Calcium pyrophosphate deposition disease

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Calcium pyrophosphate deposition (CPPD) disease is a consequence of the immune response to the pathological presence of calcium pyrophosphate (CPP) crystals inside joints, which causes acute or chronic inflammatory arthritis. CPPD is strongly associated with cartilage degradation and osteoarthritis, although the direction of causality is unclear. This clinical presentation is called CPPD with osteoarthritis. Although direct evidence is scarce, CPPD disease might be the most common cause of inflammatory arthritis in older people (aged >60 years). CPPD is caused by elevated extracellular-pyrophosphate concentrations in the cartilage and causes inflammation by activation of the NLRP3 inflammasome. Common risk factors for CPPD disease include ageing and previous joint injury. It is uncommonly associated with metabolic conditions (eg, hyperparathyroidism, haemochromatosis, hypomagnesaemia, and hypophosphatasia) and genetic variants (eg, in the *ANKH* and osteoprotegerin genes). Apart from the detection of CPP crystals in synovial fluid, imaging evidence of CPPD in joints by mainly conventional radiography, and increasingly ultrasonography, has a central role in the diagnosis of CPPD disease. CT is useful in showing calcification in axial joints such as in patients with crowned dens syndrome. To date, no treatment is effective in dissolving CPP crystals, which explains why control of inflammation is currently the main focus of therapeutic strategies. Prednisone might provide the best benefit–risk ratio for the treatment of acute CPP-crystal arthritis, but low-dose colchicine is also effective with a risk of mild diarrhoea. Limited evidence suggests that colchicine, low-dose weekly methotrexate, and hydroxychloroquine might be effective in the prophylaxis of recurrent flares and in the management of persistent CPP-crystal inflammatory arthritis. Additionally, biologics inhibiting IL-1 and IL-6 might have a role in the management of refractory disease.

Introduction

Calcium pyrophosphate deposition (CPPD) disease is the consequence of an immune response to the pathological presence of calcium pyrophosphate (CPP) crystals inside joints, causing CPP-crystal inflammatory arthritis,[1–3] which can be acute (previously known as pseudogout) or chronic. The deposition of CPP crystals is strongly associated with cartilage degradation and osteoarthritis, although the direction of causality is unclear. This clinical presentation is called CPPD with osteoarthritis. The causes of progressive, pathological deposition of CPP crystals in joints remains incompletely understood.[1] The mechanisms of the inflammatory response are better known and, like in gout, involve the activation of the NLRP3 inflammasome.[4] The prevalence of the disease is thought to be high, particularly in older people (>60 years), but epidemiological evidence to support this observation is scarce, particularly outside the hospital setting.[5] Clinical presentation varies greatly and CPPD disease is an umbrella term grouping together various phenotypes, ranging from acute and recurrent episodes of inflammatory arthritis to chronic, persistent inflammatory arthritis and CPPD with osteoarthritis. Asymptomatic CPPD is an ambiguous aspect of the disease that is described as the deposition of CPP crystals found on imaging without any apparent symptoms that can be attributed to it. CPPD disease is often mistaken for other rheumatic diseases such as gout, rheumatoid arthritis, polymyalgia rheumatica, or osteoarthritis.[6–8] Diagnosis involves a compatible, clinical presentation and the identification of CPP crystals in the synovial fluids by polarised-light microscopy or typical imaging evidence of CPP crystal deposition.[7] Treatment options are limited to controlling inflammation as no drug has shown the ability to dissolve CPP crystals to date. Treatment strategies include conventional drugs (mainly corticosteroids and colchicine) in the acute presentation,[9] whereas chronic presentation might require the use of long-term use of colchicine; hydroxychloroquine; or low-dose, weekly methotrexate.[10] Biologics inhibiting IL-1 and IL-6 pathways are being increasingly considered for the treatment of refractory presentations[10] and targeted therapies might be considered for future treatments of CPPD disease. Few comprehensive reviews have been done on CPPD disease and none have included the numerous recent developments related to the disease.[1,2]

The aim of this Review is to provide an overview of the state of art developments in the field of CPPD disease, in terms of the known epidemiology, pathophysiology, clinical presentations, diagnosis, imaging techniques, and management of CPPD disease.

Nomenclature

The nomenclature used for CPPD disease has long been complex, characterised by a multitude of names and abbreviations.[11] Despite the 2011 European Alliance of Associations for Rheumatology (EULAR) recommendations to standardise CPPD terminology, many terms are still used interchangeably to describe this condition, including pseudoforms (pseudogout, pseudorheumatoid arthritis, etc) and the radiological term chondrocalcinosis used as a surrogate for CPPD disease. This interchangeable terminology hampers both patient communication and clinical research. It is necessary to clarify that CPPD denotes the presence of CPP crystals in joints or periarticular tissues regardless of the presence of symptoms,[12] whereas CPPD disease refers only to symptomatic forms. In 2023, the Gout, Hyperuricemia,

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For more on the **Gout, Hyperuricemia, and Crystal-Associated Disease Network** see https://www.g-can.org

	Points
CPPD classification criteria order	
(1) Entry criterion:* ever had at least one episode of joint pain, swelling, or tenderness†	NA
(2) Absolute exclusion criterion:* all symptoms are more likely explained by an alternative condition (rheumatoid arthritis, gout, psoriatic arthritis, osteoarthritis, etc)	NA
(3) Sufficient criteria:* either crowned dens syndrome‡ or synovial fluid analysis showing CPP crystals in a joint with swelling, tenderness, or pain§	NA
Scoring of criteria¶	
Age at onset of joint symptoms (pain, swelling, with or without tenderness)	
≤60 years	0
>60 years	4
Time course and symptoms of inflammatory arthritis	
No persistent|| or typical** inflammatory arthritis	0
Persistent inflammatory arthritis||	9
One typical acute arthritis episode**	12
More than one typical acute arthritis episode**	16
Site of typical episodes** of inflammatory arthritis in peripheral joints	
First MTPJ	–6
No typical episodes	0
Joint other than wrist, knee, or first MTPJ	5
Wrist	8
Knee	9
Related metabolic diseases††	
None	0
Present	6
Synovial fluid crystal analysis‡‡ from a symptomatic joint	
CPP crystals absent on two or more occasions	–7
CPP crystals absent on one occasion	–1
Not performed	0
Osteoarthritis of hand or wrist on imaging (defined as present if the Kellgren and Lawrence score is ≥2)	
None of the following findings or no wrist or hand imaging performed	0
Bilateral radiocarpal joints	2
Two or more: STTJ osteoarthritis without first CMCJ osteoarthritis, second MCPJ osteoarthritis, or third MCPJ osteoarthritis	7
Imaging evidence of CPPD in symptomatic peripheral joint or joints§§	
None on ultrasound, CT, or DECT (and absent on CR or CR not performed)	–4
None on CR (and ultrasound, CT, or DECT not performed)	0
Present on either CR, ultrasound, CT, or DECT	16
(Table continues in next column)	

(Continued from previous column)

	Points
Number of peripheral joints with evidence of CPPD on any imaging modality§§ regardless of symptoms	
None	0
1	16
2–3	23
≥4	25

Reproduced from Abhishek et al,[7,8] by permission of BMJ Publishing Group. CPPD=calcium pyrophosphate deposition. NA=not available. CPP=calcium pyrophosphate. DECT=dual-energy CT. CR=conventional radiography. MTPJ=metatarsophalangeal joint. STTJ=scaphotrapeziotrapezoid joint. CMCJ=carpometacarpal joint. MCPJ=metacarpophalangeal joint. *An individual is classified as having CPPD if the entry criterion is met, exclusion criteria are not met, and at least one sufficient criterion is fulfilled. If none of the sufficient criteria are present, an individual is classified as having CPPD disease if the sum of the criteria is more than 56 points. †In a peripheral joint or axial joint such as C1–C2 in the case of crowned dens syndrome. ‡Crowned dens syndrome is defined by clinical and imaging features, which must both be present. Clinical features: acute or subacute onset of severe pain localised to the upper neck with elevated inflammatory markers, limited rotation, and often fever. Mimicking conditions such as polymyalgia rheumatica and meningitis should be excluded. Imaging features: conventional CT with calcific deposits, typically linear and less dense than cortical bone, in the transverse retro-odontoid ligament (transverse ligament of the atlas), often with an appearance of two parallel lines in axial views. Calcifications at the atlantoaxial joint, alar ligament, or in pannus adjacent, or all to the tip of the dens are also characteristic. DECT features include a dual-energy index between 0·016 and 0·036. §Sufficient criteria are also met if CPP crystals are shown in histopathology of joint tissue, provided the patient is eligible for classification (ie, does not already meet the exclusion criteria). For instance, articular cartilage CPPD in patients with end-stage osteoarthritis cannot be used to classify the patient as having CPPD disease when all symptoms are better explained by osteoarthritis (exclusion criteria). ¶Items can be scored if they were ever present during a patient's lifetime. If a patient fulfills more than one item in a given domain, only the highest weighted item will be scored. Imaging of at least one symptomatic joint by CR, ultrasound, CT, or DECT is required. ||Persistent inflammatory arthritis was defined as ongoing joint swelling with pain or warmth in one joint or more. **Typical episode was defined as an episode with acute onset or acute worsening of joint pain with swelling or warmth that resolves irrespective of treatment. ††Hereditary haemochromatosis, primary hyperparathyroidism, hypomagnesaemia, Gitelman syndrome, hypophosphatasia, or familial history of CPPD disease. ‡‡Synovial fluid analysis should be done by an individual trained in the use of compensated polarised light microscopy for crystal identification. §§Imaging of at least one symptomatic peripheral joint by CR, ultrasound, CT, or DECT is required to be considered for classification if sufficient criteria are not met. Imaging evidence of CPPD refers to calcification of the fibrocartilage or hyaline cartilage. Do not score calcification of the synovial membrane, joint capsule, or tendon. Imaging definitions are published elsewhere.[13] Only consider involvement of peripheral joints.

Table: **American College of Rheumatology and European Alliance of Associations for Rheumatology classification criteria for CPPD disease**

and Crystal-Associated Disease Network launched a project aiming to redefine CPPD nomenclature to harmonise the terminology used in research and to develop a lay language to facilitate effective communication with patients and other stakeholders. While this project is in progress, in this Review, the term CPPD will refer to the deposition of CPP crystals and CPPD disease will be used to describe the clinical, symptomatic presentations as recommended by the 2011 EULAR guidelines.[12]

Classification criteria

The inability to classify patients as having CPPD disease is a substantial barrier to clinical and epidemiological research in CPPD disease. In response to this unmet need, in 2023, the American College of Rheumatology (ACR) and EULAR developed classification criteria for CPPD disease (table).[7,14] These criteria, developed by a multinational panel of experts, were methodologically guided and clinically driven. They represent a major advancement in the field as no validated classification criteria previously existed for CPPD disease. Prior to 2023, the only criterion published was a diagnostic

criterion developed in the 1960s that required CPP crystals on synovial fluid examination and chondrocalcinosis on conventional radiography, or the detection of CPP crystals by advanced microscopy techniques that are not available in most clinical research facilities.[15] It did not consider different clinical presentations of CPPD disease and could not consider advanced imaging techniques such as ultrasonography, CT, and dual-energy CT (DECT) as they were not available at the time of publication. We anticipate that the development of new classification criteria will result in an advancement in clinical research for this disease.

The 2023 ACR–EULAR classification criteria[7,8] for CPPD disease considers risk factors (ie, age, metabolic or inherited risk factors, and hand osteoarthritis), clinical presentations (ie, crowned dens syndrome or pattern of inflammatory arthritis), and findings from synovial fluid examination and imaging (ie, presence or absence of chondrocalcinosis in symptomatic joints and number of joints affected) to classify a patient as having CPPD disease. Patients with symptoms consistent with CPPD disease and CPP crystal deposition on synovial fluid examination or with crowned dens syndrome meet sufficient criteria and are automatically classified as having CPPD disease according to the new criteria. Patients who do not meet the sufficient criteria are scored against items in the classification criteria. A threshold score of more than 56 points had a very high sensitivity and specificity in an independent validation cohort.[7]

Epidemiology

The prevalence of CPPD is poorly understood. Radiographic, articular chondrocalcinosis has been used as a surrogate for CPPD. Its prevalence depends on joint location, imaging modality, and ethnicity.[5,16,17] Previous estimates among European and North American adults from radiographs of the appendicular skeleton suggested a prevalence of between 7% and 13·7% at approximately 60 years of age, which increased with age to 50% among people older than 80 years, with no predilection for sex.[2,5,16,18] The distribution of CPPD is not uniform worldwide; for example, it is more common in populations with European ancestry compared with Chinese ancestry,[19] although data from other ethnicities are scarce. The low sensitivity of conventional radiography[20] suggests that the prevalence of CPPD is actually much higher than reported and future studies, using sensitive techniques[21] such as ultrasonography[22,23] and CT,[24–26] are needed to better understand the epidemiology of CPPD. A 2024 study investigating the prevalence of CPPD in the knees of patients with knee pain by use of ultrasonography found an overall prevalence of 9·8% in hyaline cartilage and 22·4% in fibrocartilage. The prevalence of CPPD rose to 23·3% for hyaline cartilage and 46·7% for fibrocartilage in patients older than 80 years.[27] Knees and wrists are the most frequently involved peripheral joints on imaging[28] and are most often symptomatic in our experience.

Although the incidence of acute CPP-crystal arthritis is not well understood, the recurrence rate of acute CPP-crystal inflammatory arthritis seems to be high.[15,29,30] In a small, hospital-based study in the USA, the incidence of recurrent, acute CPP-crystal inflammatory arthritis was 11·4 per 100 person-years.[30] Another study from South Korea reported a cumulative recurrence rate of 19% over a median follow-up of 46 weeks among 102 patients with acute CPP-crystal inflammatory arthritis.[31] A nationwide study from France that used inpatient records reported a similar number of admissions to hospital for which gout and CPPD disease were recorded as the primary cause for hospitalisation.[29] The incidence and prevalence of chronic phenotypes, crowned dens syndrome, and CPPD disease in the community remains unknown.[1]

Risk factors

Ageing is the most common risk factor for CPPD, whereas osteoarthritis is the most common association.[15,32–34] Other risk factors include local joint injury (eg, meniscectomy in the knee).[33] Sex and BMI do not seem to be risk factors for CPPD.[35]

Several inherited and acquired metabolic diseases have been suggested to cause CPPD disease. The most convincing causes of CPPD disease are, by order of frequency, primary hyperparathyroidism, hereditary haemochromatosis, hypomagnesaemia (eg, due to short bowel syndrome), diseases of renal magnesium wasting (particularly Gitelman disease), familial hypocalciuric hypocalcaemia, and hypophosphatasia.[36–40] There is little consistent or robust evidence of any drug being a clear risk factor for CPPD disease.[41]

Inherited CPPD disease caused by mutations in the *ANKH* (inorganic pyrophosphate transport regulator) gene and the osteoprotegerin gene are causes of rare, familial, usually severe disease and ought to be considered in patients with premature-onset CPPD disease or in patients with particularly florid chondrocalcinosis.[42,43] A single nucleotide polymorphism in the *ANKH* gene (G to A transition in the *ANKH* 5□-untranslated region at 4 bp upstream of the start codon) has also been associated with apparently sporadic CPPD disease in two separate cohorts.[44,45]

Comorbidities

CPPD disease is a polyarticular, systemic condition associated with comorbidities.[46–51] These include osteoporotic fractures and soft tissue and vascular calcification.[47,48,52] Since 2022, CPPD disease has been associated with chronic kidney disease and cardiovascular events, specifically acute myocardial infarction, acute coronary syndrome, and stroke.[48–50] Patients with acute CPP-crystal arthritis were found to have an

elevated risk of cardiovascular events within the next 2 years in a small, single-center study.[51] These results indicate a need for thorough cardiovascular risk and bone health assessment in people with CPPD disease.

Although there is currently no high-quality evidence, clinical experience suggests that in people with CPPD disease, screening for common secondary causes should be done in patients younger than 60 years at onset and should also be considered in patients aged 80 years or younger at onset. The screening tests should include serum calcium, phosphate, parathyroid hormone, ferritin, transferrin saturation (and *HFE* gene testing if iron overload), and magnesium as a minimum. When the patient's age of onset is 80 years or older, the high prevalence of CPPD would suggest that searching for secondary causes of CPPD would be less productive, although this association has never been evaluated in a study. Testing for *ANKH* (and *TNFRSF11B*) genetic variants should be considered in patients with very early disease (eg, onset before the age of 50–60 years) or in the presence of a strong family history of CPPD disease. Variants in the *ANKH* gene commonly cause recurrent flares of acute CPP-crystal arthritis and screening for them should be considered when early onset of recurrent acute CPP-crystal arthritis is found, whereas mutations in the osteoprotegerin gene causes CPPD in the context of severe structural arthritis.[42,43]

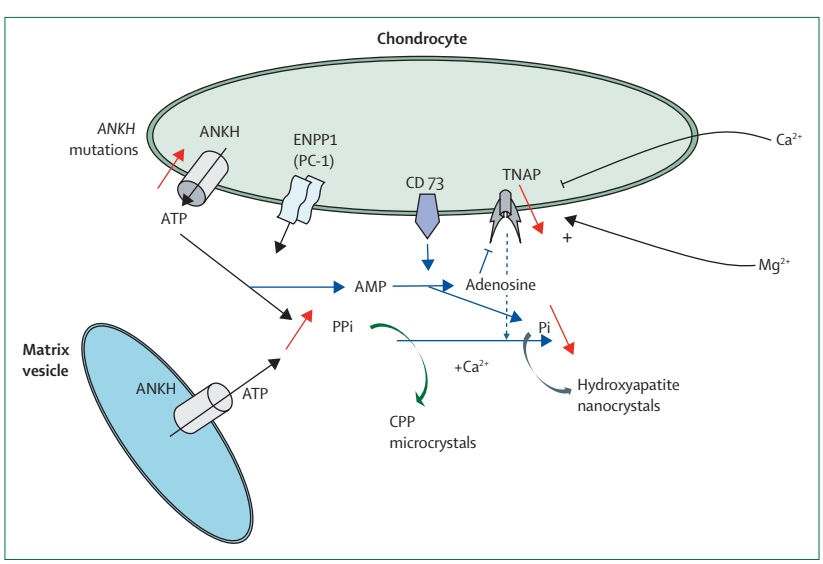


Figure 1: **CPP-crystal formation within the cartilage**
The progressive ankylosing homologue (ANKH) enzyme is a transporter of ATP, which will be cleaved into inorganic pyrophosphate (PPi) and adenosine monophosphate (AMP) by ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1), present at the chondrocyte surface membrane. Matrix vesicles are similarly involved in increasing extracellular PPi. PPi can be hydrolysed by tissue alkaline phosphatase (TNAP) into bone, tissue-producing, inorganic phosphate (Pi), leading to hydroxyapatite formation. Inhibition of TNAP by calcium ions (Ca^{2+}) or by decreased magnesium ion (Mg^{2+}) concentrations will reduce the conversion of PPi into Pi and increase extracellular PPi concentrations, ultimately increasing calcium pyrophosphate (CPP) crystal formation. By contrast, Mg^{2+} augment TNAP activity and stimulates the cleavage of PPi into Pi. CD73 transforms AMP into adenosine, a TNAP inhibitor, and into Pi. PPi with Ca^{2+} will ultimately form CPP crystals in the extracellular milieu within the hyaline cartilage.

The association of CPPD disease with comorbidities is a recent finding and further confirmatory research in other datasets is needed to establish whether specific interventions are required to screen for cardiovascular diseases[51] and osteoporosis[52] in people with CPPD disease.

Pathophysiology of CPPD disease

CPPD disease results from a two-step pathophysiology: the pathological formation and deposition of CPP crystals and an excessive immune response to these CPP-crystal deposits. A potential direct role of CPP crystals on cartilage degradation is currently the matter of active debate.[53]

Mechanism of crystal deposition

CPP-crystal formation results from the complexation of inorganic pyrophosphate after cleavage of ATP by the ectonucleotide pyrophosphatase/phosphodiesterase-1 and calcium ions. This process is enhanced when inorganic pyrophosphate concentrations are increased and is inhibited by magnesium (which promotes inorganic pyrophosphate clearance by stimulating tissue alkaline phosphatase).[54] The cartilage matrix provides a favourable environment for these mechanisms to occur and therefore CPP crystals predominantly form in the fibrocartilage (ie, the meniscus), hyaline cartilage, or in tissue undergoing chondroid metaplasia,[2] and seem to implicate both chondrocytes and matrix vesicles (figure 1).[55]

Rare familial cases of CPPD disease with identified causal genetic mutations[42,43] have provided further understanding of disease pathogenesis. Two genes in particular have been linked to early and severe familial phenotypes of CPPD disease: gain-of-function mutations of *ANKH* that code for an anion transporter of ATP and citrate, which leads to an accumulation of extracellular inorganic pyrophosphate in the tissues;[54,56] and *TNFRSF11B* (encoding osteoprotegerin, a cytokine receptor of the tumour necrosis factor family), with a loss-of-function mutation and no abnormality in inorganic pyrophosphate metabolism.[43]

The ANKH protein is present in the matrix vesicle and chondrocyte membranes. Beyond the genetic gain-of-function mutations that might also be found in sporadic CPPD disease,[45] studies have shown that growth factors and cytokines can modify the expression of the normal ANKH protein. Transforming growth factor β in particular induces *ANKH* expression very strongly.[57] By contrast, the mutation in *TNFRSF11B* coding for osteoprotegerin, reported in three families from the Netherlands, USA, and Israel, appears to be of the loss-of-function type and the direct effects of the mutant form of osteoprotegerin have not been observed in vitro on inorganic pyrophosphate or ANKH protein concentrations in chondrocytes.[43,58] The mechanisms underlying CPPD and arthritis in people with these genetic variants are not known, but increased

remodelling of subchondral bone has been suggested.[43] Although *ANKH*-associated mutations appear to be responsible for the onset of chondrocalcinosis well before the development of any substantial, structural arthritis, people with osteoprotegerin mutations present with the onset of polyarticular, generalised osteoarthritis and chondrocalcinosis.[43]

Mechanism of crystal-induced inflammation

Once released in the joint space cavity, CPP crystals trigger typical, acute inflammation, with key characteristics observed in all acute, crystal-induced inflammations, such as those observed during gout flares. Two types of conformations of CPP crystals, monoclinic (needle-shaped) crystals and triclinic (rectangular rods) crystals, are both observed in human synovial fluids during acute CPP arthritis. Monoclinic CPP crystals appear to be the most proinflammatory crystals in in-vitro and in-vivo models.[59] Uncoated CPP crystals can directly trigger inflammation via crystal–cell membrane contact or through toll-like receptors (TLRs), mostly TLR2 and TLR4.[60] Alternatively, protein coating of CPP crystals can be involved in the modulation of this inflammatory response.[61] CPP crystals induce a strong, innate immune response, mainly through the activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3) inflammasome via mitogen-activated protein kinases and nuclear factor κ-light-chain-enahncer of activated B cells, which causes a high production and secretion of IL-1β. IL-1β induces the activation of various cells (eg, fibroblasts, endothelial cells, and synoviocytes), which in turn produce other inflammatory cytokines, in particular IL-8, that are responsible for the consequent recruitment of neutrophils from the blood into the joint cavity. Other proinflammatory cytokines, such as IL-6 (figure 2), are secreted under IL-1β stimulation.

Metabolic changes are also involved in CPP-crystal-induced inflammation, including glucose consumption.[62] The presence of CPP crystals leads to a metabolic rewiring towards the aerobic glycolysis pathway,

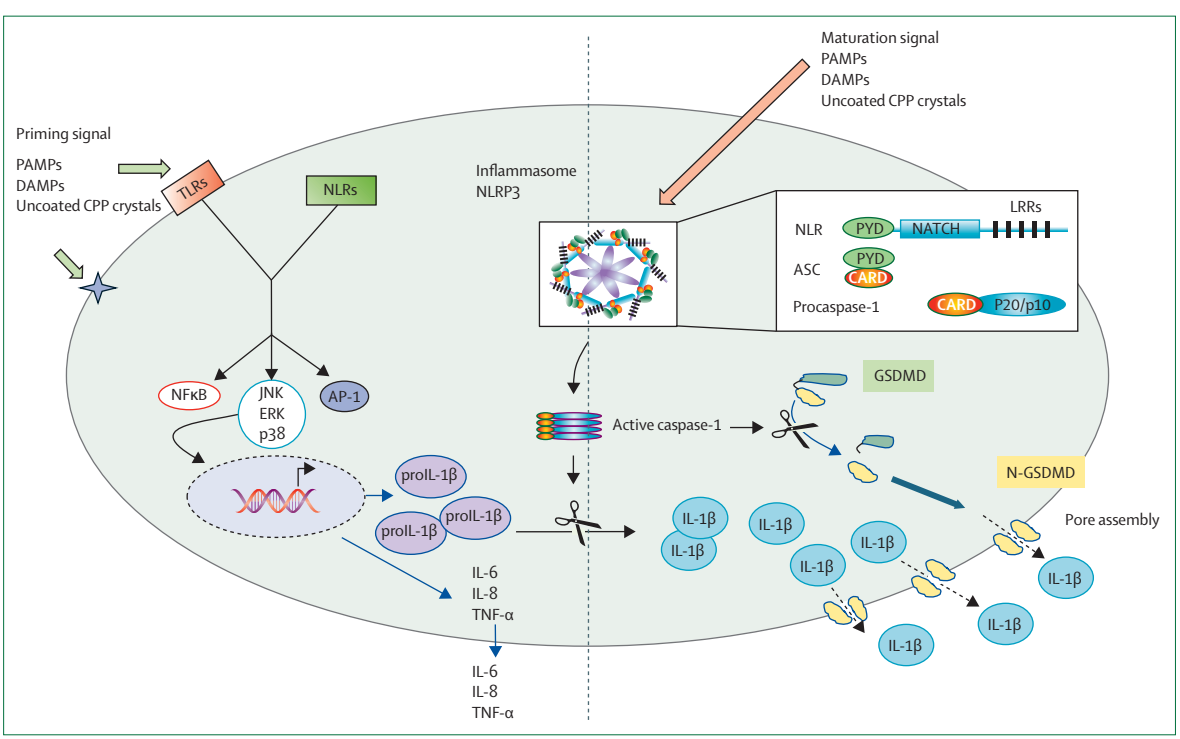


Figure 2: **CPP crystal-induced inflammation**
Schematic representation of the inflammatory potential of CPP crystals depending upon both NF-κB (priming signal) and NLRP3 inflammasome (maturation signal) activation. In in-vitro macrophage models (THP-1 [a human leukemia monocytic cell line] or murine bone marrow-derived macrophages), uncoated CPP crystals act in synergy with phorbol myristate acetate or lipopolysaccharide used for cell differentiation and activation. CPP crystals amplify NF-κB activation through a MAPK-dependent signalling pathway leading to an increased production of proinflammatory cytokines, including IL-6, IL-8, TNF, and proIL-1β (left part of figure: priming signal). CPP crystals also stimulate NLRP3 production and activation which induces apoptosis-associated speck-like protein containing a caspase recruitment domain and procaspase-1 oligomerisation (NLRP3 assembly), leading to caspase-1 activation and subsequently cleavage of proIL-1β into active IL-1β (right part of the figure: maturation signal). Active caspase-1 also cleaves inactive GSDMD into active N-GSDMD, which forms pore assembly to allow IL-1β secretion and drives pyroptosis. Each CPP crystal type (monoclinic and triclinic) has a different ability to differentially activate the MAPK or NF-κB pathways and NLRP3 inflammasome complex. Mechanisms of NF-kB and NLRP3 modulation by CPP crystals remain unknown. CPP=calcium pyrophosphate. DAMPs=damage-associated molecular patterns. GSDMD=gasdermin D. NF-κB=nuclear factor κ-light-chain-enhancer of activated B cells. NLRP3=nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3. NLRs=NOD-like receptors. MAPK=mitogen-activated protein kinase. PAMPs=pathogen-associated molecular patterns. TLRs=toll-like receptors. TNF=tumour necrosis factor.

explained by an increase in glucose transporter 1 plasma membrane expression and glucose uptake in macrophages.

CPPD and osteoarthritis

The association between CPPD and osteoarthritis continues to puzzle researchers, both in terms of pathogenesis and clinical implications. Common risk factors, such as ageing and previous joint trauma, are shared by CPPD and osteoarthritis,[2,18] which makes it difficult to clarify the direction of causality between the two conditions.[5,52] Changes to the extracellular matrix in CPPD contributes to the production of proinflammatory cytokines, potentially fostering damage to the joints, creating a complex situation in which the comorbidity of these conditions could exacerbate each other. In vitro, basic calcium phosphate crystals induce chondrocyte hypertrophy, which is typically observed in osteoarthritis, whereas CPP crystals induce a senescent phenotype.[62] The known upregulation of *TNFRSF11B* in osteoarthritis cartilage and its involvement in familial CPPD disease is another pathway to explore with regards to the link between the two conditions.[42,63] Prospective epidemiological studies do not support the theory that CPPD has a role in the progression of osteoarthritis,[64,65] although other studies have reported more pain in joints with intra-articular mineralisation[66] and joint compartments with CPPD have been associated with more rapid cartilage deterioration on MRI.[67]

From a clinical point of view, symptom attribution in patients affected by both osteoarthritis and CPPD is a major challenge as both conditions can create various degrees of inflammation, joint damage, and pain. Evidence suggests that secondary osteoarthritis due to CPPD might manifest in specific sites, such as the scaphotrapeziotrapezoid joint,[5] but it can also occur in joints typically affected by osteoarthritis like the knee,[28] reaching a prevalence of approximately 50% in patients with endstage osteoarthritis undergoing surgery and in osteoarthritic joints from cadaveric series.[23] In patients with osteoarthritis, the presence of CPPD is associated with inflammation. In a study comparing ultrasound and synovial fluid changes in patients with osteoarthritis plus CPPD versus osteoarthritis alone, no differences were observed in the concentration of inorganic elements in the synovial fluid. However, variations were noted in the white blood cell count, which was higher in patients with CPPD, and in ultrasound examinations, in which patients with CPPD exhibited a greater degree of synovitis and power Doppler signal, compared with patients with osteoarthritis alone.[69] Such findings also translate to patients with higher inflammatory cytokine production in joints with osteoarthritis and CPPD.[70] In vitro, although the pathogenic role of basic calcium phosphate (hydroxyapatite) deposits on the development of osteoarthritis is increasingly supported by evidence, the role of CPP crystals remains controversial.[71]

Clinical presentations

CPPD disease is an umbrella term encompassing many clinical phenotypes, each of which often mimics other rheumatic disorders, which explains why the disease has often been referred to as pseudogout, pseudorheumatoid arthritis or pseudo-osteoarthritis. These historic terms should be discarded in favour of terminology used specifically for CPPD disease. The different clinical phenotypes are generally grouped into three categories: the acute phenotype, the chronic inflammatory phenotype, and CPPD and osteoarthritis.[1,18]

The acute phenotype typically presents as acute crystal arthritis differing only from gout by the location of joints affected. This presentation potentially explains why it has long been referred to as pseudogout. Acute CPP-crystal arthritis can be monoarticular, oligoarticular, or polyarticular and preferentially affects the knees and wrists, but can also occur in the ankles, elbows, shoulders, and metacarpophalangeal joints[7,9] (figure 3A). The main suggested triggers for acute episodes of CPP-crystal arthritis are acute illness, including infections, trauma, postoperative states, being hospitalised,

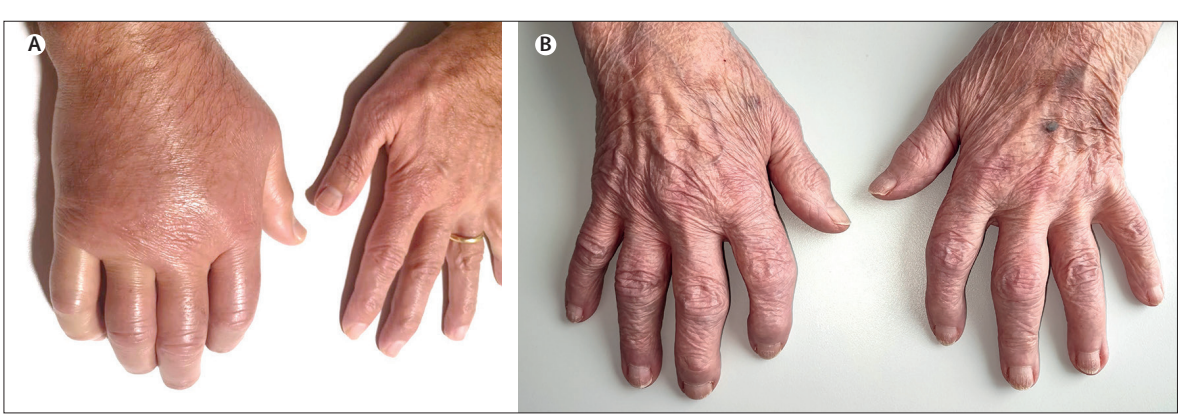


Figure 3: **Clinical presentation of hand and wrist involvement in calcium pyrophosphate deposition disease**
(A) Acute calcium pyrophosphate crystal arthritis of the wrist in a 70-year-old man 5 days after onset. (B) Persistent polyarthritis of the hands in an 84-year-old woman 3 years after onset.

hypophosphataemia, hypomagnesaemia, stage 5 chronic kidney disease, and drugs such as loop and thiazide diuretics, bisphosphonates, chemotherapy, proton pump inhibitors, and H2 blockers.[2,9,30,41,50,72]

The acute phenotype exhibits a clear and demonstrative clinical presentation, yet it occurs in the older population (first episodes commonly reported after the age of 70 years and even 80 years)[9,29,50,73] for whom symptoms can be atypical due to cognitive impairment and initial presentation could be an unexplained, inflammatory state accompanied by delirium, making it difficult for non-rheumatologists to diagnose correctly.[9] The natural history of acute CPP-crystal arthritis is unclear; some reports suggest rapid, spontaneous resolution (common to all crystal-induced inflammations),[74] whereas others suggest that symptoms might last up to 3–4 weeks.[2]

The typical and pathognomonic axial involvement of CPPD disease is crowned dens syndrome, which might represent around 5% of acute presentations of CPPD disease.[7,9] Crowned dens syndrome includes clinical features of acute (or subacute) onset of upper-neck pain, with restricted rotation of the cervical spine, sometimes with fever, and elevated inflammatory markers, as well as crowned dens on a cervical CT.[7] In addition to these features, CPP-crystal deposits can cause inflammation in facet joints and might also be responsible for spinal pain. Clinical presentations can mimic meningitis or infectious spondylodiscitis, septic arthritis of the facet joint, and can lead to ultimately destructive arthropathies of facet joints followed by spontaneous fusion.

Chronic CPP-crystal inflammatory arthritis encompasses two different phenotypes that can overlap: persistent inflammatory polyarthritis and recurrent acute flares, which might coexist.[10] Recurrent acute arthritis shares the same clinical characteristics and joint involvement as the acute phenotype, but manifests repeatedly, and is therefore readily recognisable. However, the persistent inflammatory-polyarthritis type is often mistaken for other diagnoses, particularly seronegative late-onset rheumatoid arthritis[75] or polymyalgia rheumatica. It can present as symmetrical polyarthritis of the hands and wrists, with particular involvement of metacarpophalangeal joints (figure 3B). It can also present as chronic monoarthritis or oligoarthritis involving the knees, ankles, or shoulders (mostly acromioclavicular joints), and cervical involvement is common (chronic crowned dens syndrome).[10,76] In a retrospective analysis of 503 patients from a German tertiary-care centre, the prevalence of chondrocalcinosis in seronegative rheumatoid arthritis was double that in seropositive rheumatoid arthritis (32·3% *vs* 16·6%; p<0·001) and 85% of patients who were eventually considered to have both CPPD disease and rheumatoid arthritis were negative for rheumatoid factor and anticitrullinated protein antibody, suggesting that many patients currently diagnosed with seronegative rheumatoid arthritis might in fact have persistent CPP-crystal arthritis.[6]

The third phenotype is also chronic and is characterised by the presence of structural damage (mainly joint narrowing) in unusual localisations for osteoarthritis (eg, metacarpophalangeal joints or wrists, but also ankles, shoulders, and elbows), with or without substantial chondrocalcinosis, which explains why this phenotype has long been referred to as pseudo-osteoarthritis. When structural damage is substantial, the clinical presentation is characterised by mechanical pain in the affected joints, which might be somewhat more inflammatory than is usually expected in osteoarthritis. Wrist and metacarpophalangeal joint involvement and the absence of substantial distal interphalangeal and proximal interphalangeal osteoarthritis is particularly suggestive of the phenotype.

The impact of CPPD disease on patients' lives has only recently been investigated.[77] Acute CPP-crystal arthritis results in the inability to mobilise the affected joint due to pain and a temporary but profound disability for most patients, either requiring bed rest or hindering activities of daily living. It also affects mental health and wellbeing. Chronic CPPD disease reduces mobility, with patients often requiring walking aids, which makes it difficult to perform activities of daily living and might cause substantial disability, resulting in extensive care needs. Many patients with CPPD disease have sleep disturbance due to pain and limit the amount of exercise, social interactions, leisure pursuits, and work they do.

Imaging

Imaging modalities offer a pragmatic alternative to synovial fluid analysis, especially considering its limitations in terms of accuracy and availability, particularly in chronic inflammatory and non-inflammatory phenotypes and in axial involvement.[7,12,78] Moreover, imaging makes it possible to assess the extent of CPPD, associated inflammatory changes, and structural damage to the joints, thereby enabling the disease to be monitored, the therapeutic efficacy to be evaluated, and potentially shedding light on the largely unknown natural history of CPPD.

Of all the imaging modalities, conventional radiography stands out as the preferred first-line investigation modality due to its low cost, widespread availability, standardised acquisition, and ability to visualise the entire joint. Radiographic findings in CPPD still commonly rely on the concept of chondrocalcinosis, defined as the presence of calcification in joint cartilage, which was considered not specific to CPPD, as other calcium crystals (particularly basic phosphate crystals or hydroxyapatite) might also be present.[12] In 2023, an international group of experts proposed consensus-based radiographic definitions of chondrocalcinosis that were considered specific to CPPD.[13] These definitions were validated for reliability and diagnostic accuracy

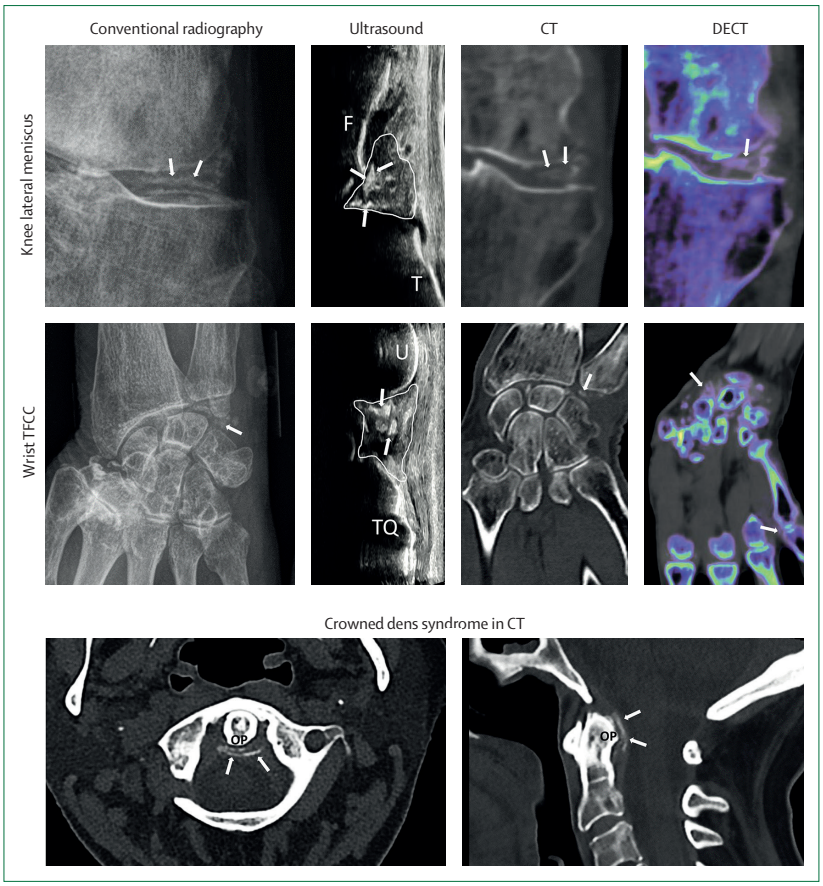


Figure 4: **Appearance of CPPD using different imaging modalities**
CPPD on conventional radiography, ultrasound, CT, and DECT at the level of the lateral meniscus of the knee and at the TFCC of the wrist. The arrows indicate CPPD. On ultrasound, the white line indicates the area of the lateral meniscus of the knee and of the TFCC of the wrist. On the lower row, typical aspect of crowned dens syndrome in CT in the axial (left panel) and sagittal (right panel) view of the atlantoepistropheal joint with typical calcifications of the periodontal ligaments (arrows). CPPD=calcium pyrophosphate crystal deposition. DECT=dual-energy CT. F=femur. OP=odontoid process. T=tibia. TFCC=triangular fibrocartilage complex. TQ=triquetrum bone. U=ulna.

against histology in the knees, proving reliable and specific for CPPD (92%), albeit with low sensitivity (54%),[20] consistent with previous studies.[21,79] Another radiographic characteristic that aids in distinguishing CPPD disease from other conditions is the distribution of joints affected by osteoarthritis, particularly in the second and third metacarpophalangeal joints and the scaphotrapeziotrapezoid joint, which differs from the typical pattern of primary osteoarthritis involvement.[7] However, radiography is a two-dimensional modality, wherein the superimposition of different structures, especially in cases of advanced osteoarthritis, could affect CPP identification.[20] However, a conventional radiograph that does not show evidence of CPPD disease should not be used to exclude CPPD.

Use of ultrasound has greatly progressed the diagnosis of CPPD and due to its availability, safety, and ability to facilitate direct joint examination, is commonly used by rheumatologists during patient visits.[80] The validation of ultrasound in CPPD has been done by the Outcome Measures in Rheumatology (OMERACT) Ultrasound working group—a CPPD subgroup that developed ultrasound definitions based on localisation, shape, echogenicity, and behaviour of crystals deposits during dynamic assessment. These definitions proved to be reliable in the knees and wrists[81,82] and accurate for CPPD identification against histology in the knees, with high sensitivity (71–87%) and specificity (68–88%) among different joint structures.[23] Moreover, it is currently the only imaging technique providing a semiquantitative assessment of CPP-crystal burden with the OMERACT scoring system.[83] Ultrasound also proves valuable in differentiating CPPD disease from other crystal-induced arthropathies due to specific sonographic features that help to distinguish CPP from other crystals.[84–86] However, ultrasound limitations lie in the restricted acoustic windows in particular joints and the need for trained sonographers.

CT detection of CPPD relies on the morphology and density of calcifications, offering the advantage of mapping CPP deposits.[13] The well recognised application of CT in CPPD lies in the assessment of axial involvement, such as in crowned dens syndrome or other symptomatic deposits, in which it is the preferred modality.[78] However, it is not routinely used in the assessment of peripheral CPPD involvement due to availability of other imaging modalities, cost considerations, and radiation exposure. More advanced techniques, such as DECT, can also provide information on the molecular composition of the deposits, allowing for the characterisation of different crystal types based on various dual energy indices.[87–89] Although there has been substantial interest in the use of DECT in CPPD detection, its ability to differentiate between calcium crystal types is limited, due to potential artifacts and low spatial resolution,[90] and it does not improve on the sensitivity provided by CT.[88] The proof of concept that DECT is in part capable of distinguishing between different calcium-containing crystal types will be useful as photon-counting CTs are being developed, with higher spatial resolution and the whole energy spectrum available (figure 4).[91]

Due to its intrinsic characteristics and the technical limitations in identifying and distinguishing between calcium crystals, MRI has not been extensively used in CPPD and the data available in the literature do not support its use in the assessment of CPPD disease.[78] In crowned dens syndrome, cervical MRI provides images of C1–C2 inflammation and might be used to exclude mimicking conditions such as discitis.

Diagnosis

The diagnosis of some typical, clinical presentations of CPPD disease, such as acute CPP-crystal arthritis, is often relatively straightforward whereas other phenotypes, such as chronic CPP-crystal arthritis and crowned dens syndrome, can be challenging to diagnose, often due to poor awareness or insufficient

referrals to hospital specialists.[77] The diagnosis of CPPD disease should be considered in patients with acute monoarthritis, oligoarthritis, or otherwise unexplained, chronic inflammatory arthritis. Suspicion of a CPPD disease diagnosis should be highest in people aged 60 years or older, although CPPD disease can also occur in people younger than 60 years.

Detection of CPP crystals in synovial fluid is the gold standard for the diagnosis of CPPD disease. In clinical practice, detection involves the use of plain light microscopy followed by polarised light microscopy. Unlike monosodium urate crystals, CPP crystals are small, often scanty, difficult to visualise when intracellular, and are only weakly, positively birefringent, resulting in poor interobserver reliability and a high false negativity rate.[92,93]

Definitions of conventional radiographic, ultrasonographic, CT, and DECT evidence of CPPD have been developed.[13,81] When deploying imaging tests, it is important to note that conventional radiography has a lower sensitivity for detecting CPPD compared with either ultrasonography or CT, and advanced CT imaging tests should be used when there is a clinical suspicion of CPPD disease in the absence of CPPD on a conventional radiograph of the affected joint.[79,88] According to EULAR recommendations, conventional radiography and ultrasound are the preferred imaging modalities in the assessment of CPPD, with CT and DECT recommended for patients with axial involvement.[78]

Treatment

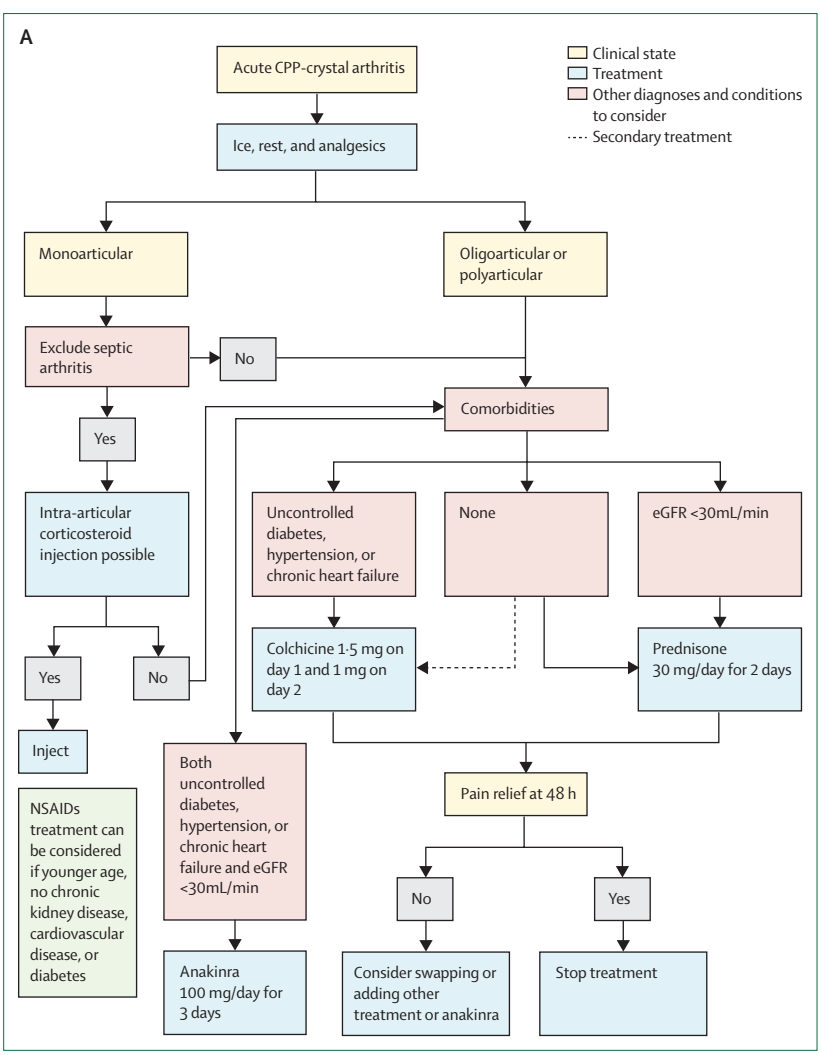
CPP-crystal dissolution

The management of CPPD disease relies exclusively on controlling inflammation and pain, as no treatments are capable of dissolving CPP crystals.[94] Magnesium supplementation has been investigated in a double-blind, randomised controlled trial including 38 patients with crystal-proven CPPD disease and radiographic chondrocalcinosis, but the extent of radiographic chondrocalcinosis at 6 months did not change.[95] Probenecid is an *ANKH* inhibitor that has a potential depletory effect on CPP crystals, but the phase 1 trial (NCT02243631) was not completed.

Acute arthritis

Guidance on the treatment of acute CPP-crystal arthritis long relied on the experience accumulated by physicians on the treatment of gout flares. In 2011, EULAR recommended the use of colchicine, systemic or, when possible, intra-articular corticosteroids, and non-steroidal anti-inflammatory drugs, bearing in mind that older age and accompanying comorbidities of patients often contraindicate the use of non-steroidal anti-inflammatory drugs.[96]

The 2023 COLCHICORT trial[9] was an open-label, randomised controlled trial comparing oral colchicine to prednisone in people with acute CPP-crystal arthritis. This first trial on the acute phenotype of CPPD randomly assigned 112 patients to receive 1·5 mg of colchicine on day 1 and 1 mg on day 2 or 30 mg prednisone on days 1 and 2. Treatment response was equivalent at 24 h after treatment initiation, with a change in the pain (measured by visual analogue scale [VAS] from 0 mm to 100 mm) in both the colchicine group (–36 mm [SD 32]) and the prednisone group (–38 mm [SD 23]). Safety considerations discriminated the two drugs, as 12 (22%) of 55 patients treated with colchicine had diarrhoea, all graded as mild, which can have more concerning consequences in older populations, whereas prednisone was generally well tolerated (three [6%] of 54 patients had hyperglycemia) despite several patients having pre-existing diabetes.[9] The results from the COLCHICORT trial advocate for the first-line use of 30 mg prednisone daily in acute CPP-crystal arthritis. A 2-day regimen of prednisone and colchicine is sufficient to obtain a good treatment response on day 3, and if colchicine is chosen, early administration of the drug (>12 h after arthritis onset) is critical. Intra-articular



(Figure 5 continues on next page)

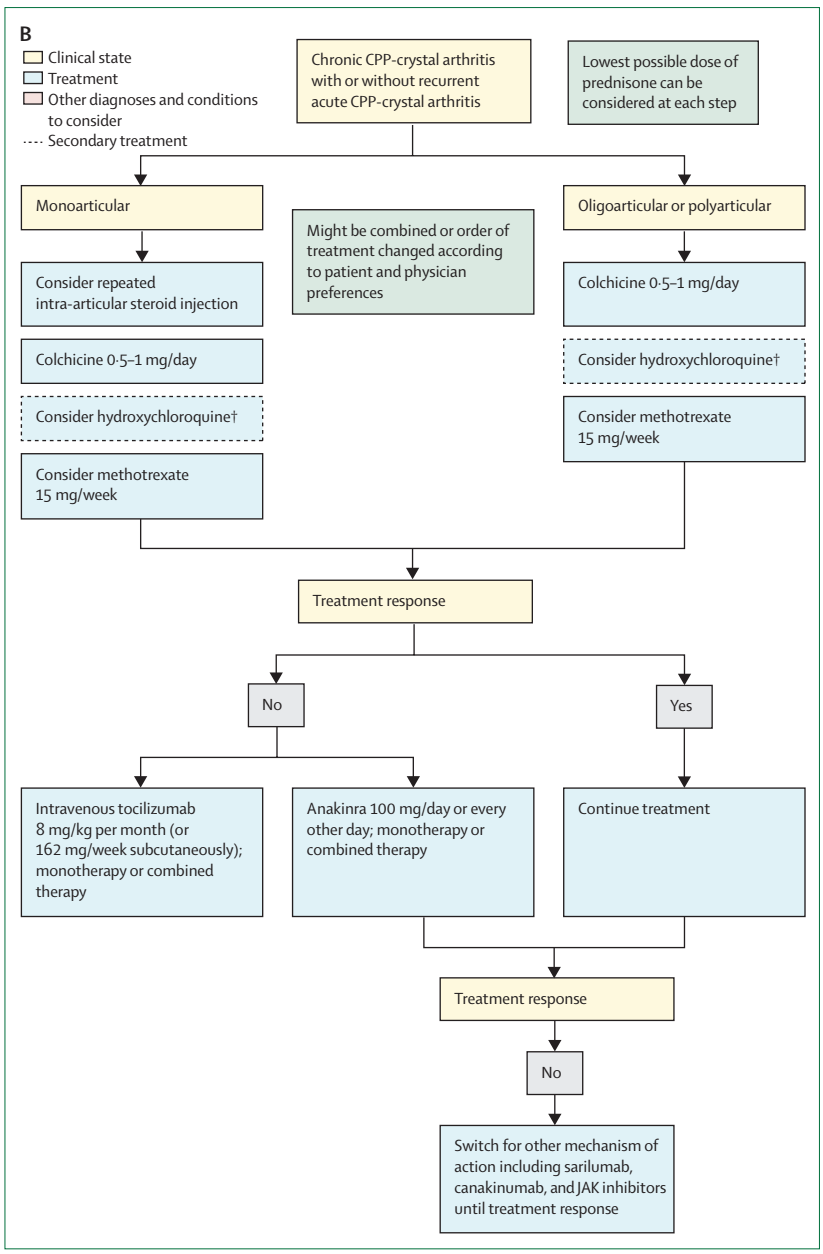


Figure 5: **Proposed treatment strategies* for CPP-crystal inflammatory arthritis**
(A) Acute CPP-crystal arthritis. (B) Chronic CPP-crystal inflammatory arthritis or recurrent acute CPP-crystal arthritis (all being off-label). CPP=calcium pyrophosphate. eGFR=estimated glomerular filtration rate. NSAIDs=non-steroidal anti-inflammatory drugs. JAK=janus kinase. *Based on the authors' expert opinion and not informed by high-quality clinical trials. †Second-choice treatment due to insufficient data and use in clinical practice.

injections of corticosteroids can be considered in patients with monoarticular involvement once the possibility of septic arthritis is ruled out. The in-vitro demonstration of the activation of the NLRP3 inflammasome by CPP crystals and subsequent production of IL-1 (and IL-6) has led to the consideration of using biologics that inhibit IL-1 for the treatment of refractory patients.[4,97] A double-blind pilot trial comparing anakinra (IL-1 receptor antagonist) to prednisone in acute CPP-crystal arthritis only recruited 15 patients and indicated that both drugs provided rapid pain relief.[98] A therapeutic strategy for the treatment of acute CPP-crystal arthritis, based on scarce evidence and our clinical experience is proposed (figure 5A).

Chronic inflammatory arthritis

For the treatment of the chronic inflammatory phenotype (ie, recurrent flares or persistent arthritis), a 2024 report on a European cohort of 128 patients showed that prolonged use of low-dose colchicine (1 mg/day or 0·5 mg/day) might be considered as a first-line therapeutic option, as it seemed to control symptoms in 30–50% of patients.[10] This effect is supported by a crossover trial of ten patients.[99] Methotrexate (15 mg/week for 3 months) was tested in recurrent acute and persistent polyarthritis in a double-blind crossover trial.[100] The study found that this drug showed no efficacy for treating this condition, but it used the disease activity score in 44 joints (DAS44) as the primary endpoint, which might not be an appropriate measure to evaluate a difference in CPPD disease, and therefore the question of the efficacy of methotrexate remains unproven.[10] A pilot, double-blind, crossover trial tested the efficacy of hydroxychloroquine on the recurrent flare phenotype and suggested a reduction in the frequency of flares, but no adequately powered confirmatory trial was ever performed to validate these findings and data from the European cohort showed that the drug was rarely used in clinical practice.[10,101] Magnesium supplementation (30 mmol/day) showed promising results versus placebo on pain relief and inflammatory symptoms (including swelling and joint stiffness) at 3 months and 6 months in a pilot study, but these results have not been confirmed in a large clinical trial.[95]

A case series of treatment with IL-1 inhibition (particularly anakinra) have reported uneven results but suggested a higher rate of good response to IL-1 inhibition in patients with elevated inflammatory markers at baseline.[94,97] IL-6 pathway inhibition is being increasingly considered to treat refractory CPPD disease, even when anakinra has not been effective and initial evidence is limited to case series (the largest with 11 patients).[10,102] In the European cohort of patients followed up for 2 years, persistence of tocilizumab use (n=25) was higher than anakinra (n=27).[10] Use of sarilumab and canakinumab is anecdotal.[10] A strategy for the treatment of chronic inflammatory CPP-crystal arthritis or recurrent acute flares, mainly based on our clinical experience, is proposed (figure 5B).

Outcomes

To date, no specific outcome has been consensually agreed on for the assessment of CPPD disease. A scoping review by the OMERACT CPPD working group identified joint pain (often assessed with a 10 cm visual analogue scale or a dichotomous scale), joint swelling

and stiffness (often assessed as present or absent), patient-reported response to treatment (often assessed with a dichotomous or a 5-point ordinal scale), physician-reported range of movement, acute CPP-crystal arthritis flares (number of, or presence or absence of flares), inflammatory markers, overall function and resource utilisation (assessed with a range of outcome measures), and joint damage and calcification (mostly assessed with conventional radiography) as the outcome domains most often reported in studies of CPPD disease.[103] In chronic CPP-crystal inflammatory arthritis studies, a DAS44 similar to that used in rheumatoid arthritis has been used. However, it might not be effective in detecting changes in disease activity.[100]

Research agenda

From basic science to clinical research, the research agenda in CPPD disease is full of major topics. Although the pathophysiology of inflammatory response to CPP crystals is well understood, the mechanisms by which deposition of CPP crystals occurs need to be clarified, with the aim of finding therapeutic targets for CPP-crystal dissolution. A key area to explore is the genetics and metabolomics of sporadic CPPD disease by assembling well-phenotyped cohorts of patients with CPPD disease and appropriate controls. In epidemiology, much research is needed to examine the incidence and prevalence of CPPD disease and its various phenotypes through the study of existing, large, health claims databases, but also through direct, prospective, epidemiological studies with means to ascertain diagnoses. The field of imaging is progressing, but more research is needed on CPP-crystal deposit quantification in conventional radiography but also CT (conventional, DECT, and photon-counting) and guidance must be provided on the hierarchy and roles of techniques to diagnose and monitor the disease. The standardisation of imaging protocols should be improved, the application of advanced imaging in longitudinal studies broadened, and the use of new imaging techniques in CPPD enhanced. Therapeutic studies are needed to explore the efficacy of existing (IL-1 and IL-6 pathway inhibitors) and new (inflammasome inhibitors and other new targets) drugs to control CPP crystal-induced inflammation, and in the future trials will be needed to explore new drugs capable of CPP-crystal dissolution.

Search strategy and selection criteria

We searched MEDLINE for publications from Jan 1, 1946, to March 15, 2024, written in English, using the search terms ("calcium pyrophosphate" AND ("crystals" OR "deposition")) OR "pseudogout" OR "chondrocalcinosis", to complement the publications already known to the authors. We largely selected the most recent publications but did not exclude older publications. We also searched the reference lists of articles identified through this search strategy and selected those that we judged relevant. Review articles are cited to provide readers with references providing indepth insight on a specific section of this Review.

Contributors

All authors contributed to the writing and editing and approved the final version of the manuscript.

Declaration of interests

TP received consulting fees from Avalo Therapeutics. GF has received a research grant from Lilly. All other authors declare no competing interests.

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