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Accuracy of dual-energy computed tomography (CT), ultrasound, cone-beam CT, and spectral photon-counting CT for detecting calcium crystal deposition in the osteoarthritic hand: a cross-sectional diagnostic test study

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Objective: To evaluate the diagnostic performance of dual-energy computed tomography (DECT), ultrasound (US), cone-beam computed tomography (CBCT), and multi-energy spectral photon-counting computed tomography (SPCCT) for detecting calcium pyrophosphate (CPP) and hydroxyapatite crystal deposition.

Method: We prospectively enrolled patients scheduled for finger-joint surgery due to osteoarthritis. Preoperative cross-sectional assessment included visual analogue scale pain, and in vivo index tests with DECT, US, and CBCT; the postoperative ex vivo index test was SPCCT of excised joint material. Reference tests comprised compensated polarized light microscopy of synovial fluid and histology with Alizarin Red S staining of excised joint material. Tests for crystals were scored on a binary basis. We calculated sensitivity, specificity, and likelihood ratios (LRs); a test with positive LR > 10 or negative LR < 0.1 was considered 'very good'.

Results: We included 12 participants, nine of whom had at least one positive reference test for calcium crystals. None of the index tests met our predefined cut-offs for a very good test. The best sensitivity and specificity were 0.29 [95% confidence interval (CI) 0.04–0.71] and 0.67 (0.09–0.99) for DECT, 0.89 (0.52–1.00) and 1.00 (0.16–1.00) for US, 0.33 (0.07–0.70) and 0.67 (0.09–0.99) for CBCT, and 1.00 (0.66–1.00) and 0.00 (0.00–0.98) for SPCCT. Wide CIs reflected the small sample size. Participants with CPP in the synovial fluid had more pain than those without.

Conclusion: SPCCT and US had high sensitivity for calcium crystal detection, although no test achieved the strict definition of a very good test.

Trial registration: ClinicalTrials.gov (NCT04585113)

Osteoarthritis (OA) is a prevalent disease that causes significant symptoms, yet our understanding of its underlying mechanisms remains incomplete. Joint-associated calcium crystal deposits are potential OA pathogens that activate inflammatory pathways, cell proliferation, and apoptotic reactions (1, 2). The term calcium crystals encompasses

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all calcium-containing crystals, but most research is centred around calcium pyrophosphate (CPP) and hydroxyapatite (HA), with HA being the dominant type of basic calcium phosphate (BCP). The typical diagnostic strategy for crystal deposition diseases involves joint arthrocentesis and compensated polarized light microscopy of synovial fluid (3). Using microscopy of joint tissue as the reference standard, the sensitivity for CPP crystal identification by synovial fluid analysis ranges from 77% to 86%, whereas the specificity and positive predictive value are 100% (4, 5). The negative predictive values range from 33% to 78%, leaving a considerable risk of false-negative results (4, 5). Arthrocentesis and synovial fluid analysis may be challenging, and small calcium-containing crystals such as HA are too small to visualize (6). Therefore, advanced but clinically available imaging techniques are needed, and may help to improve diagnosis (7).

Ultrasound (US) and computed tomography (CT) are imaging modalities used for monosodium urate (MSU) and CPP crystal detection that add information about crystal deposition in structures such as the synovium, cartilage, and ligaments, which are not assessable by synovial fluid analysis. Both dual-energy computed tomography (DECT) and US are recommended modalities for diagnosing CPP disease (3, 8), and have been demonstrated to be accurate tools for detecting CPP, especially in larger joints such as the knee (9–14). However, they have yet to be studied in hand OA. Cone-beam computed tomography (CBCT) and multi-energy spectral photon-counting computed tomography (SPCCT) are promising modalities for crystal detection. CBCT is an excellent tool for bone visualization and calcification detection, with a higher spatial resolution than DECT (15). However, CBCT has not yet been tested for crystal detection accuracy. The diagnostic performance of SPCCT has so far been limited to in vitro studies (10, 16).

In our study, we aimed to investigate the diagnostic accuracy of DECT, US, CBCT, and SPCCT for detecting CPP and HA crystal deposition in vivo and ex vivo in people with hand OA, by comparison to reference tests of compensated polarized light microscopy of synovial fluid and joint lavage fluid, and histology with Alizarin Red S stain of excised joint material. We hypothesized that all modalities would be accurate methods to identify CPP and HA in people with hand OA. We also aimed to investigate the ability of DECT to discriminate MSU crystals from calcium-containing crystals in vivo. Secondary aims included investigating the degree of inflammation and degenerative joint change, and the presence of bony erosions, and their association with crystals.

Method

This study was a cross-sectional, single-centre diagnostic test accuracy study. The study was registered prospectively at clinicaltrials.gov NCT04585113, and followed the prespecified protocol. (See the full protocol in Supplementary Appendix A.) The study protocol's primary and secondary objectives regarding crystal detection were solely related to DECT. The decision to expand the study's aim to investigate crystal detection by other modalities was made after the last patient's visit, before analysing any data. No statistical analysis plan was developed before conducting the analyses. Reporting adheres to the Standards for Reporting Diagnostic Accuracy (17). The local health research ethics committee approved the study (H-20035701), and the study followed good clinical practice. All participants signed informed consent before enrolment. An overview of the study is presented in Figure 1.

Adults were eligible if they met the American College of Rheumatology classification criteria for hand OA and were awaiting surgery on a finger joint (i.e. any interphalangeal joint or a metacarpophalangeal joint) (18). Participants were identified at the Department of Hand Surgery, Gentofte Hospital, Denmark, and were enrolled consecutively according to the surgery date. If more than one joint underwent surgery, the joint with the most pain was considered the target joint. The main exclusion criteria included other known diseases that could cause finger symptoms, e.g. rheumatic diseases other than OA, previous fractures or haemochromatosis, previous septic arthritis in the target joint, previous surgical procedures in the target joint, or foreign material and implants in the area of interest. A complete list of exclusion criteria is available in the study protocol (see Supplementary Appendix A).

Within 4 weeks before surgery, participants underwent DECT, US, and CBCT, as well as a cross-sectional examination with questionnaires and clinical assessment. Investigators conducting the assessment of index and reference tests (see the following subsections) were blinded to the results of the clinical examination, and to the results of other index and reference tests. Questionnaires included a visual analogue scale (VAS) of finger pain, a VAS patient global assessment, the Australian/Canadian Osteoarthritis Hand Index (AUSCAN; numeric rating scale format) with subscales of pain and function, and the EuroQol 5 Dimensions (EQ-5D). AD undertook the clinical assessment and recorded the number of tender and swollen joints (present or absent) at the second to fifth distal and proximal interphalangeal joints, first to fifth metacarpophalangeal joints, first interphalangeal joint, and first carpometacarpal joint, grip strength measured by a dynamometer, height, weight, and symptom duration. Age and biological sex were recorded based on the Danish Central Person Register number, where people with an odd last digit are male and those with an even last digit are female.

Radiographs, taken as part of the routine work-up at the Orthopaedic Department, were used to assess degenerative status and chondrocalcinosis by the radiologist

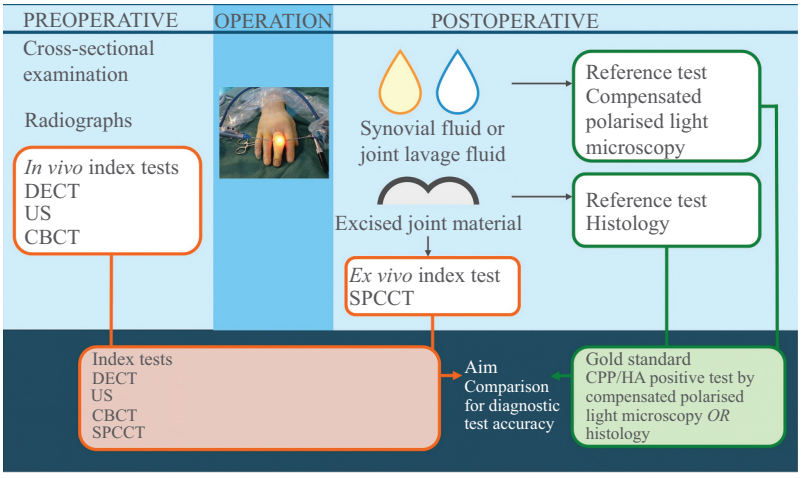


Figure 1. Trial overview. Participants with hand osteoarthritis (OA) undergoing surgery were examined with an in vivo index test 4 weeks before surgery. Calcium crystals assessed by ultrasound (US) are calcium pyrophosphate (CPP), whereas calcium crystals assessed by cone-beam computed tomography (CBCT) and dual-energy computed tomography (DECT) are CPP or hydroxyapatite (HA). Excised joint material obtained perioperatively was examined ex vivo with spectral photon-counting computed tomography (SPCCT) as an index test. Calcium crystals assessed by SPCCT are CPP or HA. The gold-standard reference combines compensated polarized light microscopy of synovial fluid and joint lavage fluid obtained during surgery and histology with Alizarin Red S stain of excised joint tissue. Calcium crystals assessed by compensated polarized light microscopy are CPP, and calcium crystals assessed by histology are CPP or HA. The gold-standard reference test is positive if calcium crystals are identified using compensated polarized light microscopy or histology. Each index test is compared separately with the reference standard for diagnostic accuracy.

(MB). Degenerative status was assessed with the Kellgren–Lawrence grade (0–4) and the Osteoarthritis Research Society International (OARSI) joint-space narrowing score (0–3) (19, 20). Chondrocalcinosis in the triangular fibrocartilage was scored as present or absent, in agreement with a consensus definition of CPP deposition in fibrocartilage (21).

Index test: DECT

The DECT scan (Somatom Force; Siemens Healthineers, Forchheim, Germany) was performed preoperatively in vivo. The full DECT scan and analysis protocol is available in Supplementary Appendix B. We used data obtained in a phantom study for crystal analysis (9). Calcium and MSU crystals were scored as present or absent at the target joint and the hand overall. We assumed that the calcium crystal deposition detected by DECT was CPP or HA, but did not specify the calcium crystal type owing to a lack of evidence for this discrimination in a population without a predefined crystal deposition disease (9, 11, 22).

Index test: ultrasound

The US was performed preoperatively in vivo. An expert US operator (KE) performed US examinations of the hand using a GE Logiq E10 is supplied by GE Healthcare, Chicago Illinois, the United States of America with a 6–15 MHz linear transducer. The full US scan and analysis protocol is available in Supplementary Appendix B. CPP was scored as present or absent, in agreement with the Outcome Measures in Rheumatology (OMERACT) recommendations, at the triangular fibrocartilage, the scapholunate ligament, and the target joint (23). US was also used to assess synovial hypertrophy, Doppler activity, and osteophytes, using the OMERACT-validated semi-quantitative scoring system (0–3) for each component, with higher values indicating more hypertrophy, activity, and osteophytes (24). We assumed that the calcium crystal deposition detected by US was CPP, as the scoring system targets this specific calcium crystal, and a proof-of-concept study suggests that HA may appear differently on US (23, 25).

Index test: CBCT

The CBCT scan (Carestream OnSight® scanner is supplied by Carestream Health, Rochester, New York, the United States of America) was performed preoperatively in vivo. The full CBCT scan and analysis protocol is available in Supplementary Appendix B. Calcium crystal deposits were scored as present or absent at the target joint and in the hand overall. We assumed that the calcium crystal deposition detected by CBCT was CPP or HA, but did not specify the calcium crystal type owing to a lack of evidence for discrimination. Erosions were also scored as present or absent at the target joint.

Index test: multi-energy SPCCT

The multi-energy SPCCT scan (MARS Bioimaging, Christchurch, New Zealand) was performed postoperatively ex vivo (26). Synovial tissue and excised joint

surfaces with attached tissue were placed in formalin immediately after surgery and stored at room temperature until scanning. The full SPCCT scan and analysis protocol is available in Supplementary Appendix B. CPP and HA were scored as present or absent. We assumed that the calcium crystal deposition detected by SPCCT was CPP or HA and specified which type it was, as previous evidence supports discrimination between these types of crystal (10, 16, 27).

Reference tests

The reference gold standard for crystal detection consisted of two tests: (i) compensated polarized light microscopy of synovial fluid and joint lavage fluid; and (ii) histological assessment of excised joint material. Histology was added to detect calcium crystals outside the synovial fluid. A sample was considered calcium crystal positive (i.e. CPP or HA positive) if either of the reference tests yielded a positive result. We planned a more robust reference test using Raman spectroscopy instead of histology, but abandoned that strategy after unsuccessful pilot testing of calcium crystal detection in biological samples (see Supplementary Appendix C).

Reference test: compensated polarized light microscopy. Synovial fluid was obtained during the operation and examined within 60 min by light microscopy and compensated polarized light microscopy, by a trained rheumatologist (LJ). The synovial fluid was examined manually and systematically for distinct crystal morphology and birefringence (i.e. MSU or CPP crystals). The presence of at least one crystal was considered a positive finding. As we anticipated that synovial fluid might not be obtained from all participants, we expanded the reference test to include compensated polarized light microscopy of joint lavage fluid collected immediately after joint arthrocentesis. The reference test was chosen as it represents the current clinical gold standard for detecting joint-associated crystals (28). We assumed that the calcium crystals detected by compensated polarized light microscopy were CPP, based on their well-defined morphology, size, and birefringent properties (28).

Reference test: histology of excised tissue. Histology was not a part of the original study protocol but was added to ensure HA detection, and proved more feasible than the initial strategy. A histology protocol is available in Supplementary Appendix D, it was finalized before analyses were conducted. Excised joint tissue placed in formalin was examined with histology performed by JB, who was blinded to the index tests and clinical examination. Alizarin Red S-stained samples scored calcium crystals as present or absent. Excised tissue was not evaluated using compensated polarized light microscopy. Although CPP and HA have distinct and different morphologies, determining the specific calcium crystal type based on stains alone has proven difficult, and we therefore assumed that the calcium crystal deposition detected by histology was CPP or HA (29). Alizarin Red S staining was not applied to the synovial fluid and joint lavage fluid.

Statistical analysis

We calculated the diagnostic accuracy (i.e. the proportion of correctly classified participants), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) with 95% confidence intervals (CIs) by comparing the index tests to the reference tests in a classic 2×2 confusion matrix. The epiR package was used for all diagnostic accuracy measures. We used prespecified cut-offs for interpretation, with PLRs above 10 and 5, and NLRs below 0.1 and 0.2, considered very good and moderately good, respectively (30). Participants with missing index tests were excluded from the analysis of the given index test. To examine the association between pain and the presence of crystals, we presented median VAS finger pain among participants with and without crystal deposits. We undertook a post-hoc analysis of agreement for crystal detection by index test using Cohen's kappa coefficient.

Sample size calculation

We expected a sensitivity of 70% for crystal detection with DECT and accepted a margin of error of ± 20% around the 95% CI, which generated a target of 20 participants. R studio version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis and sample size calculation.

Patient involvement

Two patient research partners were involved in designing and preparing the study, including reviewing and revising the protocol and patient information. Both were invited to participate in the discussion and interpretation of the results: one did not reply; the other approved a layperson's version of the scientific abstract, but declined co-authorship.

Results

We screened 13 participants for eligibility and excluded one because of known gout, leaving 12 participants for

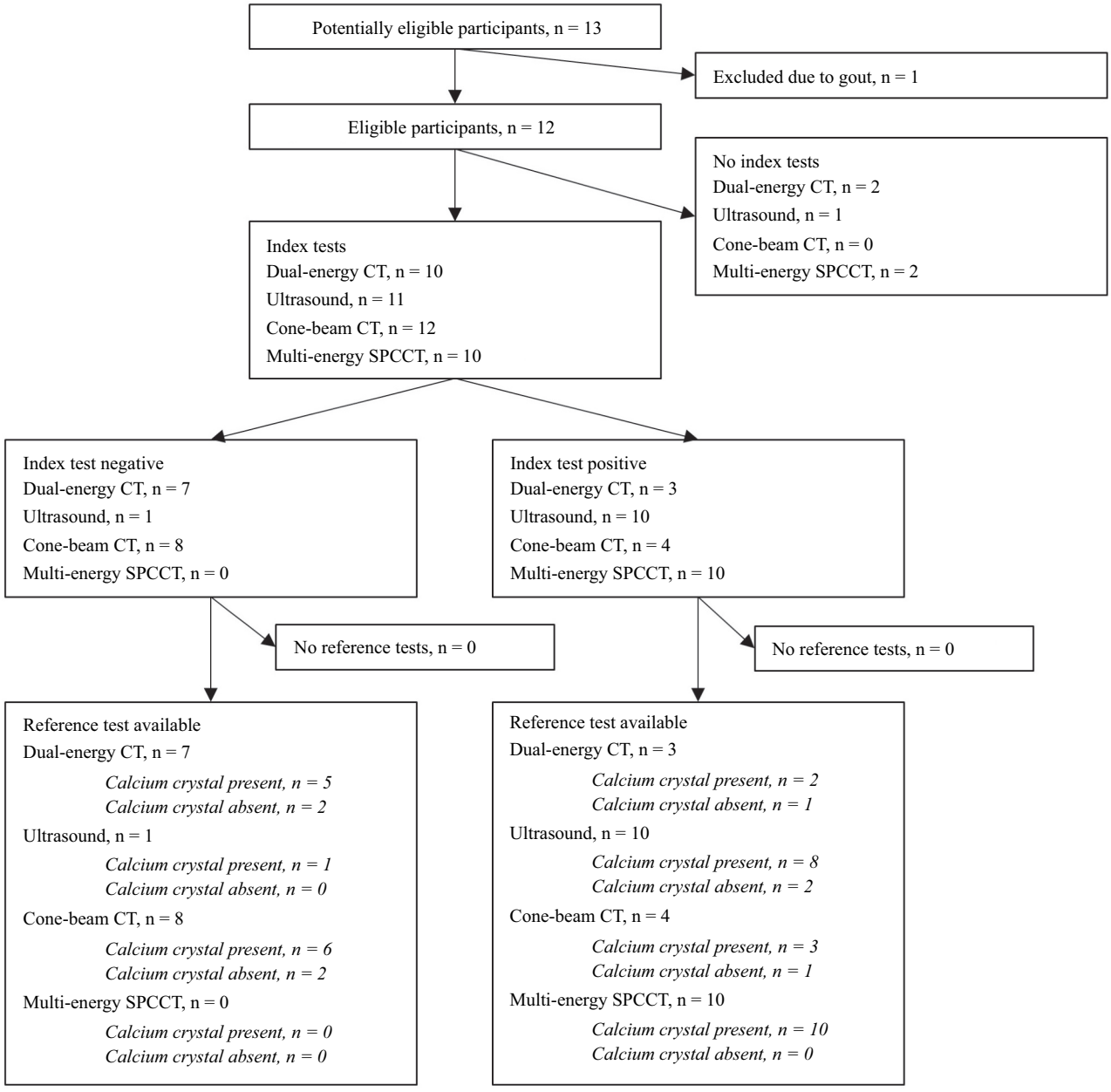


Figure 2. Flowchart showing the flow of participants throughout the study. Regarding missing index tests, one participant was unable to attend ultrasound owing to limited time, one participant could not lift their hand above the shoulder and could not position their hand in the dual-energy computed tomography (CT) scanner, one participant missed dual-energy CT owing to scanner breakdown, and two participants did not have excised joint tissue available for spectral photon-counting computed tomography (SPCCT).

inclusion between 1 October 2020 and 22 August 2022 (Figure 2). Recruitment was hampered by governmental lockdown owing to coronavirus disease 2019 (COVID-19) and a national nurses' strike. Time restrictions meant that we were forced to terminate the study before reaching the planned sample size. One participant was diagnosed with gout after terminating the study. The baseline characteristics of the included population are presented in Table 1. In 10 participants (83%), the target joint was a proximal interphalangeal, one participant (8%) had the distal interphalangeal as the target, and one (8%) had a metacarpophalangeal joint as the target. The median [interquartile range (IQR)] time between the reference test and the in vivo index test was 10 days (5–22 days). The median (IQR) time between the reference test and ex vivo SPCCT was 79 weeks (44–89 weeks).

Positive calcium crystal index tests are shown in Figure 3, and an individual image atlas of all participants' index and reference tests is available in Supplementary Appendix E. Supplementary Appendices F and G provide videos of crystal-positive compensated polarized light microscopy. All participants had a reference test available: nine participants (75%) had

Table 1. Baseline characteristics.

Participants	n = 12†
Age (years)	76.9 [68.5–82.3]
Female sex	11 (91.7)
Weight (kg)	74.6 [63.5–82.8]
Height (cm)	165.5 [162.6–166.9]
Symptom duration (years)	17.7 ± 14.0
Outcome measures	
VAS pain fingers (0–100) (mm)	58.3 ± 31.0
AUSCAN pain (0–500)	270.2 ± 130.9
AUSCAN function (0–900)	506.8 ± 279.4
VAS patient global assessment (0–100) (mm)	48.4 ± 33.2
EQ-5D (–0.624 to 1.000)	0.703 [0.592–0.766]
Grip strength (N)	93.0 [62.0–145.5]
Tender joint count (0–30)	6.8 ± 5.7
Swollen joint count (0–30)	1.8 ± 1.3
Gold standard reference test positive	
Calcium crystals (CPP or HA) present	9 (75)
Calcium crystal (CPP or HA) positive microscopy and histology	2 (17)
Calcium crystal (CPP) positive microscopy	1 (8)
Calcium crystal (CPP or HA) positive histology	6 (50)
Monosodium urate crystals present	2 (17)
Imaging features	
Ultrasound of the joint undergoing surgery	
Synovial hypertrophy (0–3)	3.0 [2.0–3.0]
Participants with synovial hypertrophy ≥ 2	9 (81.8)
Colour Doppler (0–3)	0.0 [0.0–0.0]
Participants with colour Doppler ≥ 2	2 (18.2)
Inflammation‡	9 (81.8)
Osteophytes (0–3)	1.0 [1.0–1.0]
CBCT of the joint undergoing surgery	
Erosions	8 (66.7)
Radiographs of the hand with the joint undergoing surgery	
Chondrocalcinosis in the triangular fibrocartilage	1 (8.3)
KL target joint (0–4)	4.0 [4.0–4.0]
KL sum grade DIP and PIP joints (0–32)	19.5 [16.8–25.5]
No. of DIP and PIP joints with KL ≥ 2 (0–8)	5.5 [4.0–8.0]
KL grade CMC1 joint (0–4)	2.0 [1.0–3.0]
KL ≥ 2 CMC1 joint	6 (60.0)
OARSI JSN target joint (0–3)	3.0 [3.0–3.0]
OARSI JSN sum score DIP and PIP joints (0–24)	16.5 [14.2–20.0]
OARSI JSN score CMC1 joint (0–3)	1.5 [0.0–2.0]
OARSI joint space narrowing IP joint	4 (33.3)

Data are shown as median [interquartile range], n (%), or mean ± sd.
Baseline values for participants in the trial were collected at the cross-sectional examination.
†One participant had no data for grip strength and ultrasound, and there were no data for radiographic scoring of the DIP2 and CMC1 joints owing to previous surgeries in these joints. A second participant had no data for EQ-5D. A third participant had no data for radiographic scoring of the CMC1 joint owing to previous surgery in this joint.
‡Inflammation is either synovial hypertrophy of at least 2 or a colour Doppler of at least 1 in the target joint.
AUSCAN, Australian/Canadian Osteoarthritis Hand Index; CMC1, carpometacarpal-1; CPP, calcium pyrophosphate; DIP, distal interphalangeal; EQ-5D, EurQol 5 Dimensions; HA, hydroxyapatite; IP, interphalangeal; JSN, joint space narrowing; KL, Kellgren–Lawrence; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal; VAS, visual analogue scale.

both synovial fluid and excised joint material, two participants (17%) had only synovial fluid, and one participant (8%) had joint lavage fluid and excised joint material. Using the gold-standard reference test, nine participants (75%) had calcium crystals (CPP or HA), and three (25%) did not have calcium crystals. The gold-standard reference test did not allow individual assessment of HA, but using the index test SPCCT, nine of the 10 investigated participants had calcium HA crystal deposition.

The overall diagnostic accuracy of US, CBCT, DECT, and SPCCT is presented in Table 2. (See

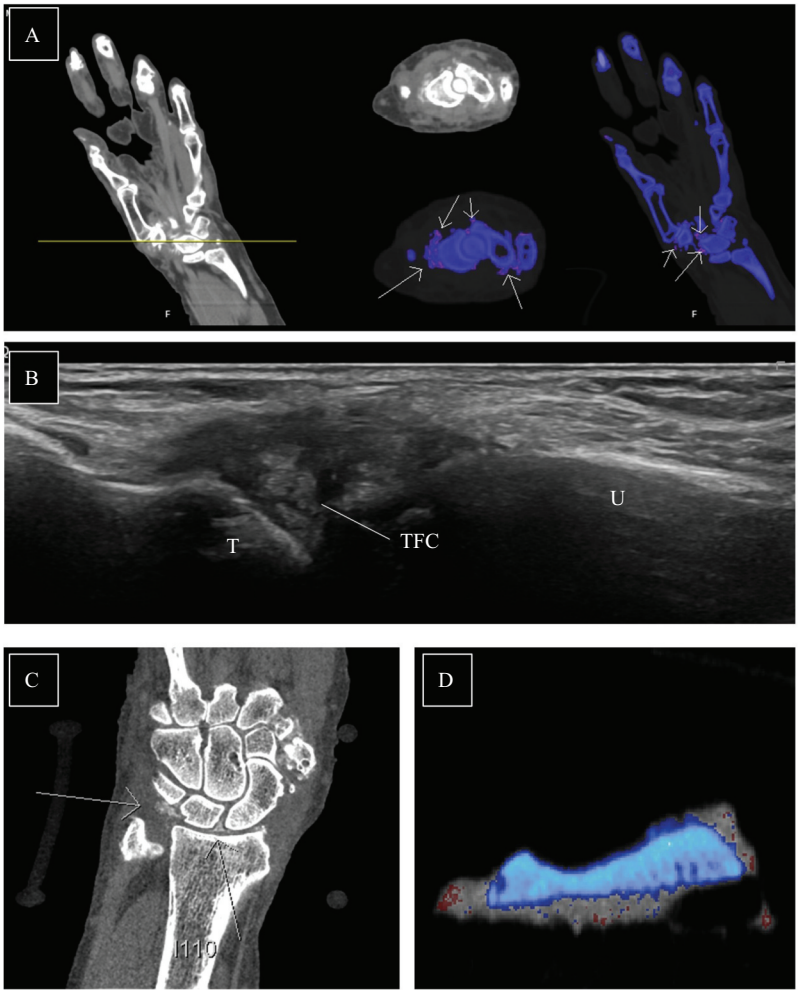


Figure 3. Images of calcium crystal positive index tests in people with hand osteoarthritis. (A) Dual-energy CT of the hand. The left image is a coronal projection of the wrist with the vertical line indicating the location for cross-sectional images. The left and top-middle images are shown without post-processing. The bottom-middle and right images are post-processed to distinguish calcium deposits by density, with arrows indicating multiple calcium depositions (CPP or HA). (B) Ultrasound with CPP deposition in the triangular fibrocartilage of the wrist. (C) Cone-beam CT with calcium depositions (CPP or HA) in the triangular fibrocartilage (left arrow) and the ligaments of the wrist (bottom arrow). (D) Multi-energy spectral photon-counting CT. Coronal projection of an excised finger joint with the joint surface facing upwards, demonstrating CPP and HA deposits in the soft tissue adhering to the excised joint surface, differentiated by material-specific reconstruction. CPP, calcium pyrophosphate. HA, hydroxyapatite. T, triquetrum. TFC, triangular fibrocartilage. U, ulna.

Supplementary Appendix H for 2 × 2 tables.) None of the modalities reached our predefined cut-offs for a very good test according to likelihood ratios and corresponding confidence intervals. Although no point estimates for likelihood ratios reached the cut-offs for a moderately good test, the cut-off values were included in the confidence interval for most of the US assessments and for the PLRs for CBCT and DECT of the hands. For index tests with a specificity of 0.00 or 1.00, it was not possible to calculate the NLR or PLR, respectively.

It was impossible to investigate DECT's ability to discriminate MSU crystals from calcium-containing crystals in vivo, as no MSU crystals were detected on DECT. Secondary outcomes investigating the association between crystals and inflammation, degenerative status, and erosions are published separately (31). The median VAS finger pain among participants with and without crystals is presented in Table 3. Participants with CPP crystals in the synovial fluid had significantly more pain than participants without such crystals. No adverse events were recorded. Kappa agreement between CBCT and DECT was 0.78 (95% CI 0.39–1.00), with a percentual agreement of 30%. Agreement between all index tests is presented in Supplementary Appendix I.

Discussion

Our study is the first to explore the diagnostic accuracy of DECT, US, CBCT, and SPCCT for detecting CPP and HA crystal deposition in vivo and ex vivo in people with hand OA, using compensated polarized light microscopy of synovial fluid and joint lavage fluid and histology with Alizarin Red S staining of excised joint material as reference tests. Contrary to our expectations, none of the modalities reached our predefined cut-off for a very good test. Despite this, SPCCT and a combined US assessment of the scapholunate ligament, the triangular fibrocartilage, and the target joint had better sensitivity than the current clinical standard with compensated polarized light microscopy of synovial fluid, whereas only US of the scapholunate ligament alone produced specificity that was comparable to the clinical standard (4, 5). Wide confidence intervals

Table 2. Diagnostic accuracy of dual-energy computed tomography (DECT), ultrasound (US), cone-beam computed tomography (CBCT), and multi-energy spectral photon-counting computed tomography (SPCCT) for calcium crystal detection using synovial fluid analysis and histology as reference standards.

Index test	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
Calcium crystal detection							
DECT, n = 10							
Joint	0.30 (0.07 to 0.65)	0.14 (0.00 to 0.58)	0.67 (0.09 to 0.99)	0.50 (0.01 to 0.99)	0.25 (0.03 to 0.65)	0.43 (0.04 to 4.82)	1.29 (0.55 to 3.02)
Hand	0.40 (0.12 to 0.74)	0.29 (0.04 to 0.71)	0.67 (0.09 to 0.99)	0.67 (0.09 to 0.99)	0.29 (0.04 to 0.71)	0.86 (0.12 to 6.23)	1.07 (0.42 to 2.71)
US, n = 11							
Joint	0.55 (0.23 to 0.83)	0.56 (0.21 to 0.86)	0.50 (0.01 to 0.99)	0.83 (0.36 to 1.00)	0.20 (0.01 to 0.72)	1.11 (0.25 to 5.00)	0.89 (0.19 to 4.26)
TFC	0.55 (0.23 to 0.83)	0.56 (0.21 to 0.86)	0.50 (0.01 to 0.99)	0.83 (0.36 to 1.00)	0.20 (0.01 to 0.72)	1.11 (0.25 to 5.00)	0.89 (0.19 to 4.26)
SLL	0.45 (0.17 to 0.77)	0.33 (0.07 to 0.70)	1.00 (0.16 to 1.00)	1.00 (0.29 to 1.00)	0.25 (0.03 to 0.65)	NE	0.67 (0.42 to 1.06)
TFC + SLL	0.64 (0.31 to 0.89)	0.67 (0.30 to 0.93)	0.50 (0.01 to 0.99)	0.86 (0.42 to 1.00)	0.25 (0.01 to 0.81)	1.33 (0.31 to 5.75)	0.67 (0.13 to 3.53)
Joint + TFC	0.73 (0.39 to 0.94)	0.89 (0.52 to 1.00)	0.00 (0.00 to 0.84)	0.80 (0.44 to 0.97)	0.00 (0.00 to 0.98)	0.89 (0.71 to 1.12)	NE
Joint + SLL	0.64 (0.31 to 0.89)	0.67 (0.30 to 0.93)	0.50 (0.01 to 0.99)	0.86 (0.42 to 1.00)	0.25 (0.01 to 0.81)	1.33 (0.31 to 5.75)	0.67 (0.13 to 3.53)
TFC + joint + SLL	0.73 (0.39 to 0.94)	0.89 (0.52 to 1.00)	0.00 (0.00 to 0.84)	0.80 (0.44 to 0.97)	0.00 (0.00 to 0.98)	0.89 (0.71 to 1.12)	NE
CBCT, n = 12							
Joint	0.17 (0.02 to 0.48)	0.00 (0.00 to 0.34)	0.67 (0.09 to 0.99)	0.00 (0.00 to 0.98)	0.18 (0.02 to 0.52)	0.00 (0.00 to NE)	1.50 (0.67 to 3.34)
Hand	0.42 (0.15 to 0.72)	0.33 (0.07 to 0.70)	0.67 (0.09 to 0.99)	0.75 (0.19 to 0.99)	0.25 (0.03 to 0.65)	1.00 (0.16 to 6.35)	1.00 (0.40 to 2.52)
Multi-energy SPCCT, n = 10							
Joint	0.90 (0.55 to 1.00)	1.00 (0.66 to 1.00)	0.00 (0.00 to 0.98)	0.90 (0.55 to 1.00)	NE (0.00 to 1.00)	1.00 (1.00 to 1.00)	NE
MSU crystal detection							
DECT, n = 10							
Hand	0.80 (0.44 to 0.97)	0.00 (0.00 to 0.84)	1.00 (0.63 to 1.00)	NE	0.80 (0.44 to 0.97)	NE	1.00 (1.00 to 1.00)

The table presents the diagnostic accuracy of index tests for detecting calcium crystals and MSU crystals in the joint undergoing surgery. (See Supplementary Appendix H for 2 × 2 tables.) The index test column notes the modality and analysis area, with n indicating the number of participants examined with the modality. The analysis areas are the target joint (joint), the hand, the TFC, and the SLL, with '+' indicating combined analysis areas with crystals present at any of these sites. The reference test for calcium crystals is CPP crystals in the synovial fluid/joint lavage fluid, or calcium crystals (CPP or HA) detected by histological preparation of excised joint material, i.e. the reference test is only obtained from the target joint. The reference test for MSU crystals is MSU crystals in the synovial fluid/joint lavage fluid.

US target joint assessment included CPP depositions in the cartilage (intra-cartilage), synovial fluid, flexor or extensor enthesis, or synovium.

CI, confidence interval; CPP, calcium pyrophosphate; CT, computed tomography; HA, hydroxyapatite; MSU, monosodium urate; NE, not estimable; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; SLL, scapholunate ligament; TFC, triangular fibrocartilage.

with uncertainty of the true diagnostic accuracy measures accompanied all estimates.

The sensitivity and specificity of DECT in our study were 29% and 67%, respectively, which are worse than those reported in previous trials using in vivo DECT, in which sensitivity was 90–100%, and ex vivo DECT, in which sensitivity and specificity were 77.8% and 93.8%, respectively (13, 14). Our study population comprised people with hand OA, whereas the previous in vivo study included people with acute CPP arthritis, and it is possible that sensitivity differs across populations. Other DECT studies mainly examined knee-related structures. Although not investigated, the anatomically smaller structures of the hand may contain smaller deposits susceptible to false-negative DECT (which would, in turn, decrease sensitivity) owing to partial volume effects and limited spatial resolution. In our study, we applied the clinically used 'Gout' application, intentionally excluding deposits with a density below 150 HU to avoid misinterpretations (32). Using a lower density threshold may have increased sensitivity, and accuracy measures may also have been different

Table 3. Finger pain among crystal-positive and crystal-negative participants.

Index test: analysis area (crystal investigated)	Crystal-positive participants		Crystal-negative participants		Difference between groups (95% CI)
	n	VAS pain (0–100) (mm)	n	VAS pain (0–100) (mm)	
DECT: target joint (CPP and HA)	2	80.0 [78.0 to 82.0]	8	68.0 [37.5 to 86.5]	−12.0 (−69.0 to 24.0)
DECT: hand (CPP and HA)	3	76.0 [57.0 to 80.0]	7	72.0 [50.0 to 88.0]	1.0 (−61.0 to 53.0)
US: target joint (CPP)	6	50.0 [20.3 to 84.3]	5	72.0 [38.0 to 84.0]	9.5 (−53.0 to 69.0)
US: triangular fibrocartilage (CPP)	6	54.0 [28.5 to 81.0]	5	64.0 [38.0 to 91.0]	9.5 (−47.0 to 65.0)
US: scapholunate ligament (CPP)	3	84.0 [48.5 to 87.5]	8	51.0 [33.5 to 75.3]	−9.0 (−65.0 to 59.0)
CBCT: target joint (CPP and HA)	1	76.0 [76.0 to 76.0]	11	64.0 [31.0 to 84.5]	−12.0 (−63.0 to 24.0)
CBCT: hand (CPP and HA)	4	80.0 [66.5 to 84.3]	8	50.0 [23.3 to 76.8]	−16.5 (−63.0 to 24.0)
SPCCT (HA)	9	76.0 [26.0 to 85.0]	1	38.0 [38.0 to 38.0]	−38.0 (−62.0 to 25.0)
Synovial fluid analysis (CPP)	3	85.0 [84.5 to 92.5]	9	38.0 [26.0 to 72.0]	−47.0 (−74.0 to −8.0)*
Synovial fluid analysis (MSU)	2	83.5 [79.8 to 87.3]	10	51.0 [28.5 to 81.0]	−32.5 (−78.0 to 24.0)
Synovial fluid analysis (CPP and MSU)	5	85.0 [84.0 to 91.0]	7	36.0 [20.5 to 51.0]	−53.0 (−72.0 to −20.0)*
Histology (CPP and HA)	8	37.0 [23.3 to 84.3]	2	88.0 [82.0 to 94.0]	45.0 (−15.0 to 87.0)

VAS pain is the median finger pain, with 25% and 75% quantiles in square brackets. The difference between groups is the median difference and corresponding 95% CI in parentheses.
*Significant difference between groups.
CBCT, cone-beam computed tomography; CI, confidence interval; CPP, calcium pyrophosphate; DECT, dual-energy computed tomography; HA, hydroxyapatite; MSU, monosodium urate; n, number of participants; SPCCT, spectral photon-counting computed tomography; US, ultrasound; VAS, visual analogue scale.

if we had analysed monoenergetic low kilo-electronvolt (keV) images. No other study has investigated CBCT, and performance in our study was similar to that of DECT, with moderate agreement between the two, indicating comparable abilities for CPP and HA detection.

In agreement with a previous study of US for detecting CPP crystals in the knee, the diagnostic accuracy measures for US varied across the investigated anatomical sites (12). US in our study also produced comparable accuracy, sensitivity, and PPVs to other diagnostic accuracy studies using histology as a reference, whereas specificity and NPVs were lower in our study (33). This may be explained by the high number of participants with a positive reference test in our study, which was 83% compared to only 61% and 50% in other studies, making true-negative cases rare (34, 35). A US study of calcium pyrophosphate deposition disease (CPPD) features at the metacarpophalangeal joints demonstrated that high-frequency US probes can detect multiple features of CPPD in small hand joints, and diagnostic accuracy measures may have differed if the assessment had extended beyond the OMERACT recommendations (36).

The sensitivity and PPV of SPCCT in our study were 1.00, which is in agreement with a study of SPCCT ex vivo from a patient with knee OA, where detection is reported as excellent (27). SPCCT has previously been used to detect and discriminate CPP and HA in a patient with knee OA, and, similarly, we detected the presence of both crystals, but our reference test did not allow for discrimination between these (10). The specificity of SPCCT was 0.00, and NPVs could not be calculated, which reflects that all SPPCT scans were calcium crystal positive.

In our study, we found higher VAS pain for participants with CPP in the synovial fluid compared to participants without. Similarly, a previous study found an association between BCP (i.e. a broader group of calcium-containing crystals, in which HA is dominant) in the synovial fluid and knee OA symptoms, although not between CPP and knee OA symptoms (37).

This study has several limitations. First, we did not reach our planned sample size of 20 participants despite active recruitment for almost 2 years, resulting in an underpowered study. The small sample size resulted in a constrained dataset, preventing the calculation of specific accuracy measures and yielding wide confidence intervals, indicating considerable uncertainty of the estimate, which should be considered when interpreting our findings. Secondly, our study deliberately uses the non-specific term calcium crystal instead of CPP and HA at multiple timepoints to acknowledge the lack of specificity of the applied tests. A study of crystal-mediated calcification in cartilage and synovial membrane from people with knee OA revealed a high frequency of BCP, but less CPP (38). Ideally, these should be studied separately as they may represent two different disease entities, and reliable differentiation of HA from CPP on DECT, US, and CBCT is debated. We might have been able to discriminate HA from CPP if we had applied Alizarin Red S staining to synovial fluid or if we had investigated sectioned paraffin-embedded, heat-fixed samples prepared on glass slides before staining with compensated polarized light microscopy, thereby using a combination of birefringence,

staining, and morphology (29). However, certainty would require more precise methods such as Raman spectroscopy, and the limited amount of synovial fluid did not allow for excess analysis (39). Thirdly, some index tests assess the hand overall, the scapholunate ligament, and the triangular fibrocartilage, and are then compared to a reference test obtained from the finger joint. This image analysis strategy agrees with the European Alliance of Associations for Rheumatology (EULAR) recommendations for the use of imaging in crystal-induced arthropathies, which recommends that imaging is applied in both the symptomatic areas and the disease-specific target sites (8). This raises some methodological concerns, especially with the lack of specificity for the reference test and compromise of the validity of diagnostic accuracy estimates outside the target joint. Lastly, generalizability may be limited. The prevalence of CPP in our population was high (75%), and accuracy measures may be different in other populations (31, 40). A key strength of the study is the incorporation of multiple imaging modalities, the use of DECT in vivo and the extensive imaging material provided as an image atlas. The prospective trial design of people without known or suspected crystal disease should also be highlighted as a strength.

Future research on imaging modalities for crystal detection would benefit from a unified reference test and image analysis strategy to ensure comparability across studies. As SPCCT becomes clinically available, the promising accuracy results observed ex vivo should be validated in vivo. In addition, further studies are necessary to confirm the accuracy measures of CBCT. The correlation between clinical outcomes and crystal deposition should also be investigated.

Conclusion

None of the tests (DECT, US, CBCT, and SPCCT) reached our predefined cut-off (PLR > 10, NLR < 0.1) for a very good test for CPP and HA detection, but both SPCCT and US had high sensitivity for calcium crystal detection. However, the findings are uncertain because of the limited sample size.

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Rolf W Berg contributed to the scientific protocol and, together with Hugo Kerdoncuff, pilot-tested Raman spectroscopy. Roy D Altman engaged in the study's design and approved the final protocol. He passed away before the results of the study were finalized. Tove Bendix participated as a patient research partner. She helped to design the study protocol and approved a layperson's version of the scientific abstract of the final article. She declined co-authorship. Lise Christensen contributed towards the scientific protocol and pilot-tested histological crystal detection.

Author contributions

AD, LKS, FB, CFM, JB, LC, PH, LG-M, GMMcC, PGC, MH, RC, RDA, LT, KE, NSN, LJ, DIR, JDN, HB, and MB engaged in the design of the study. NSN performed operations. LJ performed the microscopy of synovial fluid. MB scored radiographs. JDN set up the CT image protocols. CFM post-processed DECT images. MB, PH, DIR, CFM, and AD agreed on the DECT and CBCT image-analysis strategy. PH and DIR analysed DECT and CBCT. FB, LG-M, and AD performed multi-energy SPCCT of excised joint tissue. FB analysed multi-energy SPCCT. KE conducted and analysed US. JB conducted and analysed histological preparations. AD performed the cross-sectional examination. AD carried out the statistical analysis. AD wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Data availability statement

We did not obtain consent for data sharing from included participants. We will consider requests for data sharing on an individual basis, and we will only share data if it is ensured that the participants' anonymity is not compromised and if sharing agrees with Danish laws. Data or analytic code will be made available upon reasonable request to the corresponding author.

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Ethics and informed consent

The local health research ethics committee approved the study (H-20035701), and the study followed good clinical practice. All participants signed informed consent before enrolment.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Grammarly to spell-check. After using this tool/service, the authors reviewed and edited the content as needed, and take full responsibility for the publication's content.

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