0.2 g/ml, 0.3 g/ml, 0.4 g/ml and 0.5 g/ml) were examined.

2.1.3 Dual-energy Computed Tomography

All phantoms were scanned with a dual source CT system (Somatom Flash, Siemens Healthcare, Forchheim, Germany), which uses two x-ray sources, arranged at 95° (fig. 1), to simultaneously acquire data at 80 and 140 kV (31). Image post-processing was performed on a dedicated workstation (MMWP, syngo Dual energy, Siemens Healthcare, Forchheim, Germany). In order to gain a better separation of the x-ray spectra of both tubes, an additional tin filter (Sn), which reduces the low-energy photons from the high-energy (140 kV) spectrum, was added. The maximum tube current was 550 mA at 80 kV and 500 mA at 140 kV (32, 33).
Figure 1: Dual-energy computed tomography

2.1.4 Protocols

The acquisition parameters are given in table 1. The protocols suggested by the manufacturer were used for the examinations of the hand (H) and foot (F).
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Tube A</th>
<th>Tube current (ref. mAs) tube A</th>
<th>Tube B</th>
<th>Tube current (ref. mAs) tube B</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (foot)</td>
<td>80 kV</td>
<td>250 mAs</td>
<td>Sn 140 kV</td>
<td>125 mAs</td>
</tr>
<tr>
<td>H (hand)</td>
<td>80 kV</td>
<td>205 mAs</td>
<td>Sn 140 kV</td>
<td>103 mAs</td>
</tr>
<tr>
<td>F1</td>
<td>80 kV</td>
<td>131 mAs</td>
<td>140 kV</td>
<td>31 mAs</td>
</tr>
<tr>
<td>H1</td>
<td>80 kV</td>
<td>110 mAs</td>
<td>140 kV</td>
<td>26 mAs</td>
</tr>
<tr>
<td>F2</td>
<td>100 kV</td>
<td>125 mAs</td>
<td>Sn 140 kV</td>
<td>125 mAs</td>
</tr>
<tr>
<td>H2</td>
<td>100 kV</td>
<td>103 mAs</td>
<td>Sn 140 kV</td>
<td>103 mAs</td>
</tr>
<tr>
<td>2F (double dose)</td>
<td>80 kV</td>
<td>500 mAs</td>
<td>Sn 140 kV</td>
<td>250 mAs</td>
</tr>
</tbody>
</table>

**Table 1: DECT-protocol**

Table 2 shows the phantoms, the different concentrations and the protocols that were used for sodium ascorbate and potassium citrate.

<table>
<thead>
<tr>
<th>Material</th>
<th>Phantom</th>
<th>Concentration (g/ml)</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.2</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm and 20 cm</td>
<td>0.25</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm and 20 cm</td>
<td>0.3</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.35</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm and 20 cm</td>
<td>0.4</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm and 20 cm</td>
<td>0.45</td>
<td>H + F</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.5</td>
<td>H + F</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 cm</td>
<td>0.35</td>
<td>H1 + F1, H2 + F2</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>10 + 10 cm</td>
<td>0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5</td>
<td>H</td>
</tr>
<tr>
<td>Sodium ascorbate</td>
<td>20 + 20 cm</td>
<td>0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5</td>
<td>F + 2F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.1</td>
<td>H + F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm and 20 cm</td>
<td>0.2</td>
<td>H + F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.3</td>
<td>H + F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm and 20 cm</td>
<td>0.4</td>
<td>H + F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm, 20 cm and 30 cm</td>
<td>0.5</td>
<td>H + F</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>10 cm</td>
<td>0.2</td>
<td>H1 + F1, H2 + F2</td>
</tr>
</tbody>
</table>

Table 2: Experimental settings

2.1.5 Hounsfield Units

Hounsfield Units (HU) are used as a quantitative scale for describing radiodensity. This scale is used for the CT scanner and is calibrated with
reference to water. On current Siemens scanners (12bit format) the scale includes values from -1024 to 3071 HU.

The CT-value in HU is calculated from the X-ray attenuation coefficient $\mu$ using this formula (34):

$$ x = \left( \frac{\langle \mu_{_{\text{material}}} \rangle}{\langle \mu_{_{\text{H}_2\text{O}}} \rangle} - 1 \right) \times 1000 \text{ HU} $$

$\mu$: true attenuation coefficient; The angle brackets denote the average over the x-ray spectrum.
x: CT-value of the material in HU

The radiodensity of distilled water at a standard pressure and temperature is defined as zero HU and the radiodensity of air is -1000 HU (35, 36). Prior to the examinations, the DECT was calibrated with reference to distilled water in order to ensure exact results.

The resulting DECT images (overlay images) represent pseudo HU values. The pseudo HU are calculated from the real CT-values using this formula:

$$ y = \left( \frac{(x_{_{\text{low}}}-o_{_{\text{low}}})}{(x_{_{\text{high}}}-o_{_{\text{high}}})-\text{threshold}} \right) \times 100 \text{ HU} $$

$x_{_{\text{low}}}/x_{_{\text{high}}}$: measured CT-values in HU

$o_{_{\text{low}}}/o_{_{\text{high}}}$: CT-values of the soft tissue in which MSU is embedded (in this case (50 HU)/(50 HU))

threshold: threshold between MSU and calcium deposits

$y$: overlay-value in pseudo HU

The overlay value of MSU is approximately -36 HU and the overlay value of calcium deposits is +35 HU and can go up to +1000 HU because of the following exception rules:

$$ x_{_{\text{low}}} \times DE_{\text{composition}} + x_{_{\text{high}}} \times (1-DE_{\text{composition}}) > 500 \text{ HU} \rightarrow y=1000 $$

$$ x_{_{\text{low}}} \times DE_{\text{composition}} + x_{_{\text{high}}} \times (1-DE_{\text{composition}}) < 150 \text{ HU} \rightarrow y=0 $$

The DE composition is the linear weight of the low kV image for the calculation of the diagnostic mixed image. This value is set on the scanner for each reconstruction job.
2.1.6 Uric acid volume determination and sensitivity calculation

The volume was calculated using different threshold values (-1 to -1024 HU, 3071 to 1 HU, 3071 to -1024 HU). The different threshold values represented the different sensitivities for sodium ascorbate and potassium citrate.

\[
\text{sensitivity of sodium ascorbate} = \frac{(-1 \text{ to } -1024)}{(3071 \text{ to } -1024)}
\]

(-1 to -1024): range in which sodium ascorbate HU are represented

(3071 to -1024): full range of HU

The overlay image of sodium ascorbate (similar to MSU) had a negative pseudo HU number.

\[
\text{sensitivity of potassium citrate} = \frac{(3071 \text{ to } 1)}{(3071 \text{ to } -1024)}
\]

(3071 to 1): range in which potassium citrate HU are represented

(3071 to -1024): full range of HU

The overlay image of potassium citrate (similar to calcium deposit) had a positive pseudo HU number.

2.2 Sodium ascorbate injections into a test object

Sodium ascorbate (0.5 g/ml) was mixed with agarose gel and injected with a syringe into different locations (intramuscular, subcutaneous, capsule of the knee joint) of a pig’s leg while the mixture was still warm (body temperature). Afterwards DECT scans with different protocols (table 1) were performed. Data was analyzed as described in section 2.3.3.

The agarose gel consisted of standard agarose (agarose low EEO) mixed with a buffer ((10x) 400 mM tris base, 10 mM EDTA, 11.4 ml acetic acid with a pH-value of 8.5) and blended with 1 litre of water.
2.3 Clinical study

2.3.1 Study collective

Patients with the clinical suspicion of gout and patients under gout therapy were included in this study. Informed consent was obtained from each patient and the study was approved by the institutional review board.

A total of 150 DECT examinations (foot, n=98; hand, n=52) were performed on 86 consecutive patients. 43 DECT scans were performed on women (age 58.6 ± 12.8 years, range 28-80) and 107 on men (age 61.4 ± 11.2 years, range 42-85) between January 2011 and October 2012.

10 patients had repetitive DECT scans (15 foot, 2 hand examinations). The average scan interval was 201 days (range: 20-457 days) for the first, 166 days (range: 160-172 days) for the second and 261 days for the third follow-up scan. 14 scans were performed on male (53.6 ± 9.3 years; range: 42-70 years) and 3 on female patients (68 ± 1.7 years; 67-70 years). Using up to 3 follow-up examinations, it was possible to observe the progression of the disease.

2.3.2 Protocol

Two different scan protocols were applied, as suggested by the manufacturer, one for examining the feet (F-protocol), one for examining the hands (H-protocol) (table 1). All patients were scanned in supine position. For the hand examinations the patients’ arms were elevated (superman position). Automatic tube current modulation (CAREdose, Siemens Healthcare, Forchheim, Germany) was enabled to reduce the radiation exposure (37). Image reconstruction was performed with 0.75 mm slice thickness, 0.5 mm slice increment, FOV 10 cm and a dedicated medium sharp dual energy kernel (D 45). A parameter ratio of 1.55 was used for the reconstructions. The analysis of the examinations was conducted on a dedicated workstation (MMWP, VE36A syngo Dual Energy; Siemens Healthcare, Forchheim, Germany).

The software was set to color-code MSU deposits in green, and calcium in blue or pink.
2.3.3 Determination of the uric acid volume

A volume of interest (VOI) including the MSU deposits was segmented in the volume mode of syngo Dual Energy. As prior studies have shown, color-coding suggestive for MSU deposits can occur by mistake in the foot nails or the heel skin (38). These areas were manually excluded from the VOI. After segmentation, the MSU volume was calculated for the threshold values -1 to -1024 HU.

2.3.4 Artifacts

Artifacts caused by skin, nails or metal objects were excluded in volume calculation.
3. Results

3.1 Experimental study

3.1.1 Sodium ascorbate

In the phantom measurement sodium ascorbate could be visualized and compatible HU numbers could be detected in concentrations ≥ 0.35 g/ml. The sensitivity in DECT examinations was higher with smaller phantoms. In the 10 cm phantom, sodium ascorbate with a concentration of 0.35 g/ml could be detected with a sensitivity of 96 %, while in the 20 cm phantom it was 76 %. In the 30 cm phantom, the sensitivity dropped to 65 % (figure 2).

The results of the F-protocol (80kV-250mAs / Sn140kV-125mAs) were comparable to those of the H-protocol (80kV-205mAs / Sn140kV-103mAs). They showed the same ranges in sensitivity and the same sensitivity modifications with low or high concentrations of sodium ascorbate. The sensitivity decreased with an increase of phantom size. This was due to a steady tube current for both protocols. When working with a concentration of 0.35 g/ml sodium ascorbate the sensitivity in the 30 cm phantom was 65 % for H-protocol compared to a sensitivity of 68 % using F-protocol. A higher tube current improved sodium ascorbate detectability.
Figure 2: Sodium ascorbate (H-protocol: 80kV-205mAs / Sn140kV-103mAs; F-protocol: 80kV-250mAs / Sn140kV-125mAs): Concentration of sodium ascorbate has to be ≥ 0.35 g/ml

The threshold for the classification of sodium ascorbate was 0.35 g/ml. Depending on the protocol (x-ray exposure) and phantom diameter concentrations of sodium ascorbate ≥ 0.4 g/ml were correctly classified (≥ 96 %).

Image noise in the 30 cm phantom was too high to correctly classify low sodium ascorbate concentrations (figure 3). The error rate shows the false positive volume detections.
**Figure 3:** Sodium ascorbate in phantom 30 cm (H-protocol: 80kV-205mAs / Sn140kV-103mAs; F-protocol: 80kV-250mAs / Sn140kV-125mAs): Reliable results at concentrations of sodium ascorbate ≥ 0.4 g/ml

Figure 4 shows the examinations of 10 cm phantoms filled with different concentrations of sodium ascorbate and scanned with H-protocol. The first color-coding began to show in a concentration of 0.3 g/ml represented by some green voxels. The relevant color-coding switch was seen in the examination with a concentration of 0.35 g/ml. The intensity of color-coding increased along with higher sodium ascorbate concentrations.
Figure 4: 10 cm phantom with different concentrations of sodium ascorbate (g/ml) scanned with H-protocol (80kV-205mAs / Sn140kV-103mAs): Relevant color-coding ≥ 0.35 g/ml
In order to simulate an examination of two hands or feet an additional phantom was placed next to the phantom containing the specimen prior to the scan. Acceptable results with two 10 cm phantoms (10 cm + 10 cm) could be achieved with the H-protocol (80 kV, 205 mAs / Sn140 kV, 103 mAs) at concentrations ≥ 0.35 g/ml (sensitivity ≥ 91 %). Acceptable results with 20 cm + 20 cm phantoms could be achieved with the 2F-protocol (80kV-500mAs / Sn140kV-250mAs) at concentrations ≥ 0.35 g/ml (sensitivity ≥ 74 %). The F-protocol (80kV-250mAs / Sn140kV-125mAs) achieved acceptable results (≥ 87 %) only at high concentrations (0.45 g/ml or 0.5 g/ml) of sodium ascorbate (figure 5).

**Figure 5**: Sodium ascorbate with extra phantom body: Extra phantom body needs higher tube current

Figure 6 demonstrates the differences in color-coding. While the F-protocol (left picture) showed blue and green voxels between grey voxels, the 2F-protocol (right picture) showed green color-coding and only a few grey voxels. The sensitivity was 36 % in F-protocol compared to 93 % in 2F-protocol.
Protocol: F (80kV-250mA / Sn140kV-125mA)

Protocol: 2F (80kV-500mA / Sn250kV-125mA)

Figure 6: 20 cm plus 20 cm phantoms with concentration 0.4 g/ml of sodium ascorbate: Higher tube current is associated with less noise and improved material differentiation

In one examination with a sodium ascorbate concentration of 0.35 g/ml within the 10 cm phantom, the choice of the scan protocol had only minor impact on the correct classification rate (figure 7). The slightly different results were mainly caused by image noise. Although these deviations may not be relevant in qualitative evaluation, identical protocols should be used if quantitative results are warranted for treatment monitoring.
Potassium citrate was used as a surrogate material for calcium deposits. In the 10 cm phantom, the sensitivity for 0.2 g/ml potassium citrate was 100 % using the H-protocol (80kV-205mAs / Sn140kV-103mAs) and 99.8 % in the 20 cm phantom. Using a concentration of 0.3 g/ml in the 30 cm phantom, the respective sensitivity was 99.5 %. The results for F-protocol (80kV-250mAs / Sn140kV-125mAs) were similar to H-protocol. No false positive color-coding for MSU occurred (figure 8).

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**Figure 7**: 0.35 g/ml sodium ascorbate in phantom 10 cm: Identical protocols should be used for treatment monitoring

### 3.1.2 Potassium citrate

Potassium citrate was used as a surrogate material for calcium deposits. In the 10 cm phantom, the sensitivity for 0.2 g/ml potassium citrate was 100 % using the H-protocol (80kV-205mAs / Sn140kV-103mAs) and 99.8 % in the 20 cm phantom. Using a concentration of 0.3 g/ml in the 30 cm phantom, the respective sensitivity was 99.5 %. The results for F-protocol (80kV-250mAs / Sn140kV-125mAs) were similar to H-protocol. No false positive color-coding for MSU occurred (figure 8).
A concentration of 0.2 g/ml of potassium citrate was the lower limit for color-coding in DECT. This concentration was used for the different protocols. There was no difference in sensitivity among the protocols. F-protocols were different to H-protocols in terms of color-coding (figure 9).
Figure 9: 0.2 g/ml potassium citrate in phantom 10 cm: No difference in sensitivity when using different protocols.

Figure 10 shows the different examinations of the 10 cm phantom containing various concentrations of potassium citrate, which were scanned with H-protocol. The first color-coding and adequate HU numbers were seen at 0.2 g/ml. This was the concentration at which sensitivity rose to 100 % (figure 8).
Figure 10: 10 cm phantom with different concentrations of potassium citrate (g/ml) scanned with H-protocol (80kV-205mAs / Sn140kV-103mAs): Color-coding seen in concentrations ≥ 0.2 g/ml of potassium citrate
3.2 Sodium ascorbate injections into a test object

The injected mixture of ascorbate-agarose-gel (sodium ascorbate concentration 0.5 g/ml) simulating tophus formation could be detected and classified in each case and with every protocol, but the calculated volume differed from 5.5 to 6.38 cm³. The largest volume was calculated using H1-protocol 80kV-110mAs / 140kV-26mAs and the smallest using F2-protocol 100kV-125mAs / Sn140kV-125mAs. The different calculations of volume were caused by spectral separation and image noise (figure 11).

The HU (– 28.6 to – 16.1 HU in syngo volume mode) in these examinations were the same as the HU known for MSU.

![Figure 11: Test object with sodium ascorbate 0.5 g/ml: Different volumes measured when using different protocols](image-url)
3.3 Clinical study

3.3.1 Patients with one examination

The ranges for normal serum uric acid concentrations are 3.4-7.0 mg/dl for men and 2.4-5.7 mg/dl for women. DECT detected MSU deposits in 54% (men: 60 %, women: 25 %) of the examinations when uric acid levels were higher than 5.7 mg/dl and in 29% (men: 55%, women: 0 %) when they were lower than 5.7 mg/dl.

Low MSU volume numbers were detected in 3 out of 11 scans of women whose uric acid concentrations in serum were between 5.7 mg/dl and 7.0 mg/dl.

High serum uric acid levels and large MSU tophi volumes did not correlate well (correlation coefficient 0.11).

In 34 examinations the uric acid concentrations were not available. They are represented by a value of 0 (ellipse). These cases all had MSU volumes smaller than 1 cm³ (figure 12).

However, there might have been cases in which MSU tophi were not identified because deposits may have been located in other anatomic sites, which were not examined.
**Figure 12:** Correlation between uric acid concentrations in serum and MSU volume: A correlation between uric acid levels in serum and MSU volume is not given

The most frequent locations of MSU deposits were the distal metatarsophalangeal joints one to five and the medial malleolus in the lower extremity. In the upper extremity, MSU deposits were most frequently found in the metacarpophalangeal joints two, three and five, in the proximal and distal interphalangeal joints three and four and in the radiocarpal joint (table 3).

<table>
<thead>
<tr>
<th>Localization</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower extremity</strong></td>
<td></td>
</tr>
<tr>
<td>Metatarsophalangeal joint I-V</td>
<td>27</td>
</tr>
<tr>
<td>Medial malleolus</td>
<td>10</td>
</tr>
<tr>
<td>Lateral malleolus</td>
<td>2</td>
</tr>
<tr>
<td>Upper and lower ankle joint</td>
<td>7</td>
</tr>
</tbody>
</table>
Achilles tendon | 3
Calcaneus | 1

**Upper extremity**

| Metacarpophalangeal joint II, III, V | 5
| Proximal and distal interphalangeal joint III, IV | 7
| Radiocarpal joint | 6

**Table 3:** Localization of MSU and rate: Most often found in metatarsophalangeal joint I-V and proximal and distal interphalangeal joint III, IV

### 3.3.2 Follow-up patients

Of 10 patients repetitive scans were available after initiation or modification of therapy. In all cases decreasing MSU volumes in the follow-up scans were detected (figure 13). Decrease of serum uric acid level and the volume of MSU deposition did not correlate well (correlation coefficient -0.23 for first and second examination).

In the second examination of a 54 year old male patient, the MSU volume levels were higher compared to those of the initial examination 5 months earlier. The third and fourth follow-up examination displayed a decrease of the MSU volume (figures 13, 14).

At the initial examination of a 67 year old woman with an elevated uric acid concentration (6.3 mg/dl), MSU volume was 17.02 cm³ in the right and 6.33 cm³ in the left foot (table 13: foot right/left 67 yrs.). In the follow-up DECT examinations 4 months later, the MSU volume had dropped to 5.55 cm³ in the right and 1.2 cm³ in the left foot and the uric acid in serum was 4.7 mg/dl (figures 13, 14, 15).
Follow-up examinations

Figure 13: Follow-up examinations: MSU volume decreased in the follow-up examinations
Figure 14: Follow-up examinations: Uric acid in serum decreased or increased in the follow-up examination

Figure 15: First and second DECT examination: Success of therapy
3.3.3 Artifacts

Artifacts (false positive MSU color-coding) were mostly detected in the skin of the heel and in the toe nails (most frequently the great toe, table 4), rarely within the finger nails. Artifacts can also be caused by metal objects like rings (figure 16) or osteosynthesis hardware. Tiny spots of MSU color-coding within tendons or muscles were detected in a number of cases (n=35), and it remains unclear, whether those were artifacts or not.

![Image](image-url)

**Figure 16:** Metal artifact caused by a ring, which could not be retracted before the examination

<table>
<thead>
<tr>
<th>Localization</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot nails (esp. great toe)</td>
<td>21</td>
</tr>
<tr>
<td>Skin of the heel</td>
<td>8</td>
</tr>
<tr>
<td>Tendons, muscles, plantar aponeurosis</td>
<td>35</td>
</tr>
<tr>
<td>Ring on finger</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 4:** Artifacts: Most frequent in foot nails
4. Discussion

Over the last years DECT has gained increasing attention in the diagnosis and treatment monitoring of gout. This is due to its ability to differentiate MSU from calcium deposits. While MRI and plain radiography (XR) are established imaging modalities in rheumatic diseases, both techniques are limited in the detection and differentiation of small MSU deposits (39-41). McQueen et al. (42) found in their study that MRI and DECT were able to detect tophi in a group of gout patients with almost equal sensitivity. Soft tissue changes and MSU deposits in the bursa, tendons, ligaments and soft tissues could also be detected and observed with 3D US using high-frequency transducers (25, 43). However the specificity of US was inferior to DECT (44).

Similar to the findings in this study, Girish et al. (25) reported an average density of tophi of 160-170 HU. If lesions are large enough, they can be detected on conventional CT images as discrete masses. The major advantage of DECT is its ability to distinguish different material classes, thereby helping to differentiate MSU from other crystal deposits such as calcium pyrophosphate in pseudogout (45, 46).

The use of the sodium ascorbate-agarose-gel mixture helped to produce good test results. This experimental setting therefore provides a wide range of options for further research in the field of gout. A central aspect of such further experiments needs to be a consistent use of one single DECT protocol for each series of tests in order to produce reliable results.

The scans of this study indicated that MSU crystal deposits often envelop the tendon. This phenomenon has also been described by de Avila Fernandes et al. (47), whose examinations showed that this is true in up to 45 % of the cases. The tendon involvement was predominantly visible in the Achilles tendon and the entheses of patients with a long gout history (48).

There was barely any correlation between high levels of uric acid in serum and MSU volume. Dalbeth et al. (49) and Nicolaou et al. (46) reported similar findings. Schlesinger et al. (50) stated that up to 42 % of patients with acute gout attacks had no hyperuricemia.
The therapies of gout and other rheumatic diseases have a lot of side effects. This makes a precise diagnosis particularly important, especially for patients with clinically challenging cases (46) or patients who have already been diagnosed with a rheumatic disease. There have been cases in which gout occurred in patients with rheumatoid arthritis (51), either prior to or during the disease. In such cases, where the two diagnoses may take place simultaneously, the differentiation of the diseases is essential (52, 53).

Artifacts like those described above (3.3.3) might be diagnosed as MSU tophi (also see Manger (1)). To reduce the probability of false positive results, good knowledge of typical gout tophi locations and the easy graphic visualization is important (38).

Although DECT has a high sensitivity and specificity in showing MSU deposits in joints, tendons and periarticular soft tissues – Glazebrook et al. (54) reported a 100 % sensitivity and 79-89 % specificity – there have been cases in which MSU deposits could not be seen in DECT. Possible reasons could either be that these patients might have suffered from an acute gout attack of less than 6 weeks or that the MSU deposits might have been too small to be detected. Furthermore the concentration of the tophi might have been too low (≤ 0.35 g/ml, see 3.1.1) (42) or the tophi might have been located in different joints which were not scanned. There have also been cases in which DECT examinations showed false positive result in patients with advanced osteoarthritis (55, 56), which might cause a wrong diagnosis and therapy. Before DECT can be used as a standard diagnostic tool of gout, standardized criteria including clinical information, blood levels etc. need to be set in order to schedule the examinations as effectively as possible.

Since a variety of studies has shown that the interpretation of DECT examinations proves to be accurate, it is possible to rely on the results. Therefore the findings of this study stand in accordance with findings of Glazebrook et al. (57) and illustrate once more that using DECT examinations to track the patient outcome is a good means of assessing success of gout therapy.
5. Conclusions

The experiments of this study have shown that DECT reliably produces compatible HU numbers for tissue differentiation above certain concentrations. For sodium ascorbate/MSU, the threshold is $\geq 0.35$ g/ml and for potassium citrate/calcium deposits it is $\geq 0.2$ g/ml.

DECT needs to be performed with anatomically adapted protocols or adapted x-ray doses in order to ensure a reliable detection of deposits depending on the volume of the surrounding tissue. Furthermore the same scan-protocols need to be used in follow-up examinations in order to achieve comparable results.

DECT is an instrument to diagnose MSU deposition and seems to be able to monitor treatment effects, as it can quantitatively identify the MSU volume. Especially multimorbid patients and patients with a coagulopathy obtain benefit from this non-invasive examination, which helps to differentiate gout from other rheumatic diseases.

The clinical part of the study has illustrated that MSU tophi do not always correlate with high serum uric acid levels. A reliable diagnosis of gout therefore needs to be established including further parameters.
6. References

43. Thiele RG, Schlesinger N. Diagnosis of gout by ultrasound. Rheumatology. 2007;46(7):1116-21.
## 7. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>cm</td>
<td>Centimetres</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DE</td>
<td>Dual-energy</td>
</tr>
<tr>
<td>DECT</td>
<td>Dual-energy computed tomography</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>FOV</td>
<td>Field Of View</td>
</tr>
<tr>
<td>g/ml</td>
<td>Grams per millilitres</td>
</tr>
<tr>
<td>HU</td>
<td>Hounsfield Units</td>
</tr>
<tr>
<td>kV</td>
<td>Kilovolt</td>
</tr>
<tr>
<td>I</td>
<td>Litres</td>
</tr>
<tr>
<td>mAs</td>
<td>Milliampere-second</td>
</tr>
<tr>
<td>mM</td>
<td>Millimole</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MSU</td>
<td>Monosodium urate</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume of interest</td>
</tr>
<tr>
<td>XR</td>
<td>Plain radiography</td>
</tr>
<tr>
<td>yrs.</td>
<td>Years</td>
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