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LETTER

Pain in hand osteoarthritis is associated with crystals in the synovial fluid: a cross-sectional study of people with hand osteoarthritis undergoing surgery

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Despite the high prevalence and symptom burden of osteoarthritis (OA), our understanding of its pathogenesis is incomplete. Intra-articular crystal deposits have been implicated in OA pathogenesis, with their ability to activate inflammatory pathways as well as cell proliferative and apoptotic reactions.[1 2] For people with knee OA, basic calcium phosphate crystals in the synovial fluid are associated with worse patient-reported pain and function.[3] So far, no study has investigated the association between intra-articular crystals and symptoms in hand OA. We obtained data as part of a cross-sectional single-centre study of people with hand OA undergoing phalangeal joint surgery (ClinicalTrials.gov NCT04585113). All participants signed informed consent before enrolment, met the American College of Rheumatology classification criteria for hand OA and had no other rheumatic diseases including gout.[4] We also excluded people with skin psoriasis with or without psoriatic arthritis and individuals who had intra-articular injections within 3 months prior to enrolment. Within 4 weeks prior to surgery, participants underwent a standardised clinical examination and completed questionnaires including a Visual Analogue Scale (VAS) of finger pain, a VAS patient global assessment, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) and the European Quality of Life 5 Dimensions (EQ-5D). VAS was scored on a 100 mm with anchors 0='no pain' and 100='worst possible pain', the AUSCAN was scored on a Numerical Rating Scale by subscale pain (scored as 0–50) and function (0–90), and the EQ-5D score ranged from −0.624 (worst) to 1.000 (best). Clinically, we assessed the number of tender and swollen joints (present or absent) at second–fifth distal and proximal interphalangeal joints, first–fifth metacarpophalangeal joints, first interphalangeal joint and first carpometacarpal joint; grip strength, height, weight, pain medication use and symptom duration were recorded. Pain medication was recorded as intake in the week prior to assessment. For imaging, participants underwent ultrasound, cone-beam CT and radiographs of the hand with the joint scheduled for surgery. Synovial fluid and joint lavage fluid were obtained during surgery and examined within 60 min using light and compensated polarised light microscopy by a senior rheumatologist trained in crystal detection. Given the limited synovial fluid in the finger joints, we only obtained one to three drops from each participant. A drop of synovial fluid or joint lavage fluid was placed on a glass slide with a cover sheet and then systematically assessed for distinct crystal morphology. Negative and positive birefringent crystals were interpreted as monosodium urate and calcium pyrophosphate, respectively. We considered presence of ≥1 crystal as a positive reference test. Continuous variables are presented as mean with SD and skewed data as median with IQR. Categorical data are presented as absolute numbers with percentages. R studio V.3.6.1 was used for statistical analysis.

We screened 13 participants for eligibility and excluded 1 due to known gout, leaving 12 participants for inclusion in the study between 1 October 2020 and 22 August 2022. From synovial fluid and joint lavage fluid analyses, the prevalence of crystals was 42% (5 of 12);

Table 1 Characteristics of the included population

Characteristic	Reference negative: joint-associated crystals absent, n=7*	Reference positive: joint-associated crystals present, n=5*	Difference between groups (95% CI)
Age, years	73.3 (12.1)	74.8 (12.3)	−1.4 (−17.3 to 14.4)
Female sex, n (%)	7 (100.0)	4 (80.0)	0.2 (−0.2 to 0.6)
Weight, kg	69.1 (14.8)	83.8 (14.7)	−14.7 (−34.0 to 4.5)
Height, cm, median (IQR)	166.0 (163.5–166.2)	165.0 (154.0–168.0)	1.0 (−24.5 to 15.4)
Symptom duration, years	10.1 (11.5)	28.2 (10.1)	−18.1 (−32.3 to −3.8)
Concomitant pain medication			
Non-steroidal anti-inflammatory drug users, n (%)	0 (0.0)	0 (0.0)	0.0 (0.0 to 0.0)
Paracetamol users, n (%)	2 (28.6)	2 (40.0)	−0.1 (−0.7 to 0.4)
Paracetamol dose among users, mg per day	1000.0 (0.0)	3500.0 (707.1)	−2500.0 (−4651.3 to −348.7)
Outcome measures			
VAS pain fingers (0–100), mm	37.7 (22.9)	87.2 (8.9)	−49.5 (−73.7 to −25.2)
AUSCAN pain (0–500)	194.4 (117.6)	376.2 (47.8)	−181.8 (−307.0 to −56.5)
AUSCAN function (0–900)	354.3 (263.0)	720.4 (114.9)	−366.1 (−648.3 to −83.9)
VAS patient global assessment (0–100), mm	46.3 (29.3)	51.4 (41.5)	−5.1 (−50.4 to 40.2)
EQ-5D (−0.624 to 1.000), median (IQR)	0.740 (0.625–0.807)	0.660 (0.592–0.703)	0.092 (−0.213 to 0.465)
Grip strength, Newtons, median (IQR)	100.0 (63.5–145.5)	78.5 (59.0–121.8)	11.5 (−108.0 to 143.0)
Tender joint count (0–30)	5.4 (5.0)	8.8 (6.6)	−3.4 (−10.8 to 4.0)
Swollen joint count (0–30)	1.4 (1.0)	2.4 (1.5)	−1.0 (−2.6 to 0.6)
Laboratory measures			
Plasma urate, mmol/L, median (IQR)	0.30 (0.27–0.32)	0.36 (0.29–0.37)	−0.06 (−0.32 to 0.02)
Ionised calcium, mmol/L, median (IQR)	1.22 (1.19–1.25)	1.23 (1.21–1.23)	0.00 (−0.07 to 0.05)
Haemoglobin 1Ac, mmol/mol, median (IQR)	39.0 (37.5–41.0)	37.5 (29.5–39.8)	1.3 (−9.0 to 32.0)
Ferritin, µg/L, median (IQR)	123.0 (100.5–190.0)	90.0 (40.2–148.5)	51.5 (−71.0 to 178.0)
Baseline imaging features			
Ultrasound of the joint undergoing surgery			
Synovial hypertrophy (0–3), median (IQR)	3.0 (2.5–3.0)	1.0 (0.0–2.2)	1.3 (−0.0 to 3.0)
Participants with synovial hypertrophy ≥2, n (%)	7 (100.0)	2 (50.0)	0.5 (0.0 to 0.1)
Colour Doppler (0–3), median (IQR)	0.0 (0.0–0.5)	0.0 (0.0–0.0)	0.0 (0.0 to 2.0)
Participants with colour Doppler ≥2, n (%)	2 (28.6)	0 (0.0)	0.3 (−0.0 to 0.6)
Inflammation, n (%)†	7 (100.0)	2 (50.0)	0.5 (0.0 to 1.0)
Osteophyte (0–3), median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.2)	−0.0 (−1.0 to 0.0)
Cone-beam CT of the joint undergoing surgery			
Erosions, n (%)	4 (57.1)	4 (80.0)	−0.2 (−0.7 to 0.3)
Radiographs of the hand with the joint undergoing surgery			
Chondrocalcinosis in the triangular fibrocartilage	0 (0.0%)	1 (20.0%)	−0.2 (−0.6 to 0.2)
KL sum grade DIP and PIP joints (0–32), median (IQR)	20.0 (18.5–26.0)	18.0 (16.0–19.0)	2.0 (−12.0 to 12.0)

Continued

Table 1 Continued

Characteristic	Reference negative: joint-associated crystals absent, n=7*	Reference positive: joint-associated crystals present, n=5*	Difference between groups (95% CI)
No of DIP and PIP joints with KL ≥2 (0–8), median (IQR)	6.0 (4.0–8.0)	5.0 (5.0–6.0)	0.0 (–3.0 to 3.0)
KL grade CMC1 joint (0–4), median (IQR)	2.5 (1.2–3.0)	1.5 (0.8–2.5)	0.4 (–2.0 to 3.0)
KL ≥2 CMC1 joint, n (%)	4 (66.7)	2 (50.0)	0.2 (–0.5 to 0.8)
OARSI JSN sum score DIP and PIP joints (0–24), median (IQR)	17.0 (15.5–20.0)	15.0 (12.0–18.0)	2.0 (–8.0 to 8.0)
OARSI JSN score CMC1 joint (0–3), median (IQR)	1.5 (0.2–2.0)	1.0 (0.0–2.2)	–0.0 (–2.0 to 2.0)
OARSI joint space narrowing IP joint, n (%)	3 (42.9)	1 (20.0)	0.2 (–0.3 to 0.7)

Values are mean (SD) unless otherwise indicated. The difference between groups is the mean/median difference for continuous data and the risk difference for binary data.
*One participant with joint-associated crystals (the participant later diagnosed with gout) had no data for grip strength, ultrasound, ionised calcium, haemoglobin 1Ac and ferritin, and there were no data for radiographic scoring of the DIP2 and CMC1 joints due to previous surgeries in these joints. One participant without joint-associated crystals had no data for EQ-5D. A second participant without joint-associated crystals had no data for radiographic scoring of the CMC1 joint due to previous surgery in this joint. A third participant without joint-associated crystals had no synovial fluid and only joint lavage fluid was analysed.
†Inflammation is defined as either synovial hypertrophy ≥2 or colour Doppler ≥1 in the target joint.
AUSCAN, Australian/Canadian Hand Osteoarthritis Index; CMC1, carpometacarpal-1; DIP, distal interphalangeal; EQ-5D, European Quality of Life 5 Dimensions; IP, interphalangeal; JSN, joint space narrowing; KL, Kellgren-Lawrence; OARSI, Osteoarthritis Research Society International; PIP, proximal interphalangeal; VAS, Visual Analogue Scale.

of these, 60% (3 of 5) were calcium pyrophosphate, and 40% (2 of 5) were monosodium urate. The characteristics of the participants are presented in table 1. No participants had elevated ionised calcium (>1.32 mmol/L), ferritin (>300 µg/L) or haemoglobin 1Ac (>48 mmol/mol). One participant with monosodium urate crystals had chondrocalcinosis in the triangular fibrocartilage, elevated plasma urate and was diagnosed with gout after participation in the trial. Statistically significant differences in VAS pain persisted after exclusion of participants with monosodium urate crystals identified in joint fluid.

Calcium-containing crystals have been associated with degenerative changes in knee OA, but the relationship with hand OA symptoms has not previously been described.[3 5] In our study of participants with finger joint OA scheduled for joint surgery, we found for the first time that pain and function were worse among participants with calcium-containing crystals in the synovial fluid compared with participants without. The differences were not explained by radiographic structural differences of the hand or ultrasound inflammation. Whereas all participants without crystals in the synovial fluid had evidence of ultrasound inflammation, only two of five participants with crystals in the synovial fluid had evidence of ultrasound inflammation. The prevalence of crystals in the synovial fluid in this study is higher than a previous study on wrist and finger OA and may be explained by selecting people awaiting surgery.[6] Regardless, the result suggests the presence of a crystal phenotype in hand OA associated with increased OA symptom severity. The phenotype can be defined as hand OA with comorbid crystal arthropathies. This phenotype may be suggested as a potential stratification factor in trials enrolling people with hand OA. The small sample size limits this study, and the observed associations should be confirmed in future studies, which may also assess the clinical impact of the crystal phenotype.

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Contributors AD, PGC, LS, GMc, MH, RC, LT, KE, NS, LJ, PH, DIR, MB and HB designed the study. NS was the operation surgeon, who also identified eligible participants. AD screened all participants and did the cross-sectional examination. KE performed and scored ultrasound assessments. JDN coordinated imaging

and set up the cone-beam CT scan protocol. PH and DIR analysed cone-beam CT images. MB analysed radiographs. LJ did compensated polarised light microscopy of the synovial fluid. AD did the statistical analysis and drafted the manuscript. All authors were involved in critically reviewing, editing, revising and approving the final manuscript.

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