Seminars in Arthritis and Rheumatism 50 (2020) 719–727

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Outcome domains reported in calcium pyrophosphate deposition studies: A scoping review by the OMERACT CPPD working group

Ken Cai[a,*], Amy Fuller[b,c], Owen Hensey[d], David Grossberg[e,f], Robin Christensen[g], Beverley Shea[h], Jasvinder A. Singh[i,j,k], Abhishek Abhishek[b,c], Sara Tedeschi[l], Nicola Dalbeth[a]

[a] Bone and Joint Research Group, Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Road, Grafton, Auckland, New Zealand
[b] Academic Rheumatology, University of Nottingham, Nottingham, UK
[c] Nottingham NIHR-BRC, Nottingham, UK
[d] The Central Remedial Clinic, Dublin, Ireland
[e] Holy Cross Hospital, Silver Spring, MD, USA
[f] Suburban Hospital, Bethesda, MD, USA
[g] Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark
[h] Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada
[i] Medicine Service, VA Medical Center, Birmingham, AL, USA
[j] Department of Medicine at the School of Medicine, University of Alabama at Birmingham (UAB), Birmingham, AL, USA
[k] Department of Epidemiology, at the UAB School of Public Health, Birmingham, AL, USA
[l] Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA

ARTICLE INFO

Keywords:
CPPD
Domains
Outcomes
Scoping review

ABSTRACT

Introduction: Although calcium pyrophosphate deposition (CPPD) is common, there are no validated outcome domains and/or measurements for CPPD studies. The aim of this work was to identify domains that have been reported in prior clinical studies in CPPD, to inform the development of a core set of domains for CPPD studies.
Methods: We performed a scoping literature review for clinical studies in CPPD, searching in Medline (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases; published from January 1, 1946 to January 7, 2020. All reported outcomes and study design data were extracted and mapped to the core areas and domains as defined by the OMERACT Filter 2.1.The protocol was registered on PROSPERO (CRD: 42019137075; 09-07-2019).
Findings: There were 112 papers identified, comprising of 109 observational studies and three randomized controlled trials. Most studies reported clinical presentations of OA with CPPD or acute CPP crystal arthritis. Outcomes that mapped to 22 domains were identified; the most frequently reported measures mapped to the following domains/sub-domains: imaging (joint damage on imaging tests - 59 studies; joint calcification on imaging tests - 28 studies), joint pain (26 studies), response to treatment (23 studies), side effects of treatment (15 studies), inflammation in the joint fluid or blood (ESR or C-reactive protein - 12 studies; synovial fluid markers - 4 studies; other blood markers - 2 studies), overall function (14 studies), joint swelling (12 studies) and range of joint movement (10 studies). Very few studies mapped to domains related to life impact, societal/resource use or longevity.
Conclusion: There is substantial variability in outcomes reported in CPPD studies. Outcomes that map to imaging manifestations, joint pain and response to treatment domains are most often reported.

Introduction

Calcium pyrophosphate deposition (CPPD) is a common inflammatory arthritis with an estimated prevalence of 4.5% in the UK [1]. This condition is a manifestation of calcium pyrophosphate deposition, an umbrella term that includes acute calcium pyrophosphate (CPP) crystal arthritis (also known as "*pseudogout*"), chronic CPP crystal inflammatory arthritis, osteoarthritis (OA) with CPPD, and asymptomatic chondrocalcinosis [2, 3].

Although CPPD is common, it is understudied, and there have been very few clinical trials in this disease. A Core Domain Set is important when assessing benefits and harms in rheumatology trials [4]; however, none have been developed for CPPD. Although there has been some work by the Outcomes Measures in Rheumatology (OMERACT) ultrasound working group to develop imaging outcome measures for CPPD [5, 6], there are no validated clinical outcome measures for CPPD.

* Corresponding author.
E-mail address: k.cai@auckland.ac.nz (K. Cai).

https://doi.org/10.1016/j.semarthrit.2020.05.015
0049-0172/

The aim of this work was to identify outcomes that have been reported in prior clinical studies in CPPD, to inform development of a core set of outcome domains for CPPD trials.

Methods

This scoping review was performed in accordance with the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7, 8]. The study protocol was pre-specified and registered in advance in PROSPERO (CRD: 42019137075; 09-07-2019).

Search strategy

To identify all the available literature, a search was performed in Medline (using PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The search protocol was developed by the OMERACT CPPD working group, which included patient research partners, clinicians and representatives from OMERACT (methodologist and technical advisor). We structured our PICOC (Population, Intervention, Control, Outcome, Context) within the context of all clinical studies involving adults with CPPD. Interventions included medical therapy (including NSAIDs, colchicine, prednisone (including intra-articular injections), IL-1 inhibitors, inflammasome inhibitors, disease modifying anti-rheumatic drugs, crystal-dissolving therapies), radiosynovectomy, surgical therapy, behavioral, educational, complementary and alternative medicines. Controls included placebo, an active comparator or usual care.

Major search terms and concepts included *chondrocalcinosis, calcium pyrophosphate deposition, pseudogout, crowned dens syndrome, randomised/randomized controlled trials, longitudinal studies, cohort studies, case-control studies and cross sectional studies*. The full terms are described in the supplementary material and covered studies from 1946 to January 7, 2020. Additional studies were identified from the reference lists of studies identified for inclusion and review articles. All reported outcome domains and measurements were of interest.

Eligibility criteria

Types of studies

All published randomized controlled trials, longitudinal cohort (observational) studies, case-control studies, cross-sectional studies and qualitative studies involving people with CPPD were included. There was no restriction on length of follow-up. Studies were restricted to English language, or where applicable, an English translation was published with the original article. Case reports, editorials or commentary letters were excluded.

Types of participants

All manuscripts explicitly stating that they included adults (aged 18 years or older) with a diagnosis of CPPD of any form (acute CPP crystal arthritis [pseudogout], chronic CPP crystal inflammatory arthritis, crowned dens syndrome, osteoarthritis with CPPD and asymptomatic chondrocalcinosis) were included.

Types of outcomes

All reported outcomes were included in this review.

Study selection

All search results were screened to remove duplicates. Prior to screening titles and abstracts, two reviewers (KC and AF) discussed the study protocol and study inclusion exclusion criteria on two occasions and any queries were clarified with ND. Using the above eligibility criteria, the two reviewers (KC, AF) independently screened a random sample of 10% of the total search results by title and abstract to identify studies for full text review. Agreement for study selection was calculated based on this 10% sample (490 studies). We planned for any disagreements in study selection to be resolved by discussion between the two reviewers and input from ND. This was not needed as agreement between the 2 reviewers was 100%. One reviewer (KC) then screened all remaining titles and abstracts (90% of total search results) to identify studies for full text review.

Data extraction

Data extracted from the included studies included study characteristics (first author, year of publication, country, study design, study type (randomized controlled trial, cohort study, qualitative study, etc.), details of intervention(s) if relevant, duration of observation period, participant characteristics (number, mean [SD] age, range of age, % female sex, disease duration if available), CPPD clinical presentation(s), definitions of CPPD and outcomes or measurements used. We also extracted the instruments and study results used for each outcome. Similar to the study selection process, two reviewers (KC, AF) independently extracted the above data from a random 10% sample of the included full-text papers into a Microsoft Excel spreadsheet. Agreement for data extraction was calculated based on this 10% sample (12 studies). Any disagreements in the extracted data were resolved by discussion between the two reviewers. For data extraction on the random sample of the included studies, the agreement between the 2 reviewers was 95.8%. This was due to one reviewer omitting to extract adverse event data. A third reviewer (ND) was available in order to reach final consensus. The third reviewer was consulted once to discuss the need to extract biomarker data collected at baseline and this was deemed unnecessary, as the biomarker data was not a reported outcome in these studies. After consensus was reached, KC completed the data extraction for the remaining 90% of the included studies. Extracted data from the included studies are available in the supplementary.

Synthesis

The search results after identification, screening and full-text review as well as reasons for exclusion were summarized in a PRIMSA flow diagram. Study type and predominant clinical presentation of CPPD were summarized into separate tables.

Outcomes identified from the included studies were mapped to one of four core areas (manifestations/abnormalities, life impact, longevity, societal/resource use) in accordance with the OMERACT 2.1 Filter [9]. We further subdivided domains in the manifestations/abnormalities category into symptoms/signs and biomarkers (imaging or soluble). The frequency of each reported domain was tabulated. Study characteristics, participant characteristics and domain instruments from the included studies are described in the supplementary (Supplementary Tables 1-5).

Clinical presentations

We separated studies according to the predominant clinical presentation of CPPD based on the EULAR recommendations of CPPD terminology: acute calcium pyrophosphate (CPP) crystal arthritis, chronic CPP crystal inflammatory arthritis, and osteoarthritis (OA) with CPPD [3]. Where the predominant CPPD clinical presentation was unable to be determined, the clinical presentation was categorized as “unclear”.

Results

Search Results

As illustrated in Fig. 1, the search strategy identified 5615 papers and an additional 13 papers were identified from reference lists of included papers and review articles. After removal of duplicates, 4920 papers were screened at the title and abstract level. Of these, 4724 papers were excluded, as they did not fulfill the eligibility criteria. The remaining 196 papers underwent full-text review, of which a further 84 were excluded. Reasons for ineligibility at this stage included outcome measure (32 studies), study design (22 studies), diagnostic study (15 studies) and different patient population (10 studies) and duplicate study (5 studies). This left 112 papers that were included in the synthesis (Fig. 1).

Characteristics of studies and participants

The majority of studies were retrospective (109/112, 97.3%) and observational (109/112, 97.3%) (Supplementary Table 1). There were

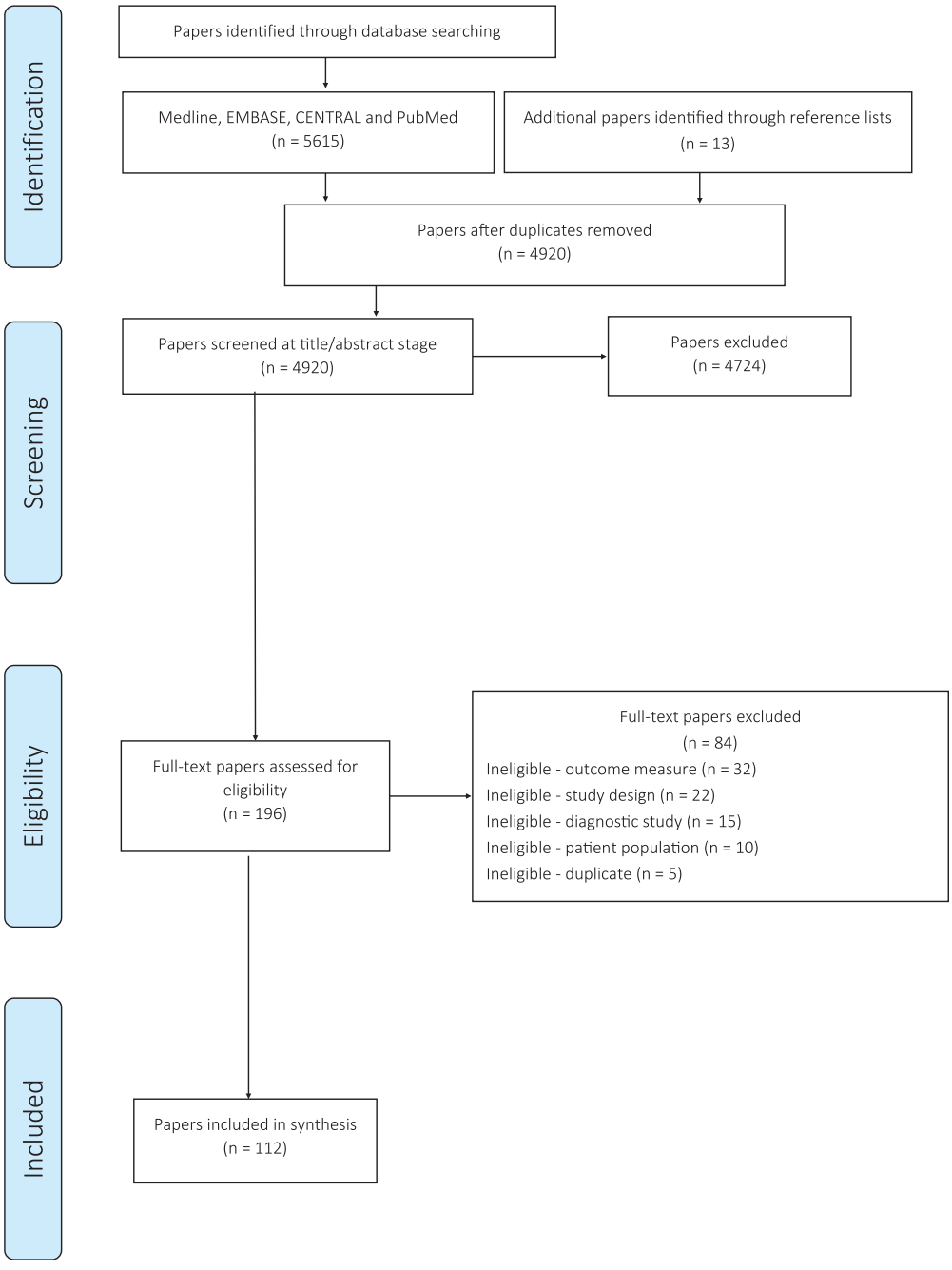

Fig. 1. PRISMA flow diagram

17 studies that investigated the utility of various treatments including methotrexate [10–12], colchicine, anakinra [13–16], ACTH [17, 18], triamcinolone acetonide [19], hydroxychloroquine [20], diclofenac [21], laser irradiation [21], joint lavage [22] and knee arthroplasty [23]. Of these 17 studies, 3 studies were randomized controlled trials [12, 20, 21]. There were no qualitative studies.

The study sample sizes ranged from 2 to 25,157 subjects although the largest study with a clear predominant CPPD clinical presentation contained 435 subjects [24]. Observation periods varied from 2 hours to 41 years. In the majority of the studies, participants were over the age of 65 years and approximately one-third of studies were from the USA (38/112, 33.9%) (Supplementary Tables 3 and 4).

Characteristics of CPPD clinical presentations

Most studies included participants with OA with CPPD or acute CPP crystal arthritis (Supplementary Table 2). The predominant CPPD clinical presentations were OA with CPPD (47/112, 42.0%), acute CPP crystal arthritis (24/112, 21.4%) or chronic CPP crystal inflammatory arthritis (10/112, 8.9%) with a small number of studies of asymptomatic chondrocalcinosis (7/112, 6.3%) and crowned dens syndrome/spinal CPPD (3/112, 2.7%). In 21 studies (18.8%), the predominant CPPD presentation was unclear and contained a combination of the aforementioned CPPD clinical presentations. Of those with acute CPP crystal arthritis clinical presentations, 12 studies met the definition of definite acute CPP crystal arthritis (acute synovitis with synovial fluid aspirate positive for CPP crystals) and 12 studies met the definition of probable acute CPP crystal arthritis (acute synovitis with radiologic evidence of chondrocalcinosis, symptoms not better attributed to another cause such as gout, septic arthritis, or other inflammatory arthritis).

Domains mapped from all CPPD Studies

Table 1 shows how the reported outcomes for all CPPD studies mapped to core areas and domains of OMERACT Filter 2.1.

Manifestations/Abnormalities

Domains within this core area were categorized into symptoms/signs, imaging biomarkers, soluble biomarkers and other manifestations. Outcomes that mapped to symptoms/signs were joint pain (26 studies), joint swelling (12 studies), joint stiffness (7 studies), range of joint movement (10 studies) and flares or attacks of CPPD (6 studies). Outcomes mapped to imaging biomarkers were joint damage on imaging tests (59 studies) and joint calcification on imaging tests (28 studies). Outcomes mapped to soluble biomarkers were inflammation in blood or joint fluid (blood inflammatory markers (ESR or CRP) - 12 studies; synovial fluid markers – 4 studies; other blood markers – 2 studies) and CPP crystals in the joint fluid (1 study). Outcomes mapped to other manifestations included harm from related medical conditions such as osteoarthritis (9 studies).

Life impact

In the core area of life impact, outcomes mapped to the impact of manifestations were response to treatment (23 studies), overall function (14 studies) and satisfaction with treatment (1 study). There were no studies that had outcomes mapped to domains related to unintended impacts of treatment or related medical conditions.

Longevity

Only two studies had outcomes mapped to the core area of survival.

Societal/Resource Use

In the core area of societal/resource, outcomes mapped to health care utilization were use of pain-relieving medications (2 studies), number of treatments needed (3 studies) and need for joint surgery (7 studies). One study had outcomes mapped to duration of hospital stay and direct costs [25]. No studies had outcomes that mapped to the domain of indirect costs.

Table 1
Reported outcomes for all CPPD studies mapped to core areas and domains of OMERACT Filter 2.1 (n=112 papers).

Concepts	Pathophysiology	Impact of health conditions		
Areas	Manifestations/Abnormalities	Life Impact	Longevity	Societal/Resource Use
Intended effects	*Symptoms/Signs*: Joint pain (26) Joint swelling (12) Joint stiffness (7) Joint movement (10) Flares or attacks of CPPD (6) *Biomarkers – Imaging or Soluble:* Joint damage on imaging tests (59) Joint calcification on imaging tests (28) Inflammation in blood or joint fluid ESR or CRP (12) Other blood markers (2) Synovial fluid markers (4) Crystals in the joint fluid (1)	*Impact of manifestations on:*		↑ Health care utilization: Use of pain-relieving medications (2) Number of treatments needed (3) Need for joint surgery (7) Duration of hospital stay (1) Costs: Direct costs (1) Indirect costs (0)
		Overall function (14) Response to treatment (23) Satisfaction with treatment (1)	Survival (2)	↓
Harms	*Other manifestations:* Related medical conditions such as osteoarthritis (9) Side effects of treatment (15)*	*Unintended impacts of treatment or related medical conditions on:*		
		Overall function (0)	Mortality (0)	

(n): number of studies, * reporting of adverse events (including death) is mandatory in trials

Adverse Events

There were 15 studies with outcomes mapped to side effects of treatment.

Domains mapped to CPPD clinical presentation

Fig. 2 shows the percentage of studies that reported outcomes mapped to the most common domains categorized according to CPPD clinical presentation. The reported outcomes for each CPPD clinical presentation mapped to core areas and domains of OMERACT Filter 2.1 are presented in detail in the supplementary material.

Acute CPP crystal arthritis

There were 24 studies of acute CPP crystal arthritis (Table 2). Outcomes mapped to the core area of manifestations/abnormalities were joint pain (6 studies), joint swelling (6 studies), joint movement (1 study), blood inflammatory markers (ESR/CRP, 7 studies), synovial fluid markers (1 study), joint damage on imaging tests (11 studies) and related medical conditions such as osteoarthritis (2 studies). In the core area of life impact, outcomes mapped included overall function (1 study), response to treatment (11 studies) and satisfaction with treatment (1 study). One study had outcomes that mapped to the core area of survival in the context of acute CPP crystal arthritis in joint arthroplasty (26). In the area of societal/resource use, two studies had outcomes that mapped to the number of treatments needed and one study to need for joint surgery. There were no outcomes that mapped to duration of hospital stay or cost. Eight studies had outcomes that mapped to side effects of treatment.

Chronic CPP crystal inflammatory arthritis

There were 10 studies of chronic CPP crystal inflammatory arthritis (Table 3). Outcomes mapped to the core area of manifestations/abnormalities included joint pain (4 studies), joint swelling (3 studies), joint stiffness (2 studies), flares or attacks of CPPD (2 studies), blood inflammatory markers (ESR/CRP, 3 studies), joint damage on imaging tests (4 studies), joint calcification in imaging tests (2 studies) and related medical

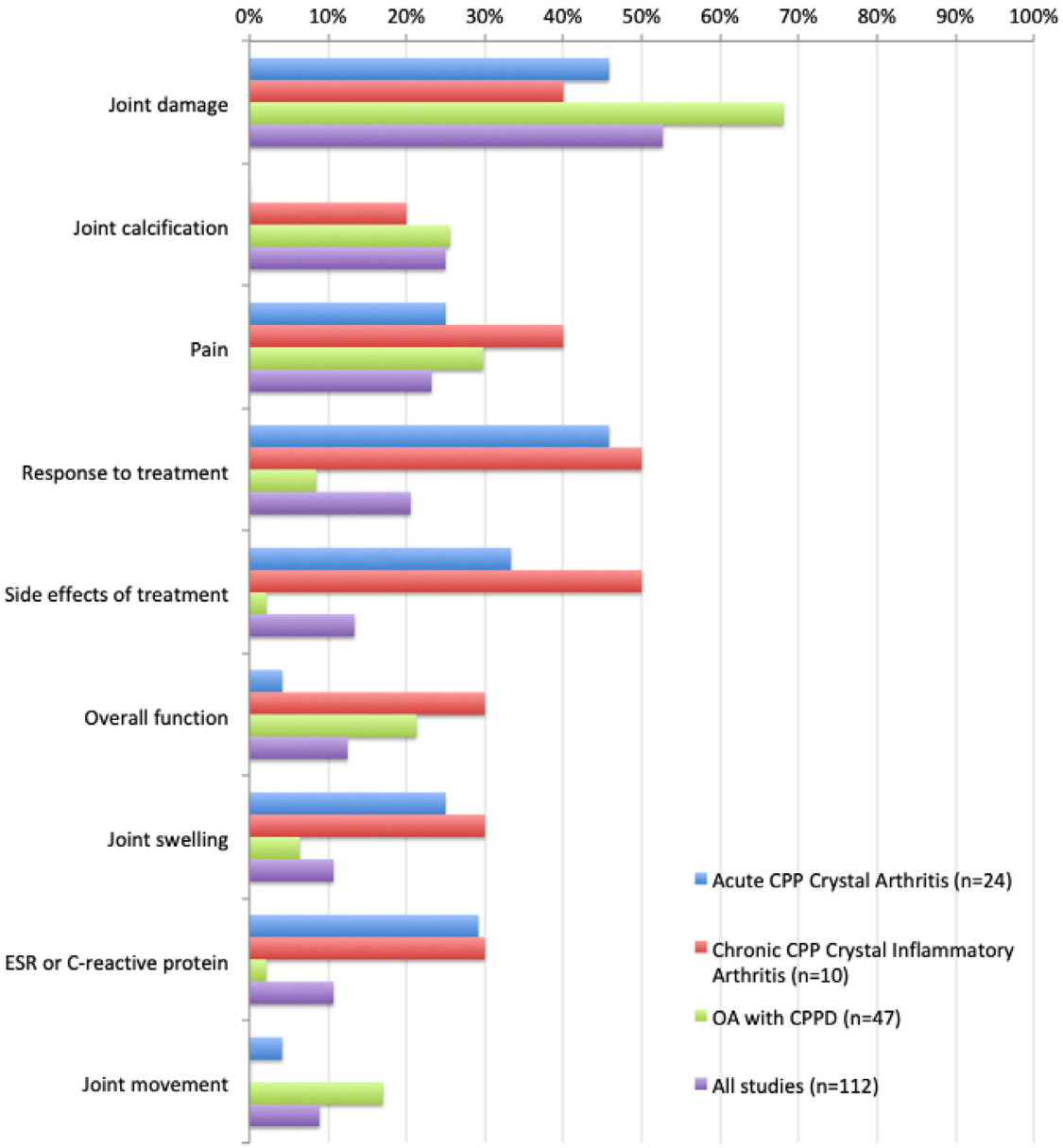

Fig. 2. Percentage of studies that reported outcomes mapped to the most common domains categorized according to CPPD clinical presentation.

Table 2
Reported outcomes for acute CPP crystal arthritis studies mapped to core areas and domains of OMERACT Filter 2.1 (n=24 papers).

Concepts	Pathophysiology	Impact of health conditions		
Areas	Manifestations/Abnormalities	Life Impact	Longevity	Societal/Resource Use
Intended effects	*Symptoms/Signs*: Joint pain (6) Joint swelling (6) Joint stiffness (0) Joint movement (1) Flares or attacks of CPPD (0) *Biomarkers – Imaging or Soluble:* Joint damage on imaging tests (11) Joint calcification on imaging tests (0) Inflammation in blood or joint fluid ESR or CRP (7) Other blood markers (0) Synovial fluid markers (1) Crystals in the joint fluid (0)	*Impact of manifestations on:*		Health care utilization: Use of pain-relieving medications (0) Number of treatments needed (2) Need for joint surgery (1) Duration of hospital stay (0) Costs: Direct costs (0) Indirect costs (0)
		Overall function (1) Response to treatment (11) Satisfaction with treatment (1)	Survival (1)	
Harms	*Other manifestations:* Related medical conditions such as osteoarthritis (2) Side effects of treatment (8)*	*Unintended impacts of treatment or related medical conditions on:*		
		Overall function (0)	Mortality (0)	

(n): number of studies, * reporting of adverse events (including death) is mandatory in trials

conditions such as osteoarthritis (1 study). In the core area of life impact, outcomes mapped included overall function (3 studies), response to treatment (5 studies) and satisfaction with treatment (1 study). One study had outcomes that mapped to the core area of survival (27). In the core area of societal/resource use, one study had outcomes mapped to use of pain-relieving medications and one study had outcomes mapped to need for joint surgery. There were no outcomes mapped to duration of hospital stay or cost. Five studies had outcomes that mapped to the side effects of treatment.

OA with CPPD

There were 47 studies of OA with CPPD (Table 4). Outcomes mapped to the core area of manifestations/abnormalities included joint pain (14 studies), joint swelling (3 studies), joint stiffness (5 studies), joint range of movement (8 studies), flares or attacks of CPPD (2 studies), blood inflammatory markers (ESR/CRP, 1 study), synovial fluid markers (1 study), joint damage on imaging tests (32 studies), joint calcification on imaging tests (12 studies) and related medical conditions such as osteoarthritis (4 studies). In the core area of life impact, outcomes mapped included overall function (10 studies) and response to treatment (4 studies). No studies had outcomes that mapped to survival or mortality. In the core area of societal/resource use, one study had outcomes mapped to use of pain-relieving medications, one study had outcomes mapped to number of treatments needed and five studies had outcomes mapped to need for joint surgery. There were no outcomes mapped to duration of hospital stay or cost. One study had outcomes mapped to the side effects of treatment in the context of knee arthroplasty [23].

Spinal CPPD/Crowned dens syndrome

There were 3 studies of spinal CPPD/Crowned Dens syndrome [13, 28, 29]. Outcomes mapped to the core area of manifestations/abnormalities included joint pain (1 study) and blood inflammatory markers (CRP, 1 study). In the core area of life impact, outcomes mapped included response to treatment (2 studies). No studies had outcomes that mapped to survival or mortality or to the core area of societal/resource use.

Studies with unclear predominant CPPD clinical presentation

There were 21 studies where the predominant CPPD clinical presentation was unclear (Supplementary Table 3). Within these studies, outcomes mapped to the core area of manifestations/abnormalities included joint pain (1 study), joint range of movement (1 study), flares or attacks of CPPD (1 study), other blood biomarkers (1 study), synovial fluid markers (1 study), joint damage on imaging tests (9 studies), joint calcification on imaging tests (9 studies) and related medical conditions such as osteoarthritis (3 studies). None of these studies had outcomes mapped to the core area of life impact. None of these studies had outcomes that mapped to survival or mortality. In the core area of societal/resource use, one study had outcomes mapped to duration of hospital stay and direct costs [25].

Instruments reported in the Included Studies

The primary aim of this study was to identify domains in CPPD. The domain instruments used in the included studies are shown in Supplementary Table 5.

Discussion

This study demonstrates the substantial heterogeneity in clinical outcomes reported in studies on CPPD. Joint damage on imaging tests was by far the most commonly mapped domain and assessed in more than half of the included studies (52.7% of studies). This was followed by joint calcification on imaging tests (25% of studies). Almost one quarter of studies had outcomes that mapped to joint pain (23.2% of studies) followed by response to treatment (20.5% of studies). Across all CPPD clinical presentations, only 12.5% studies had outcomes that mapped to life impact. This finding highlights the limited data we have so far in understanding the impact of this condition on function, quality of life, participation and productivity. Very few studies had outcomes mapped to longevity, survival, or societal/resource use.

The first descriptions of CPPD are from the 1960s [2, 30] and yet we identified only 112 studies with reported outcomes in this condition. Despite being relatively common amongst rheumatological

Table 3
Reported outcomes for chronic CPP crystal inflammatory arthritis studies mapped to core areas and domains of OMERACT Filter 2.1 (n=10 papers).

Concepts Areas	Pathophysiology Manifestations/Abnormalities	Impact of health conditions Life Impact	Longevity	Societal/Resource Use
Intended effects	*Symptoms/Signs*: Joint pain (4) Joint swelling (3) Joint stiffness (2) Joint movement [0] Flares or attacks of CPPD (2) *Biomarkers – Imaging or Soluble:* Joint damage on imaging tests (4) Joint calcification on imaging tests (2) Inflammation in blood or joint fluid ESR or CRP (3) Other blood markers (0) Synovial fluid markers (0) Crystals in the joint fluid (0)	*Impact of manifestations on:*		Health care utilization: Use of pain-relieving medications (1) Number of treatments needed (0) Need for joint surgery (1) Duration of hospital stay (0) Costs: Direct costs (0) Indirect costs (0)
		Overall function (3) Response to treatment (5) Satisfaction with treatment (1)	Survival (1)	
Harms	*Other manifestations:* Related medical conditions such as osteoarthritis (1) Side effects of treatment (5)*	*Unintended impacts of treatment or related medical conditions on:*		
		Overall function (0)	Mortality (0)	

(n): number of studies, * reporting of adverse events (including death) is mandatory in trials

Table 4
Reported outcomes for Osteoarthritis with CPPD studies mapped to core areas and domains of OMERACT Filter 2.1 (n=47 papers).

Concepts Areas	Pathophysiology Manifestations/Abnormalities	Impact of health conditions Life Impact	Longevity	Societal/Resource Use
Intended effects	*Symptoms/Signs*: Joint pain (14) Joint swelling (3) Joint stiffness (5) Joint movement (8) Flares or attacks of CPPD (2) *Biomarkers – Imaging or Soluble:* Joint damage on imaging tests (32) Joint calcification on imaging tests (12) Inflammation in blood or joint fluid ESR or CRP (1) Other blood markers (0) Synovial fluid markers (1) Crystals in the joint fluid (0)	*Impact of manifestations on:*		Health care utilization: Use of pain-relieving medications (1) Number of treatments needed (1) Need for joint surgery (5) Duration of hospital stay (0) Costs: Direct costs (0) Indirect costs (0)
		Overall function (10) Response to treatment (4) Satisfaction with treatment (0)	Survival (0)	
Harms	*Other manifestations:* Related medical conditions such as osteoarthritis (4) Side effects of treatment (1)*	*Unintended impacts of treatment or related medical conditions on:*		
		Overall function (0)	Mortality (0)	

(n): number of studies, * reporting of adverse events (including death) is mandatory in trials

conditions, CPPD is severely understudied. The results of this review will inform development of an OMERACT Core Domain Set for CPPD. This process has already been undertaken in gout, another crystal arthritis, leading to the development of two OMERACT Core Domain Sets for gout; one for short-term studies of gout flares (the 'acute gout' core domain set) and one for long-term studies (the 'chronic gout' core domain set) [31]. Development of different Core Domain Sets for different CPPD clinical presentations or study designs (e.g. short-term studies of acute CPP crystal arthritis, long-term management of CPPD, long-term management of OA with CPPD), may be appropriate, analogous to the OMERACT endorsed Core Domain Set for gout.

Strengths of this study include the broad inclusion criteria to maximize the number of potential CPPD studies for screening. We performed the search in multiple databases and utilized two reviewers to ensure concordance with application of eligibility criteria and extracted data. However, we did not specifically analyze the quality of the papers themselves as the primary intention of this review was

to identify all possible domains reported in the literature. Limitations include that we only included published papers in English and did not specifically search through abstracts of major rheumatology conference proceedings or contact the authors of papers that underwent full-text review but were ineligible as the paper was an abstract.

Conclusion

There is substantial variability in outcomes reported in CPPD studies. Outcomes that map to imaging manifestations, joint pain and response to treatment domains are most often reported. Very few studies mapped to domains related to life impact, longevity or societal/resource use. The development of a Core Domain Set for CPPD is needed for future CPPD studies.

Author contributions

KC - data curation, formal analysis, investigation, validation, visualization, writing - original draft; ND: - supervision, validation, project administration; AF - data curation, investigation. All authors were involved in the design of the study. KC, AF and ND had access to the data. KC and AF analysed the data. KC interpreted the data and completed the original draft of the manuscript. All authors revised and approved the final manuscript.

Funding

This study was funded by OMERACT and Arthritis Australia. The Parker Institute, Bispebjerg and Frederiksberg Hospital (Prof. R. Christensen) is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). Dr. Tedeschi receives support from the National Institutes of Health (K23 AR075070, L30 AR070514). The views expressed in this publication are those of the author(s) and not necessarily those of the funding bodies.

Declaration of Competing Interest

KC reports a research fellowship grant from Arthritis Australia. RC is a member of the Technical Advisory Group of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, Practice Point communications, the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in Amarin pharmaceuticals and Viking therapeutics. JAS is on the speaker's bureau of Simply Speaking. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. JAS serves on the FDA Arthritis Advisory Committee. JAS is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS previously served as a member of the following committees: member, the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee. ND reports grants and personal fees from AstraZeneca, grants from Amgen, personal fees from Dyve, personal fees from Hengrui, personal fees from Selecta, personal fees from Horizon, personal fees from Abbvie, personal fees from Pfizer, personal fees from Janssen, personal fees from Arthrosi, outside the submitted work. The other authors have no disclosures.

Acknowledgements

This study was funded by OMERACT and Arthritis Australia. The Parker Institute, Bispebjerg and Frederiksberg Hospital (Prof. R. Christensen) is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). The views expressed in this publication are those of the author(s) and not necessarily those of the funding bodies.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.05.015.

References

[1] Salaffi F, De Angelis R, Grassi W, Grp MPPI. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clin Exp Rheumatol 2005;23(6):819–28.
[2] McCarty D Jr KN, Faires JS. The significance of calcium pyrophosphate crystals in the synovial fluid of arthritic patients: the "pseudogut syndrome." 1. Clinical aspects. Ann Intern Med 1962;56:711–37.
[3] Zhang W, Doherty M, Bardin T, Barskova V, Guerne PA, Jansen TL, et al. European league against rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70(4):563–70.
[4] Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. Trials 2012;13:132.
[5] Filippou G, Scire CA, Adinolfi A, Damjanov NS, Carrara G, Bruyn GAW, et al. Identification of calcium pyrophosphate deposition disease (CPPD) by ultrasound: reliability of the OMERACT definitions in an extended set of joints-an international multiobserver study by the OMERACT calcium pyrophosphate deposition disease ultrasound subtask force. Ann Rheumatic Dis 2018;77(8):1195–200.
[6] Filippou G, Scire CA, Damjanov N, Adinolfi A, Carrara G, Picerno V, et al. Definition and reliability assessment of elementary ultrasonographic findings in calcium pyrophosphate deposition disease: a study by the OMERACT calcium pyrophosphate deposition disease ultrasound Subtask Force. J Rheumatol 2017;44(11):1744–9.
[7] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019): Cochrane; 2019.
[8] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–73.
[9] Boers M, Beaton DE, Shea BJ, Maxwell LJ, Bartlett SJ, Bingham 3rd CO, et al. OMERACT Filter 2.1: elaboration of the conceptual framework for outcome measurement in health intervention studies. J Rheumatol 2019;46(8):1021–7.
[10] Andres M, Sivera F, Pascual E. Methotrexate is an option for patients with refractory calcium pyrophosphate crystal arthritis. J Clin Rheumatol 2012;18(5):234–6.
[11] Chollet-Janin A, Finckh A, Dudler J, Guerne PA. Methotrexate as an alternative therapy for chronic calcium pyrophosphate deposition disease: an exploratory analysis. Arthritis Rheum 2007;56(2):688–92.
[12] Finckh A, Mc Carthy GM, Madigan A, Van Linthoudt D, Weber M, Neto D, et al. Methotrexate in chronic-recurrent calcium pyrophosphate deposition disease: no significant effect in a randomized crossover trial. Arthritis Res Ther 2014;16(5):458.
[13] Aouba A, Deshayes S, Frenzel L, Decottignies A, Pressiat C, Bienvenu B, et al. Efficacy of anakinra for various types of crystal-induced arthritis in complex hospitalized patients: a case series and review of the literature. Mediators Inflamm 2015;2015 792173.
[14] Molto A, Ea HK, Richette P, Bardin T, Liote F. Efficacy of anakinra for refractory acute calcium pyrophosphate crystal arthritis. Joint Bone Spine 2012;79(6):621–3.
[15] Ottaviani S, Brunier L, Sibilia J, Maurier F, Ardizzone M, Wendling D, et al. Efficacy of anakinra in calcium pyrophosphate crystal-induced arthritis: a report of 16 cases and review of the literature. Joint Bone Spine 2013;80(2):178–82.
[16] Thomas M, Forien M, Palazzo E, Dieude P, Ottaviani S. Efficacy and tolerance of anakinra in acute calcium pyrophosphate crystal arthritis: a retrospective study of 33 cases. Clin Rheumatol 2019;38(2):425–30.
[17] Daoussis D, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. ACTH as first line treatment for acute calcium pyrophosphate crystal arthritis in 14 hospitalized patients. Joint Bone Spine 2014;81(1):98–100.
[18] Ritter J, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: effective treatment for acute crystal induced synovitis in patients with multiple medical problems. J Rheumatol 1994;21(4):696–9.
[19] Roane DW, Harris MD, Carpenter MT, Finger DR, Jarek MJ, Alloway JA, et al. Prospective use of intramuscular triamcinolone acetonide in pseudogout. J Rheumatol 1997;24(6):1168–70.
[20] Rothschild B. Yakubov LE. Prospective 6-month, double-blind trial of hydroxychloroquine treatment of CPDD. Compr Ther 1997;23(5):327–31.
[21] Soriano F, Campana V, Moya M, Gavotto A, Simes J, Soriano M, et al. Photobiomodulation of pain and inflammation in microcrystalline arthropathies: experimental and clinical results. Photomed Laser Surg 2006;24(2):140–50.
[22] Bennett RM, Lehr JR, McCarty DJ. Crystal shedding and acute pseudogout. An hypothesis based on a therapeutic failure. Arthritis Rheum 1976;19(1):93–7.

[23] Willems JH, Rassir R, Sierevelt IN, Nolte PA. There is no difference in postoperative pain, function and complications in patients with chondrocalcinosis in the outcome of total knee arthroplasty for end-stage osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2019.
[24] Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M. Evidence of a systemic predisposition to chondrocalcinosis and association between chondrocalcinosis and osteoarthritis at distant joints: a cross-sectional study. Arthritis Care Res (Hoboken) 2013;65(7):1052–8.
[25] Maravic M, Ea HK. Hospital burden of gout, pseudogout and other crystal arthropathies in France. Joint Bone Spine 2015;82(5):326–9.
[26] George MP, Ernste FC, Tande A, Osmon D, Mabry T, Berbari EF. Clinical presentation, management, and prognosis of pseudogout in joint arthroplasty: a retrospective cohort study. J Bone Jt Infect 2019;4(1):20–6.
[27] Doherty M, Dieppe P, Watt I. Pyrophosphate arthropathy: a prospective study. Br J Rheumatol 1993;32(3):189–96.
[28] Fenoy AJ, Menezes AH, Donovan KA, Kralik SF. Calcium pyrophosphate dihydrate crystal deposition in the craniovertebral junction. J Neurosurg Spine 2008;8(1):22–9.
[29] Muthukumar N, Karuppaswamy U. Tumoral calcium pyrophosphate dihydrate deposition disease of the ligamentum flavum. Neurosurgery 2003;53(1):103–8 discussion 8-9.
[30] Zitnan D, Sit'Aj S. Chondrocalcinosis articularis Section L Clinical and radiological study. Ann Rheum Dis 1963;22:142–52.
[31] Schumacher HR, Taylor W, Edwards L, Grainger R, Schlesinger N, Dalbeth N, et al. Outcome domains for studies of acute and chronic gout. J Rheumatol 2009;36(10):2342–5.