CLINICAL SCIENCE

Systematic literature review to inform the EULAR recommendations for the use of imaging in crystal-induced arthropathies in clinical practice

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ABSTRACT

Objective To summarise current data regarding the use of imaging in crystal-induced arthropathies (CiAs) informing a European Alliance of Associations for Rheumatology task force.

Methods We performed four systematic searches in Embase, Medline and Central on imaging for diagnosis, monitoring, prediction of disease severity/treatment response, guiding procedures and patient education in gout, calcium pyrophosphate dihydrate deposition (CPPD) and basic calcium phosphate deposition (BCPD). Records were screened, manuscripts reviewed and data of the included studies extracted. The risk of bias was assessed by validated instruments.

Results For gout, 88 studies were included. Diagnostic studies reported good to excellent sensitivity and specificity of dual-energy CT (DECT) and ultrasound (US), high specificity and lower sensitivity for conventional radiographs (CR) and CT. Longitudinal studies demonstrated sensitivity to change with regard to crystal deposition by US and DECT and inflammation by US and structural progression by CR and CT. For CPPD, 50 studies were included. Diagnostic studies on CR and US showed high specificity and variable sensitivity. There was a single study on monitoring, while nine assessed the prediction in CPPD. For BCPD, 56 studies were included. There were two diagnostic studies, while monitoring by CR and US was assessed in 43 studies, showing a reduction in crystal deposition. A total of 12 studies with inconsistent results assessed the prediction of treatment response. The search on patient education retrieved two studies, suggesting a potential role of DECT.

Conclusion This SLR confirmed a relevant and increasing role of imaging in the field of CiAs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is an increasing interest in the application of imaging in crystal-induced arthropathies, with many studies on diagnosis, monitoring and predicting treatment response or severity. However, there are no recommendations on the use of imaging in crystal-induced arthropathies clinical practice.

WHAT THIS STUDY ADDS

⇒ We performed a systematic literature review, encompassing the applications of imaging for making a diagnosis, monitoring, predict treatment response or disease severity, guiding procedures and patient education in gout, calcium pyrophosphate dihydrate deposition and basic calcium phosphate deposition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of the systematic literature review provided the basis for the development of evidence-based European Alliance of Associations for Rheumatology recommendations for the use of imaging in crystal-induced arthropathies in clinical practice.

INTRODUCTION

Crystal-induced arthropathies (CiAs) are the most common inflammatory arthropathies in adults and include various crystal deposition diseases such as gout, calcium-pyrophosphate (CPP) deposition (CPPD) and basic calcium phosphate deposition (BCPD), which also includes hydroxyapatite deposition.[1–3] While these conditions present with heterogenous symptoms and disease courses, they share some common attributes. The demonstration of the respective crystals in synovial fluid analysis (SFA) is traditionally regarded as the gold standard in the diagnosis of CiA.[1 2] However, fluid aspiration might not always be possible or feasible, especially in the intercritical periods common to these diseases.[3 4]

Imaging plays an increasing role in the diagnosis of and as an aid for treatment decisions in rheumatic and musculoskeletal diseases (RMD).[5] An increasing evidence of the diagnostic capacity of various imaging methods exists in CiA, especially in gout.[6 7] This is reflected in the gout and (preliminary) CPPD classification criteria, respectively.[1 2 8 9] In contrast, evidence of the diagnostic capacity of various imaging methods for BCPD is scarce and classification criteria are lacking.

Imaging has shown to be very useful for detection, monitoring or predicting the disease course in several RMDs. Guidance for physicians on the use of such techniques has been published either as part of diagnostic and treatment guidelines or as imaging recommendations for individual RMDs.[10–12] However, such recommendations are missing for CiA and evidence regarding the application of imaging for monitoring or prediction in this group is scarce.

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The aim of this study was to systematically assess published evidence regarding the use of imaging in CiA. Specifically, we wanted to evaluate the utility and the added value of imaging to help clinicians in the diagnostic, monitoring and prediction workup of patients with CIA in daily practice as well as its role in guiding interventions and patient education.

METHODS

Search strategy

Systematic literature reviews (SLRs) were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist.[13] The areas of interest in the application of imaging in CiA were identified by the task force, covering the aspects of diagnosis, follow-up, prediction of treatment response/disease severity, guided interventions and patient education in three different CIA: gout, CPPD and BCPD. 14 research questions (RQ) (RQ1–RQ4 for gout, RQ5–RQ8 for CPPD, RQ9–RQ12 for BCP, RQ13: guiding procedures, RQ14: patient education) were formulated and rephrased according to the PICOS (Patient, Intervention, Comparator, Outcome, Study design) framework, featuring predefined inclusion and exclusion criteria. Four search strategies for gout, CPPD, BCPD and patient education were developed together with an expert librarian (BW) (online supplemental table 16–26). Searches in Medline, Embase and Central were run from inception to 31 March 2022. The retrieved records were imported into a citation manager software (Zotero) and duplicates were removed. The two reviewers performing the SLR (IG and GS) screened the titles and abstracts independently, disagreement was resolved by consensus. The presence of studies fulfilling the inclusion criteria for the RQ on imaging-guided procedures and patient education was also checked in the disease-specific searches.

A protocol was shared among the reviewers, but the study was not registered.

Inclusion criteria

Original research studies as well as SLRs in the English language on adult (≥18 years old) patients with confirmed or suspect CiA were eligible for inclusion. Studies assessing conventional radiography (CR), ultrasound (US), dual-energy CT (DECT), MRI, CT or other imaging modalities were included. Narrative reviews, case reports and case series were excluded while the study designs eligible for inclusion varied depending on the RQ (online supplemental table 1).

Data extraction

The full texts of the eligible articles were retrieved and data were extracted into a standardised form, including, if possible, 2×2 tables for diagnostic studies to allow the calculation of sensitivity, specificity, positive and negative predictive value, as well as OR, risk ratio (RR) or HR for prognostic studies, along with 95% CI. The same article could be included in more than one RQ. In addition, the references of the included SLRs were handsearched, looking for additional studies. The results were summarised in tables. Due to an expected strong degree of clinical heterogeneity across studies, meta-analyses were not prespecified before study selection and extraction.

Risk of bias assessment

Risk of bias (RoB) of the included studies was assessed with different tools, depending on the RQ and study design. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used for diagnostic studies,[14] the Newcastle-Ottawa scale (NOS) for cohort and case–control studies,[15] the Cochrane RoB (RoB2) for randomised controlled trials (RCTs) and the ROBIS tool for SLRs.[16]

RESULTS

Four searches were performed, retrieving 3.043 records (gout search), 687 records (CPPD search), 1389 records (BCPD search) and 254 records (education search). We included 45 studies from the gout search for RQ1–4 (online supplemental figure 1) 50 studies from the CPPD search for RQ 5–8 (online supplemental figure 2), 52 studies for RQ 9–12 for BCPD (online supplemental figure 3), no study for RQ13 for imaging-guided procedures and 2 studies for RQ14 on patient education (online supplemental figure 4).

Gout

Out of 3.043 records retrieved by the search, 256 manuscripts were selected for full-text review and 88 studies were finally included for RQ1–4. Of those, seven studies were retrieved from the hand search (online supplemental figure 1).

RQ1: diagnostic value of individual imaging methods in gout

For RQ1, 45 papers were included. The majority of the studies assessed the diagnostic capacity of DECT (28 studies) and US (23 studies) while CR, CT and MRI were evaluated in 7, 3 and 0 studies, respectively (table 1).

For gout, 31 cross-sectional studies, 6 case–control studies and 8 SLRs were included. The comparator was SFA or fulfilled classification criteria in all but four studies,[17–20] in which imaging was compared with clinical diagnosis or tophi tissue samples (online supplemental table 2).

Among studies assessing the diagnostic capacity of DECT for the diagnosis of gout, 21/28 (75%)[6 18 19 21–38] and 21/28 (75%)[6 18 19 21–24 26 29–31 33–36 38–43] reported sensitivity and specificity, respectively of ≥80%. The sensitivity ranged from 52.8% to 100.0%, the specificity from 50.0% to 100.0%. Five studies out of 28 (17.9%) reported on the performance of DECT to diagnose gout in groups of patients with different disease duration.[6 31 38 41 44] Three out of these five studies (60%)[6 38 41] found numerically lower sensitivity (35.7% vs 92.9%, 38.0% vs 77.6% and 55% vs 81%) with similar specificity in the group with shorter disease duration of 1 year or less while two studies (40%)[31 44] found no difference between the subgroup with a shorter disease duration and the overall cohort. In 16/28 (57.1%) studies performing DECT, only the (previously) symptomatic side was assessed,[18 19 22 26–28 33 37–41 43–46] in 5/28 (17.9%) studies, a predefined set of joints was assessed[21 24 25 29 34] and in the remaining 1/28 study (3.6%), the (most) symptomatic joint or recently symptomatic joint as well as the contralateral metatarsophalangeal one joint was assessed.[42] The remaining studies[23 30–32 35 47] were meta-analyses without data on the assessed joints. Sensitivity and specificity in studies assessing only a prespecified set of joints ranged from 82% to 92% and 75% to 93% compared with 55% to 100% and 50% to 100% in studies assessing (previously) symptomatic joints only. The set of joints included the feet in all studies (figure 1, online supplemental table 2).

Of the 23 included studies reporting on the diagnostic value of US in the detection of gout, 16 (69.6%)[20 23 28 29 31 32 34 40 48–55] reported on overall diagnosis, while several studies reported (additionally) on the diagnostic value of specific findings: 17 (73.9%) on double contour (DC) sign,[31 32 34 45 48–54 56–61] 15

Table 1 Overview of included studies for each RQ and imaging method

	Number of included studies						
	CR	US	MRI	DECT	CT	Other*	Total†
Gout							
RQ1: diagnosis	7	23	0	28	3	1	45
RQ2: monitoring	7	12	1	11	3	0	30
RQ3: prediction of disease severity outcome	2	0	0	0	0	0	2
RQ4: prediction of treatment effect	0	3	0	1	0	0	3
CPPD							
RQ5: diagnosis	23	26	2	3	6	0	44
RQ6: monitoring	1	0	0	0	0	0	1
RQ7: prediction of disease severity outcome	9	0	0	0	0	0	9
RQ8: prediction of treatment effect	0	0	0	0	0	0	0
BCPD/HADD							
RQ9: diagnosis	1	1	1	0	0	0	3
RQ10: monitoring	38	7	0	0	0	0	45
RQ11: prediction of disease severity outcome	0	0	0	0	0	0	0
RQ12: prediction of treatment effect	9	5	1	0	0	0	15
Imaging-guided interventions							
RQ13: imaging guide	0	0	0	0	0	0	0
Imaging for patient education							
RQ14: patient education	0	0	0	2	0	0	2

*Shear wave elastrography.
†31 studies assessed multiple imaging modalities.
BCPD, basic calcium phosphate deposition disease; CPPD, calcium pyrophosphate deposition disease; CR, conventional radiograph; DECT, dual-energy CT; HADD, hydroxyapatite crystal deposition disease; RQ, research question; US, ultrasound.

(65.2%) tophi,[20 31 32 34 48 49 51–54 56 57 59–61] 11 (47.8%) aggregates,[20 32 45 48 49 51–54 56 57] 5 (21.7%) erosions[20 48 51 56 57] and 3 (13.0%)[20 53 56] inflammation. Only affected joint(s) were assessed in 12/23 (52.2%) studies,[20 28 34 40 45 48 50 52 53 57 60–62] while 2/23 (8.7%) studies[49 55] assessed the symptomatic site as well as additional joints and in 5 studies[29 34 56 58 59] a predefined set of sites was assessed. The remaining four studies[23 31 32 51] were meta-analyses. In 12/16 (75%) and 10/16 (62.5%) studies reporting on overall diagnosis, a sensitivity[20 23 28 29 31 32 34 40 48 49 54 55] and specificity,[28 31 32 40 48 51–55] respectively, of ≥80% was reported. Sensitivity ranged from 61.1% to 100.0% and specificity from 60.0% to 100.0%. The frequency of studies with a sensitivity and specificity of ≥80%, respectively, was 5/17 (29.4%)[34 45 50 56 61] and 14/17 (82.4%)[31 32 45 48 51–54 56–61] for the DC sign, 0/15 (0%) and 15/15 (100%)[20 31 32 34 48 49 51–54 56 57 59–61] for tophi, 2/11 (18.2%)[20 56] and 7/11 (63.6%)[32 45 49 51–54] for aggregates, 0/5 (0%), 2/5 (40%)[51 57] for erosions and finally 2/3 (66.7%)[20 56] and 0/3 (0%) for inflammation (figure 1, online supplemental tables 2–9).

A specificity of ≥80% was found in all (3/3, 100%)[21 37 39] included studies assessing the diagnostic capacity of CT to diagnose gout, while a sensitivity of ≥80% was found in 1/3 (33.3%)[37] studies. All included studies assessed additional sites besides the symptomatic joint(s) by CT (figure 1, online supplemental table 2).

All (7/7, 100%) included studies assessing the value of CR to diagnose gout reported a specificity of ≥80%, while no (0/7, 0%) study reported a sensitivity of ≥80% (figure 1, online supplemental table 2).

The RoB was high in at least one area in 20/37 including diagnostic studies assessed by QUADAS-2, mostly due to patient selection. Among included SLRs, no high RoB was observed. (online supplemental figure 5)

RQ2: the ability of imaging modalities for monitoring inflammation, damage or crystal deposition in gout

For the second RQ, 30 papers were included, of which 11/30 (36.7%) studies investigated monitoring in gout by DECT, while US was assessed in 12/30 (40%) studies, CR in 7/30 (23.3%) studies and CT in 3/30 (10%) studies. In the majority (23/30, 76.7%) of the included studies, urate-lowering therapy (ULT) was initiated or increased, at least in one separately examined group (table 1).

Studies using DECT to monitor crystal deposition in gout used either a (semi)quantitative score or the total monosodium urate (MSU)/tophi volume. All (11/11, 100%) studies found a significant decrease after 6 months to 3 years (online supplemental table 3).

With regard to the studies investigating US, 8/8 (100%) reporting on the DC sign showed a reduction after 3–12 months, 5/6 (83.3%)[63–67] reporting on aggregates showed a reduction after 3–12 months and 8/10 (80%)[63 64 66 68–72] reporting on tophi showed a reduction after 3 months to 4 years. Four out of five studies (80%) reporting on inflammation (power Doppler (PD), grey scale, synovial thickness or Global OMERACT-European Alliance of Associations for Rheumatology (EULAR) Synovitis Score)[64 65 67 73] found a significant change after 3–12 months. The single study revealing no significant result assessed PD score after 4 weeks only.[74] Two studies assessed change in erosions after 3 and 6 months, respectively, and found no significant differences[64 67] (online supplemental table 3).

In total, three studies[75–77] assessed change in the erosion score by CT after 1–2 years. Of these, a single (33.3%) study[76] found a significant increase after 1 year (online supplemental table 3).

Change of damage over time assessed by CR was reported in 6/7 (85.7%) studies. Significant increases were found in two

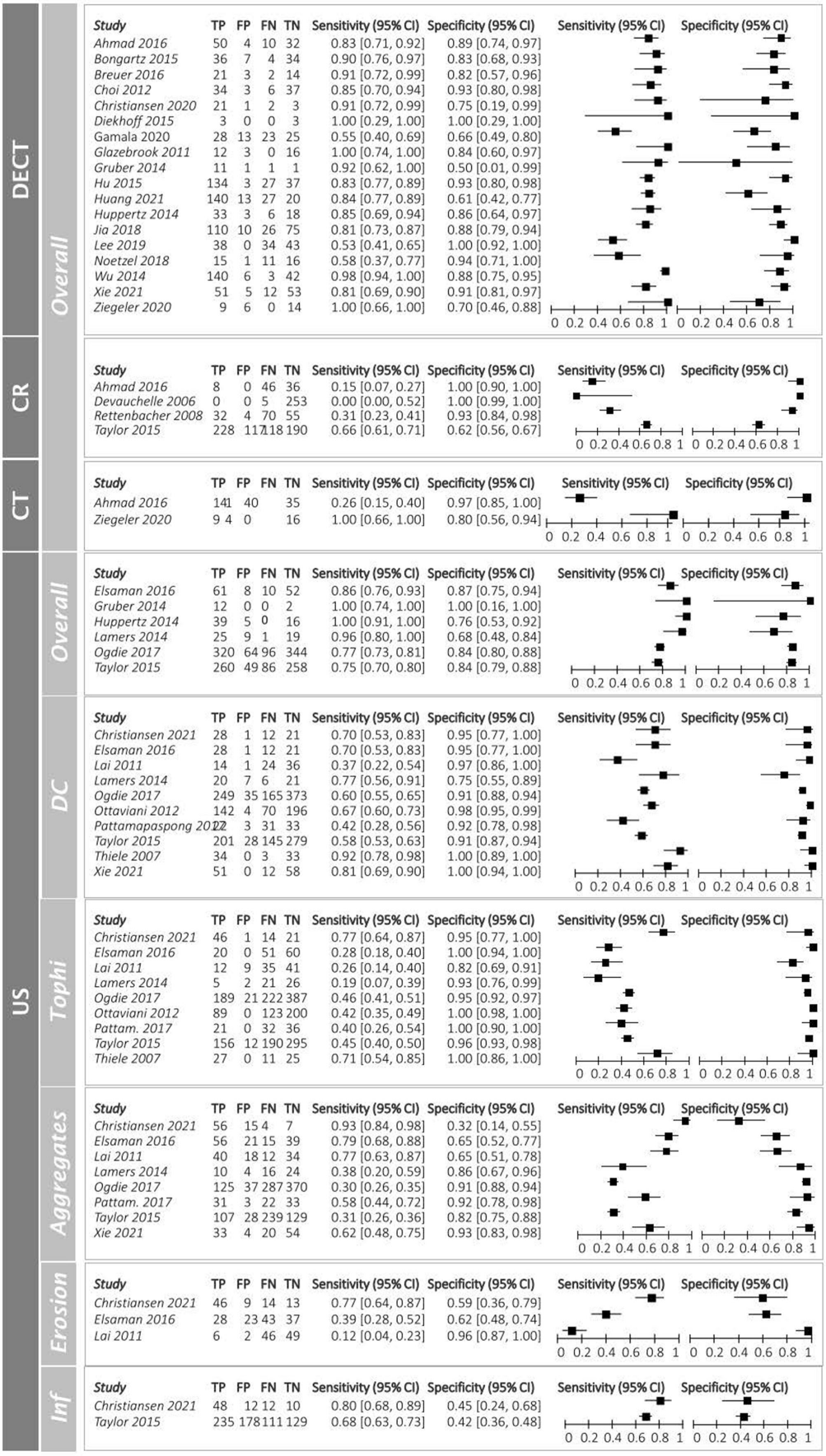

Figure 1 Overview of included studies for research question 1: Diagnostic utility of imaging methods for the diagnosis of gout. CR, conventional radiograph; DC, double contour sign; DECT, dual-energy CT; FN, false negative; FP, false positive; Inf, inflammation; TN, true negative; TP, true positive; US, ultrasound.

studies after 12 months.[76 77] One additional study 1/7 (14.3%)[78] found a significant decrease of tophi semiquantitatively assessed on CR after ULT initiation over a time of at least 18 months (online supplemental table 3).

Only a single study assessing MRI changes over time was included,[79] reporting small numerical changes in the Rheumatoid Arthritis MRI Score from baseline with no statistical tests performed (online supplemental table 3).

Included studies had good quality according to the NOS except for the missing control group in most studies. No RoB was found in the included RCTs for RQ 2 (online supplemental figure 5).

RQ3: the ability of imaging modalities to predict disease severity outcome in gout

For RQ3, two studies were included, both of them using baseline CR for the prediction of disease severity outcome in gout[80 81] (table 1).

One study[80] found the baseline damage score to be predictive of change in damage over 3 years while its erosion and joint space narrowing (JSN) subscores were not predictive. A second study[81] found no association between the baseline JSN and erosion score and health assessment questionnaire II[81] score after 1 year (online supplemental table 10).

Included studies had good quality assessed by the NOS, however, a control group was missing in all included studies (online supplemental figure 6).

RQ4: the ability of imaging modalities to predict treatment effect in gout

Three studies were included for RQ4 assessing the utility of baseline US (three studies) and DECT (one study) in predicting treatment effect in gout (table 1). One study[82] found the absence of MSU crystal deposits, aggregates, DC sign and tophi assessed by US to be predictive of remission after 12 months in patients with ongoing ULT. In this study, neither baseline serum uric acid (SUA) nor the highest SUA level was predictive of remission. Two additional studies[83 84] found no significant association between baseline sonographic signs for crystal deposition and flare within 12 months (table 2).

One study[84] additionally assessed the association of baseline DECT with flare within 6 months and found higher MSU volume in patients with flare compared with patients without flare (table 2). Only one study[1] included a multivariate analysis to assess the predictive value of imaging as well as other factors on treatment effect in gout. Pascart *et al*[84] calculated a multivariate analyses including baseline US, DECT, ongoing ULT, baseline serum urate, comorbidities and other clinical variables. Only baseline MSU deposition assessed by DECT remained significant in the model. In another study, ongoing flare prophylaxis was significantly associated with remission after 12 months in a univariate analysis. Both C reactive protein and ongoing flare prophylaxis were included as covariates into a multivariate analysis assessing the predictive value of US. Except for a missing control group, the studies had good quality according to the NOS (online supplemental figure 5).

Calcium pyrophosphate deposition

Out of 687 records retrieved by the search, the full text of 116 manuscripts were assessed and 50 studies were finally included (online supplemental figure 2) for RQ 5–7, that is, on diagnosis, monitoring and prediction of disease severity outcome, while no studies could be included for RQ8 on the prediction of treatment effect. Handsearch did not retrieve additional studies.

RQ5: diagnostic value of individual imaging methods in CPPD

44 studies were included (online supplemental table 11, figure 2), mostly presenting data on CR (23 studies)[17 40 55 85–103] and US (24 studies),[40 49 55 86–88 90–93 95 96 98 99 102–111] with only 6 studies on CT,[37 95 112–115] 3 on DECT[37 40 116] and 2 on MRI.[117 118] The reference standard for making a diagnosis of CPPD was histology in 3 studies,[96 108 111] SFA in 13,[40 55 85 86 92 97–100 106 107 119] McCarty criteria in 19,[37 40 87–93 95 103 105 112–116 120] clinical diagnosis in 3[49 104 116] and evidence of CPPD on CR in 3.[94 117 118] There were 4 SLRs,[96 101 102 110] 15 cross-sectional cohort studies,[40 49 55 86 95 97–99 106 108 109 111 112 117 119] 19 case–control studies[37 85 87–94 100 103 107 113–116 118 120] and 2 longitudinal cohort studies.[17 104] The knee and the wrist were the most commonly investigated sites, with 17[93–96 98–100 105–108 111 116–119] and 8[17 37 89–92 112 120] studies assessing exclusively these areas, respectively.

Among studies assessing the performance of CR to diagnose CPPD, only 5/23 (21.7%) reported a sensitivity ≥80% (ranging from 0% to 100%) while 18/23 (78.3%) reported a specificity ≥80% (ranging from 40% to 100%). At the level of the knee, CR had a maximal sensitivity to diagnose CPPD in cohort studies of 75%,[96] while the minimal sensitivity was 13%[86] for CPP deposits of the knee.

Regarding the specific differentiation of CPPD from gout, at the level of the knee, the highest reported sensitivity (95% CI) to was 84% (73% to 91%)[93] for calcification of the menisci, while the lowest was 0% (0% to 18%)[100] for patellar tophus-like opacity; the highest specificity to differentiate CPPD from gout was 100% (82% to 100%) for popliteal tophus-like opacity, while the lowest was 74% (54% to 93%) for cartilage icing (deposition of CPP crystals on the surface of the cartilage) in the same population.[100] At the wrist, the highest sensitivity for making a diagnosis of CPPD was 86% (70% to 95%) for deposition at the triangular fibrocartilage complex[90] and the lowest was 44% (36% to 52%) for scaphotrapeziotrapezoidal osteoarthritis (OA).[120] At this site, specificity ranged from 100% (98% to 100%) for diagnosis of CPPD[17] to 40% for scaphotrapeziotrapezoidal OA.[89]

A sensitivity ≥80% was found in 14/24 (58.3%) studies on US (range 0%–100%), while specificity was ≥80% in 23/24 (95.8%%) studies (range 4%–100%). At the level of the knee, sensitivity ranged from 100%[99] to 44%[111] for CPP deposition, while specificity (95% CI) ranged from 4% (0.1% to 20%) for joint effusion to 100% (95% to 100%) for crystal deposition in the hyaline cartilage.[98] At the wrist, however, the sensitivity ranged from 50%[92] to 95% (86%–99%)[91] and specificity from 85% (84%–95%)[91] to 92%[98] both for intraarticular CPP depositions. Two studies[87 103] assessed the Achilles tendon and the plantar fascia, reporting a high specificity, up to 100% for intratendineous calcifications, with lower sensitivities (58%) in both studies for Achilles tendon calcifications. Six studies assessed multiple joint sites,[55 85 86 91 104 109] with sensitivities ranging from 11% (2.8%–48%)[104] to 84% (69%-84%)[86] and specificities from 19% (5%–42%)[104] to 100% (85%–100%).[86] Studies assessing the symptomatic joint showed a sensitivity ranging from 0% (0%–41%)[49] to 91% (59%–100%)[40] and a specificity from 92% (74%–99%)[40] to 100% (92%–100%).[49]

Three studies assessed the value of CT scan of the cervical spine to diagnose CPPD,[113–115] with sensitivities ranging from 67% (43%–85%)[113] to 72% (54%–87%)[114] and specificities

Table 2 Overview of included studies for research question 4: predictive value of imaging methods for the treatment effect in gout

Study	No of subjects	Study design	Treatment	Follow-up	Outcome	Imaging modality, imaging lesion		Results	
								Significant	Not significant
Ebstein[83]	79	Cohort	ULT initiation+flare prophylaxis for 6 months	12 months	Flare	US	Tophus size in mm, mean±SD		No flare: 12.0±3.8 vs 13.4±5.9, p=n.s.
							Decrease in tophus size in %, mean±SD		OR: 3.35 (0.98–11.44) −36.0%±31.2% vs −54.1%±34.2%, p=0.082
							DC sign disappearance after 6 months in %, mean±SD		63.3%±46.1% vs 61.6%±43.4%, p=n.s.
Cipolletta[82]	50	Cohort	Ongoing ULT: 100%; ongoing flare prophylaxis with colchicine at baseline: 54.0%	12 months	Remission	US	Absence of MSU crystal deposits	Multivariable analysis: OR 10.83 (1.14–22.76), p<0.01	
							Absence of aggregates	Multivariable analysis: OR 5.53 (1.34–22.76), p<0.01	
							Absence of DC sign	Multivariable analysis: OR 7.33 (1.71–31.44), p<0.01	
							Absence of tophi	Multivariable analysis: OR 3.88 (1.08–13.92, p=0.02)	
Pascart[84]	62	Cohort	Ongoing ULT: 46.2%; ongoing flare prophylaxis at baseline: 32.1%	12 months	Flare	US	DC, n of joints with US DC sign (of 6), mean±SD		Multivariable analysis: No flare: OR 1.80 (95% CI 0.07 to 46.40) 2.5±0.9 vs 2.9±1.5, p=0.67
							Tophi, n		Multivariable analysis: No flare: OR 1.60 (95% CI 0.49 to 5.24) 19/33 (57.6%) vs 13/19 (68.4%), p=0.63
						DECT	MSU volume (cm^3), mean±SD	Multivariable analysis: Feet: No flare: 0.9±0.8 vs . 2.1±1.9, p=0.05	
								Multivariable analysis: Knee: No flare: 0.6±1.2 vs 1.1±1.6, p=0.24	

DC, double contour; DECT, dual-energy CT; MSU, monosodium urate; n, number; ULT, urate-lowering therapy; US, ultrasound.

from 94% (86%–98%)[114] to 100% (84%–100%).[113] CT scan of the peripheral joints (knees and wrist) was assessed in three studies, showing similar diagnostic performance.[37 95 112] Studies on MRI reported only sensitivity, ranging from 50% (41%–58%)[118] to 92% (61%–99%).[117] Studies on DECT demonstrated low sensitivity (from 23% (14%–36%)[37] to 55% (23%–83%)[40]) but high specificity, ranging from 92% (74%–99%)[40] to 100% (66%-100%).[37]

The assessment of the RoB via QUADAS-2 of the included studies highlighted some issues in the area of patient selection, with a high or unclear RoB in many studies. The remaining items of the QUADAS-2 were fulfilled satisfactorily, with low/unclear RoB. The SLRs included had mostly low RoB, with a single SLR[101] carrying higher risk (online supplemental figure 6).

RQ6: the ability of imaging modalities for monitoring CPPD

A single longitudinal cohort study[121] dating back to 1993, enrolling 104 patients with probable CPPD, followed for 4–5 years was included. CR of multiple sites (knee, wrist, pelvis, shoulders, spine and symptomatic joints) was performed, reporting descriptive data. In this context, 68% of patients showed an increased extension of CPP deposits, and 19% developed CPP deposits at new sites (online supplemental table 12). The study had good methodological quality

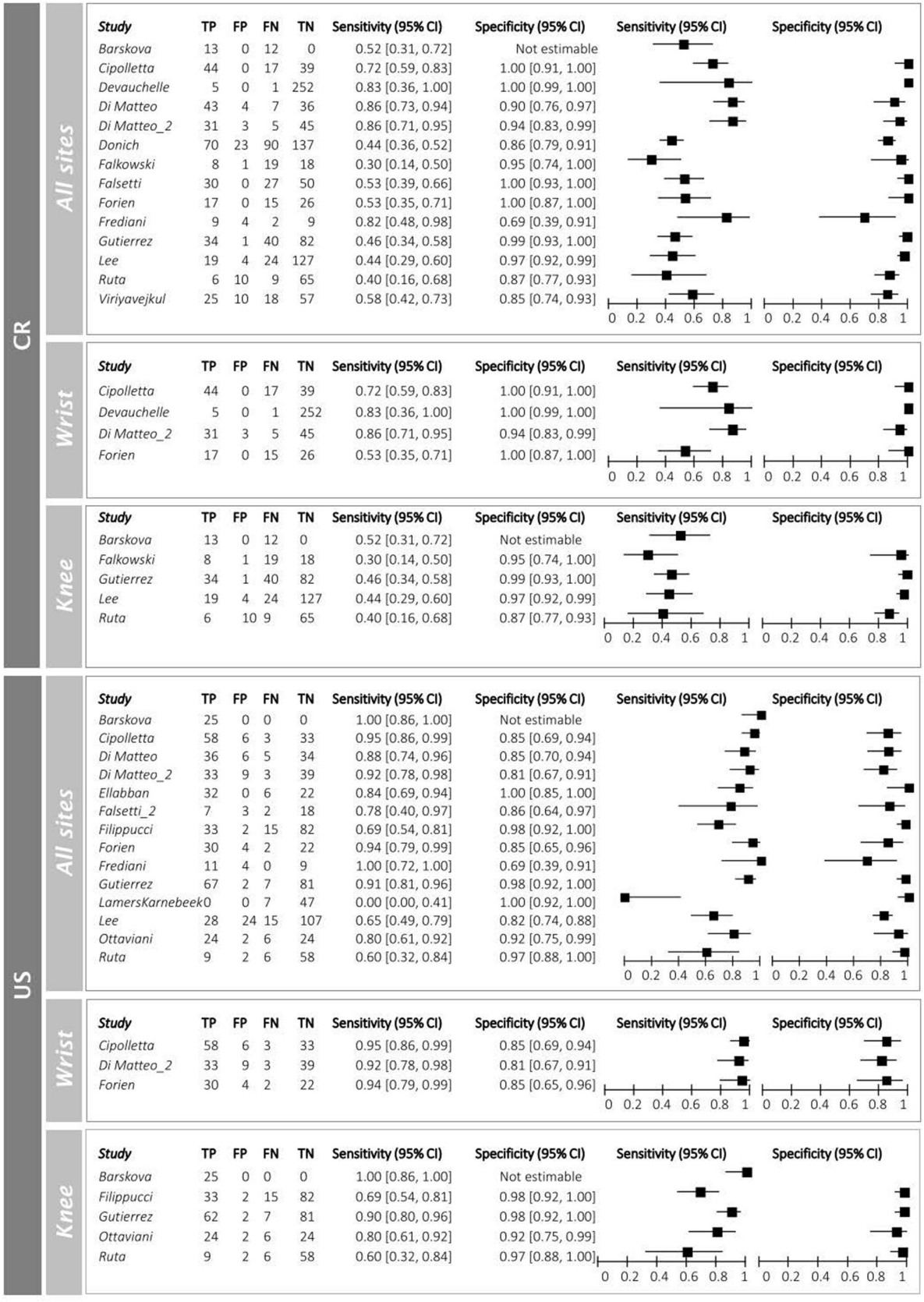

Figure 2 Overview of included studies for research question 5: Diagnostic capacity of imaging methods for the diagnosis of calcium pyrophosphate deposition disease. CR, conventional radiograph; US, ultrasound.

according to the NOS for the items on selection and outcome assessment, but not for comparability (online supplemental figure 6).

RQ7: the ability of imaging modalities to predict disease severity outcome in CPPD

Nine studies were included[118 122–129] (table 3).

All but one study assessed CR, while the remaining evaluated MRI[118]; none of the studies had a comparator. All studies had a longitudinal design, with six cohort studies[122 124–126 128 129] and three case–control studies.[118 123 127] Interestingly, the majority 6/9 (%) of studies pertained to large epidemiological OA cohorts.[118 122–126] Most of the studies assessed the knee,[118 122–127] while two studies evaluated multiple sites.[128 129] The follow-up varied between 2.26[129] and 10 years.[122] Two studies assessed CPPD as a risk factor for developing OA[122 126] and two studies as a risk factor for progression of existing OA,[124 128] all of them reporting no significant association. A single study evaluated CPPD to predict total knee replacement in OA,[124] without showing a significant predictive effect of imaging, while a second study assessed the risk of failure of knee replacement in patients with CPPD[127] and found no significant effect. Symptoms (pain in particular) were the outcome of interest in two studies,[123 129] of which one reported a significant increase in symptoms and pain in patients with CPPD,[129] while the other did not show any significant association. Finally, a single study assessed the impact of CPP depositions on MRI,[118] showing increased joint damage assessed by MRI in patients with depositions, while a second study did not show any association between CPP depositions on CR and cartilage damage on MRI.[125]

The methodological quality of the included studies, assessed by the NOS, was overall good (online supplemental figure 6).

RQ8: the ability of imaging modalities to predict treatment effect in CPPD

No studies on the value of imaging predict treatment effect in CPPD fulfilled the inclusion criteria and could be included in the final review.

Basic calcium phosphate deposition

Out of 1389 records retrieved by the search, the full text of 89 studies was assessed and 52 studies were finally included (online supplemental figure 3) for RQs 9, 10 and 12, that is, on diagnosis, monitoring and prediction of treatment effect, while no studies were included for RQ11 on the prediction of disease severity outcome. Three of the included studies were retrieved by hand search of the references.

RQ9: diagnostic value of individual imaging in BCPD

Three studies were included,[17 130 131] a cohort study on CR of hand and wrist against clinical diagnosis,[17 130] a case–control study on MRI arthrography of the shoulder against diagnosis on CR and an SLR on US of the shoulder against surgery[131] (online supplemental table 13). The detection of ≥6 BCP deposits yielded high sensitivity (100% (48%–100%)) and specificity (100% (98%–100%)) to diagnose BCPD.[17] In contrast MRI arthrography demonstrated lower sensitivity (54% (32%–76%)) and specificity (66% (52%–77%)). The RoB was high in the case–control study and low in the cohort study and the SLR (online supplemental figure 7).

RQ10: the ability of imaging modalities for monitoring BCPD

42 studies assessed the value of imaging to monitor BCPD,[132–174] presenting data on CR in 38 studies[133 135–169 172 173] and on US in seven studies[132–134 139 170 171 173] (online supplemental table 14, figure 3). Study design included 4 SLRs,[139 164 172 173] 26 RCTs on a variety of interventions, including, injection, aspiration, needling, extracorporeal shockwave therapy and systemic therapy,[132 136 137 140–142 144–157 160 161 166 169–171] and 12 cohort studies.[133–135 138 143 158 159 162 163 165 167 168] All studies but one on the hip,[158] assessed the shoulder, and in all studies the diagnosis of the condition was imaging based. 30 out of 38 (78.9%) studies on both US and CR showed a reduction in the size of depositions after the intervention,[132–134 138–144 146–157 159–164 168 170 171] while in 6/38 (15.8%) the depositions were unchanged; no study reported an increase in depositions[145 158 165–167 169] (figure 2). Only 7/38 (18.4%) studies assessed imaging in relation to other clinical measures,[132–138] all of them suggesting an association between the clinical response to treatment and the size and reduction of the depositions. No study assessed the value of imaging over clinical measures for monitoring, or the optimal frequency of imaging. The ROB of the included RCTs was mostly high or unclear for the items regarding allocation concealment and blinding, while it was generally low for the remaining aspects. The methodological quality of the cohort studies, assessed by the NOS, was mostly acceptable for selection and outcome assessment, while it was lower for comparability (online supplemental figure 7).

RQ12: the ability of imaging modalities to predict treatment effect in BCPD

11 studies, all on the shoulder, fulfilled the inclusion criteria[153 157 175–183] (table 4).

CR was assessed in nine studies,[153 157 175–180 183] US in five[179–183] and MRI in a single study.[178] Study design included one SLR without meta-analysis, whose references were reviewed,[176] two RCTs[153 179] and eight cohort studies.[157 175 177 178 180–183] Treatment included injections, aspiration, needling, lavage, extracorporeal shockwave therapy and radiotherapy. The results across studies were variable, with some suggesting that the morphology and size of the calcifications on CR and US could predict response to treatment,[157 177 180–182 184] while others yielded negative results.[153 175 178 179 183] One study on US and one on MRI investigating inflammatory changes suggested a predictive role,[178 181] while two US studies did not.[179 182] A single study reported a predictive role of acromial shape on CR.[175]

The RoB of the RCTs and the SLR was low, while the methodological quality of cohort studies was good for selection and outcome assessment, and lower for comparability (online supplemental figure 7).

Guided procedures and education

RQ13: the ability of imaging modalities for guiding procedures in CiA

No studies on the value of imaging to guide intra-articular and periarticular procedures in CiA, retrieved from the disease-specific search strategies, fulfilled the inclusion criteria and could be included in the final review.

RQ14: the ability of imaging modalities for patient education in CiA

Out of 254 retrieved studies, only 2 studies were finally included[185 186] (online supplemental figure 4). No additional studies were retrieved by the disease-specific searches. The first study was an RCT on 60 patients with gout, who were shown generic or personal DECT images, as well as illustrations. The

Table 3 Overview of included studies for research question 7: predictive value of imaging methods for the outcome of calcium pyrophosphate deposition (CPPD)

Study	No of subjects	Study design	Follow-up	Outcome	Imaging modality	Imaging lesion	Results
Felson[122]	598	Cohort	12 months	Development of knee KLG≥2	CR	CPP deposits	Multivariable analysis: OR (95% CI) 1.2 (0.5 to 2.7)
Foreman[118]	70 cases with CPP at CR 70 controls	Nested case–control	4 years	Development of cartilage damage at MRI of the right knee measured by WORMS	MRI	CaCs at the knees	***CaCs+*** ► cartilage lesions frequently progressed in the PAT and MF ► new full-thickness lesion 34/70 (49%) ► cartilage lesions increased more vs CaCs—in the PAT (coefficient: 0.33; 95% CI: 0.04 to 0.63; p=0.024), MF (coefficient: 0.51; 95% CI: 0.18 to 0.83; p=0.003) and LT (coefficient: 0.36; 95% CI: 0.01 to 0.71; p=0.044) ► More progression of medial and lateral meniscus lesions (coefficient: 0.38; 95% CI: 0.00 to 0.75; p=0.049 and coefficient: 0.72; 95% CI: 0.12 to 1.32; p=0.020) ► Subchondral cysts increased more (coefficient: 0.64; 95% CI: 0.19 to 1.10; p=0.006) ► BMEP, ligamentous changes and effusion did not progress more ► Higher numbers of circumscribed CaCs at baseline are associated with increased joint damage over 4 years ► Knees with higher numbers of CaCs had increased cartilage degeneration in the PAT and the MF compartment (coefficient: 0.09; 95% CI: 0.05 to 0.14; p<0.001 and coefficient: 0.08; 95% CI: 0.02 to 0.14; p=0.005) ► more changes of the cartilage sum score (coefficient: 0.03; 95% CI: 0.01 to 0.06; p=0.016) ► Changes in meniscal lesions, BMEP, subchondral cysts, ligamentous changes, and effusion WORMS subscores not associated ***CaCs–*** ► cartilage lesions most frequently progressed in the PAT and TRO ► new full-thickness lesion 22/70 (31%)
Han[123]	151 CPPD 1894 controls	Nested case–control	4 years	Knee pain: >50% days of a month in the past 12 months Any knee pain in the past 30 days Knee pain >50% the days in the past 30 days	CR	CPP deposits	***Multivariable analysis: OR (95% CI)*** ***Knee pain more than half the days of a month at 4 years*** 1.3 (0.9 to 1.9) ***Any knee pain, past 30 days*** 1.4 (1.0 to 2.1) ***Knee pain more than half the days, past 30 days*** 1.3 (0.9 to 2.0)
Kumar[127]	87 cases 174 controls	Case–control	10 years	all cause surgical revision of unicompartmental knee prosthes	CR	CPP deposits	***Univariable analysis: HR (95% CI)*** 2.9 (0.5 to 18.1) p>0.05
Latourte[124]	656	Cohort	5 years	Primary: time TKR Secondary: structural progression (KLG) clinical worsening (WOMAC subscores) time to first total joint replacement (including the hip)	CR	CPP deposits	***Multivariable analysis: OR (95% CI)*** Worsening of KLG: 0.9 (0.4 to 1.7) WOMAC function ≥12: 1.1 (0.7 to 1.4) WOMAC pain ≥17: 0.9 (0.4 to 2.0) ***Univariable analysis: HR (95% CI)*** Total joint replacement: 1.26 (0.74 to 2.17) Time to first TKR:1.01 (0.58 to 1.77)

Continued

Table 3 Continued

Study	No of subjects	Study design	Follow-up	Outcome	Imaging modality	Imaging lesion	Results
Ledingham[128]	136	Cohort	At least 1 year	Radiographic progression at the hip	CR	CPP deposits	Univariable analysis: The presence of CPP deposits did not influence radiographic progression
Ledingham[129]	188	Cohort	2.26 years (mean)	Progression of OA at the knee (radiographic progression, worsening of symptoms, attrition)	CR	CPP deposits	Multivariable analysis: OR (95% CI)) *Worsening symptoms:* 1.89 (1.06 to 3.38) *Increased pain score:* 1.88 (1.17 to 3.16) *Decreased exercise tolerance:* 1.85 (1.04 to 3.29)
Neogi[125]	265 (BOKS)+230 with 373 knees (Health ABC)	Cohort	30 months BOKS 3 years Health ABC	Cartilage loss at MRI	CR	CPP deposits	Multivariable analysis: RR (95% CI) BOKS: 0.4 (0.2 to 0.7), p<0.002 Health ABC 0.9 (0.6 to 1.5), p=0.7
McAlindon[126]	608	Cohort	8 years	TF or PF OA	CR	CPP deposits	Multivariable analysis: OR (95% CI) *Isolated PF OA* 1.8 (0.7 to 4.7) *Isolated TF OA* 1.5 (0.8 to 2.6) *Combined PF and TF* 1.5 (0.8 to 2.9)

Subgroups are highlited in bold and italics.
BMEP, bone marrow oedema pattern; BOKS, Boston Osteoarthritis of the Knee Study; CaCs, calcium-containing crystals; CPP, calcium pyrophosphate; CR, conventional radiograph; KLG, Kellgren and Lawrence grade; LT, lateral tibia; MF, medial femur; OA, osteoarthritis; PAT, patella; PF, patellofemoral; RR, risk ratio; TF, tibiofemoral; TKR, total knee replacement; TRO, trochlea; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

intervention reduced the perceived stigma of gout, the patients were more motivated to take medication and had a greater understanding of its importance. Personal images were perceived as being more useful.[185] The second study was a quasi-randomised study, recruiting people (with a small proportion of patients) at a supermarket, where they received a leaflet with images (including DECT) related to gout, or a leaflet with no images as the control intervention. Illness perception, perceived gout severity or perceived gout stigma did not vary between groups. Medical illustrations were perceived as more useful, while DECT images had a more limited impact on understanding, compared with the anatomical drawing[186] (online supplemental table 15).

The included articles had high RoB related to the items of blinding, and low RoB with regard to the remaining aspects (online supplemental figure 8).

DISCUSSION

Technical advances in imaging, with reference to both conventional imaging, such as CR and advanced imaging (US, CT including DECT, MRI), along with increased availability in the last years, have led to significant developments also in the context of CiA. This SLR provides an overview of the available evidence of the use of imaging in this field, serving as the basis for the work of an international task force to develop recommendations for clinical practice.

Most of the evidence for the role of imaging in clinical practice was found for gout. The majority of the diagnostic studies for gout retrieved by this SLR assessed DECT and/or US. All included DECT studies and all but one included US studies were published after 2010 reflecting recent advances and an increasing interest in this field. Most studies assessing the diagnostic utility of DECT reported good sensitivity and specificity, which further underlines the importance and value of DECT. A lower sensitivity was found in 3/5 included studies in patients with shorter disease duration. This should be kept in mind when interpreting DECT results of patients with suspected gout and recent onset of symptoms. Further studies are needed to assess the sensitivity of various imaging methods to detect gout in patients with short disease duration.

The majority (12/16 (75%) and 10/16 (62%), respectively) of studies assessing the utility of US to diagnose gout found a sensitivity and specificity of ≥80%. Interestingly, when the specific features were assessed, DC sign, which is the only sonographic feature included in the 2015 American College of Rheumatology (ACR)/EULAR classification criteria,[8] had a sensitivity of ≥80% in only about one-third of the studies which investigated this feature. This implies that it might be useful to assess several sonographic features associated with gout, in particular tophi, erosions or synovitis to increase sensitivity without losing specificity. CR, primarily referring to the feature of radiographically detected 'gout-related' erosions is included in the 1977 ACR criteria[187] as well as the 2015 ACR/EULAR criteria.[8] Most included studies assessing the detection of erosions both by US and CR found high specificity but lower sensitivity.

All included studies assessing DECT or DC in US found a significant decrease in crystal deposition in patients who initiated or were receiving ULT. Some, but not all included studies found an increase in erosions detected by CR. This non-significant result might be explained by the short observation period of mostly 2 years. The amount of baseline crystal deposition detected by US or DECT predicted flares within 6–12 months in two included studies. Both studies observed no association of SUA levels with subsequent flares, while only one study included a direct comparison by calculating a multivariate analysis. The benefit or added value of a regimen with target SUA levels needs to be assessed in future studies. Cipolletta *et al*[82] suggest performing a sonographic examination on patients to assess crystal deposition and consider this information in the management of these patients.

Study	Intervention	Reduction	No change
CR			
Al-Abbad 2020	SWT	■	
Albert 2007	SWT	■	
Arooj 2022	SWT	■	
Cacchio 2009	ionophoresis	■	
Cacchio 2006	SWT	■	
Cho 2010	NSAIDs, self-managed exercise	■	
Cosentino 2003	SWT vs sham	■	
Darrieurtort-Laffite 2019	Lavage followed by steroids vs saline solution		■
De Boer 2017	US needling, vs radial SWT	■	
De Witte 2013	US-guided barbotage + steroid injection VS steroid injection	■	
Ebenbichler 1999	Ultrasound therapy vs sham	■	
Farr 2011	middle-energetic SWT vs lower dosed middle-energetic SWT	■	
Gerdesmeyer 2003	High-energy SWT, low-energy ESWT, or sham	■	
Hsu 2008	SWT vs sham	■	
Ioppolo 2012	SWT 0.2 j/mm vs 0.1 j/mm	■	
Kim 2014	US needling vs SWT	■	
Krasny 2005	US needling + SWT vs SWT	■	
Louwerens 2021	US needling+injection vs SWT	■	
Maugars 2009	Shoulder bursoscopy (BS), needling fragmentation irrigation (NFI), and control (CT)	■	
Moretti 2004	SWT	■	
Oudelaar 2021	Needle aspiration+corticosteroids or needle aspiration+PRP	■	
Park 2014	Non operative methods		■
Rompe 2001	SWT vs arthroscopy	■	
Shomoto 2002	Ultrasound therapy vs exercise	■	
Tornes 2011	SWT neutral position vs hyperextension	■	
Wang 2003	SWT	■	
Yokoyama 2003	cimetidine	■	
Yoo 2010	ultrasound-guided needle decompression and subacromial corticosteroid injection	■	■
Zhang 2019	US-guided lavage	■	
Loew 1999	SWT: control group vs low energy vs high energy once vs high energy twice		■
Pleiner 2004	SWT and controls		■
Charrin 2001	SWT		■
Jakobeit 2002	SWT	■	
Peters 2004	ESWT (low energy vs high energy) vs sham		■
US			
Abo Al-Khair 2015	Radial SWT	■	
Al-Abbad 2020	SWT	■	
Del Castillo Gonzalez 2016	US guided lavage vs SWT	■	
Pan 2003	SWT vs TENS	■	
Porcellini 2003	arthroscopy	■	

Figure 3 Overview of included studies for research question 10: The ability of imaging methods for monitoring inflammation and damage in basic calcium phosphate deposition (BCPD). CR, conventional radiograph; NSAIDs, non-steroideal anti-inflammatory drugs; SWT, shockwave therapy; US, ultrasound.

Table 4 Overview of included studies for research question 12: predictive value of imaging methods for assessing the treatment effect in basic calcium phosphate disease/ hydroxyapatite deposition disease (BCPD/HADD)

Study	No of subjects	Study design	Follow-up	Outcome	Imaging modality	Imaging lesion	Results
Adamietz[183]	29	Cohort	18 months	Response to treatment by CMS	CR and US	CR BCPD/HADD deposits	The radiographic classification of the calcific deposits according to Gärtner did not provide a significant difference in the response to therapy.
						US BCPD/HADD deposits	Farin type III calcifying tendonitis: complete pain relief with increasing mobility. Type I calcifying tendonitis: excellent result 5/11, good result 3/11, 3/11 no response.
Bazzocchi[181]	147	Cohort	1 month	CMS NRS pain	US	BCPD/HADD deposits	Calcification classified as: Hard Medium Soft (type 2) Fluid (type 3) The success was related to sonographic features per type of calcific deposit (p<0.02; rho 0.274). Greatest improvement for type 2–3 calcifications (117.6% in CMS)
						SAD bursa	Strong relationship (p<0.0005; r 0.424) between CMS increase and thickening of subacromial/subdeltoid bursa
Dietrich[175]	98	Cohort	1 month	NRS pain PGIC	CR	Posterior acromial slope	Univariable analysis: Patients with grade 3 (>36°) posterior acromial slope 2.16 times more likely to improve (95% CI, 1.11 to 4.22).
Dumoulin[179]	132	RCT	12 months	DASH<15	CR and US	CR Molé calcification A vs B	Prediction of a DASH score <15, multivariable analysis: (OR, 95% CI) 0.774 (0.351 to 1.711)
						US calcification pattern	Multivariable analysis: 0.864 (0.521 to 1.431)
						Doppler signal	Multivariable analysis : 1.262 (0.488 to 3.262)
Kim[153]	54	RCT	12 months	VAS pain ASES SST	CR	BCPD/HADD deposits	Univariable analysis: No significant correlation between the initial size of the calcium deposit and clinical outcomes
Le Goff[182]	62	Cohort	11 months	VAS pain 30% lower at the end of the follow-up	US	Arc shaped calcification	Univariable analysis: Prediction of the outcome (OR, 95% CI) 0.60 (0.07 to 5.44)
						Fragmented calcification:	Univariable analysis, OR 95% CI: 6 (0.81 to 44)
						Nodular calcification	Univariable analysis, OR 95% CI: 0.2 (0.02 to 0.56)
						Power Doppler	Univariable analysis, OR 95% CI: 3 (0.25 to 36.32)
						SAD bursitis	Univariable analysis, OR 95% CI: 1.4 (0.07 to 21,12)
Maier[178]	62	Cohort	18 months	CMS≥75% satisfactory clinical outcome CMS <75% inadequate outcome	CR and MRI	CR calcifications >1.5 cm	Univariable analysis (OR, 95% CI) 2.21 (0.77 to 6.63)
						CR Type II and III vs Type I calcification	Univariable analysis (OR, 95% CI) 1.05 (0.37 to 2.95)
						CR Size and morphology of calcifications	Univariable analysis: No significant prediction
						MRI uptake around deposits	Univariable analysis: (OR, 95% CI) 0.09 (0.01 to 0.72)
						MRI synovial uptake	Univariable analysis: (OR, 95% CI) 0.23 (0.06 to 0.80)
						MRI bursal uptake	Univariable analysis: (OR, 95% CI) 0.19 (0.05 to 0.77)
Ogon[180]	420	Cohort	4.4. years	Clinical improvement allowing cessation of non-operative treatment Failure of non-operative therapy	CR and US	CR Bilateral vs unilateral calcification	Univariable analysis: (OR,95%CI) 3.95 (2.30 to 6.77)
						CR Gartner type II vs type I–II	Univariable analysis: OR (95% CI) 0.52 (0.31 to 0.89)
						CR medial extension of the calcific deposit	Univariable analysis: Negative prognostic factor
						CR localisation of calcific deposits in sector 1	Univariable analysis: negative prognostic factor
						CR high volume of calcific deposits	Univariable analysis: negative prognostic factor
						US lack of sound extinction	Univariable analysis: OR (95% CI) 0.11 (0.03 to 0.36)
Oudelaar[189]	431	Retrospective cohort	6 months	Complete relief of symptoms at 6 months (free/not free of symptoms) Need for multiple procedures	CR	Type 1 calcification	Multivariable analysis: OR (95% CI) 3.4 (1.6 to 7.5)

Continued

Table 4 Continued

Study	No of subjects	Study design	Follow-up	Outcome	Imaging modality	Imaging lesion	Results
Notarnicola[177]	158	Cohort	3 months	Disappearance of calcification	CR	Medium size according to Bosworth	Multivariable analysis: OR (95% CI) 0.03 (0.004 to 0.23)
						Type A according to Mole	Multivariable analysis: OR (95% CI) 0.05 (0.03 to 0.91)

ASES, American Shoulder and Elbow surgeon's scale; CMS, Constant and Murley Scale; CR, conventional radiograph; DASH, Disability of the Arm, Shoulder and Hand; NRS, Numerical Rating Scale; PGIC, Patients' Global Impression of Change; SAD, subacromial-subdeltoid.; SST, simple shoulder test; US, ultrasonography; VAS, Visual Analogue Scale.

In the context of CPPD, our SLR confirmed a significant body of evidence of the diagnostic applications of imaging, in particular with regard to US and CR, while CT was specifically applied to cervical involvement. A potential role of imaging for this purpose had already been recognised in the EULAR recommendations presented in 2011, with CR being an additional tool to support diagnosis, and US being recognised as a promising technique.[2] In the following years, many studies have investigated the role of both CR and US for diagnosing CPPD, demonstrating high diagnostic accuracy for the detection of crystal deposition in both hyaline cartilage and fibrocartilage. This applies especially to the wrist and the knee, which were the joints assessed more frequently. In particular, both CR and US displayed high specificity, while sensitivity was more variable with fair to good values. These results were consistent throughout studies adopting different reference standards, including SFA and histology. Although many studies adopted a case–control design, leading to an overestimation of accuracy, there were several studies with low RoB, supporting the validity of the results. The enrolment of consecutive patients with a suspect diagnosis in future studies will provide further high-quality evidence in this field. The result of our SLR supports the use of CR and US as imaging methods to confirm the diagnosis of CPPD, in the context of clinical presentation in order to define if CPPD is the cause of symptoms or a concurrent condition.

While there is abundant evidence of the applications of imaging to diagnose CPPD, studies on sequential imaging to monitor changes in crystal deposition are scarce, most likely as a consequence of the absence of effective treatment. The same considerations apply to studies assessing the prognostic and predictive role of CPPD as shown by imaging, where a few studies in the setting of OA led to conflicting results on the application of CR.

When assessing the literature regarding BCPD, the amount of published evidence was low. The number of diagnostic studies was very limited, with three studies on different techniques with suboptimal design leading to inconsistent results. Future research should follow a cohort design, enrolling consecutive patients. On the other hand, there were many RCTs and cohort studies reporting data on the follow-up for calcific deposition at the level of the rotator cuff, without a specific focus on correlation with clinical findings. No information on the optimal interval to repeat imaging could be retrieved and there was no possibility to compare different techniques. We found a few studies reporting a possible predictive role of imaging for the response to treatment for rotator cuff calcifications, however, once again, the results did not allow to draw solid conclusions. Studies included for follow-up and prediction did not account for possible confounders; this aspect should be addressed in future research.

Interestingly, there were no studies addressing the accuracy of imaging-guided intra-articular or periarticular procedures in CiA. While it has been demonstrated that imaging guidance enhances accuracy in other conditions, a specific conclusion for these diseases cannot be drawn due to lack of data.[188]

A new field of application of imaging is also represented by its use to improve patient's understanding of their condition. Our SLR identified two studies, showing a potential positive impact of presenting DECT images to improve patient understanding of gout, thus opening the way to research in this area.[185 186]

The results of this SLR highlight the increasing interest in the application of imaging in CiA, including both long-established methods such as CR or CT but also modern techniques, in particular US and DECT. While we found a relevant amount of information on the diagnosis of gout and CPPD, evidence of BCPD was more limited and there was a lack of predictive and prognostic studies throughout all CIA conditions, with no studies addressing imaging-guided interventions. Imaging was also tested as a potential tool for patient education. As the interest in CiAs, including the use of imaging, continues to grow, it is expected that in a few years' time it will be necessary to repeat this review, as relevant research has been published already after the completion of the SLRs presented here. Despite this possible limitation, our results will support the development of the first EULAR recommendations on the use of imaging for the clinical management of CiA and will underpin the areas in which additional research will be needed.

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