Calcium pyrophosphate crystal deposition

Even though frequently asymptomatic, for some patients calcium pyrophosphate crystal deposition remains a troublesome disorder; these patients can present with recurrent episodes of painful monoarthritis, with persistent polyarticular inflammation or with mechanical joint pain and osteoarthritic changes. The features of the disease may mimic other rheumatic and nonrheumatic conditions, with misdiagnosis being a common problem. Frequently, calcium pyrophosphate crystal deposition is discovered through the incidental finding of chondrocalcinosis on x-rays. Despite being a relevant and poorly understood disorder, it has received little attention from the medical community and the flux of new insights is low when compared with other rheumatic diseases. This paper will review calcium pyrophosphate crystal deposition, stressing the significance of recent contributions in terminology, pathogenesis and management.

Keywords: calcium pyrophosphate crystals, chondrocalcinosis, CPP, pseudogout, pyrophosphate arthropathy, synovial fluid analysis

Arthropathy related to calcium pyrophosphate (CPP) dihydrate crystals has received little critical attention. In the most typical cases – acute knee monoarthritis in a joint showing radiological chondrocalcinosis – its diagnosis and management may be appropriate; in other instances diagnosis and management are far from optimal even though it is one of the most common forms of arthritis in the elderly. This review seeks to emphasize the variability in clinical presentations, the need for establishing a definite diagnosis and the therapies that are currently available.

Terminology
The complexity produced by the variety of clinical phenotypes is increased by the use of different and poorly defined terminology. Zitnan et al. first described chondrocalcinosis articularis and the related arthropathy [1]. The term chondrocalcinosis has since been used for both the cartilage calcification visible in plain x-rays (with or without symptoms) or for the complete spectrum of CPP crystal deposition (CPPD) causing considerable confusion. McCarty coined the term pseudogout after identifying CPP dihydrate crystals in synovial fluids (SFs) obtained from acutely swollen knees of patients with presumed gout [2]. Identification of other clinical phenotypes gave rise to a complex clinical classification with a proliferation of pseudo-syndromes: pseudogout (type A), pseudo-rheumatoid arthritis (RA) (type B), pseudo-osteoarthritis with (type C) or without acute inflammatory episodes (type D), lanthanic or asymptomatic (type E), pseudoneuropathic (type F) and others [3]. Furthermore the term pyrophosphate arthropathy has been used, mainly in the UK, for the structural arthropathy resembling osteoarthritis (OA) related to crystal deposition.

The European League Against Rheumatism (EULAR) has recently led an effort to develop a clear consensus terminology [4]. CPPD has been suggested as the umbrella term for all instances of CPP crystal occurrence. Chondrocalcinosis is a purely descriptive term referring to the presence of cartilage calcification identified by imaging techniques or through histological examination. Pseudo-syndromes have been discouraged and the self-explanatory descriptive terms acute CPP crystal arthropathy, chronic CPP crystal inflammatory arthritis and OA with CPPD have been coined. This terminology will be used throughout this paper.

Epidemiology
CPPD is associated with age. Chondrocalcinosis – taken as a surrogate marker of CPPD – is infrequent under the age of 50 years; when present it should suggest a familial or secondary form. Prevalence increases with age; a recent community study in England showed the prevalence of knee chondrocalcinosis increasing from 3.7% in those aged 55–59 years to 17.5% in those aged 80–84 years [5]. Prevalence may be lower in the Chinese population [6]. The influence of gender on CPPD remains controversial.

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CPPD is commonly idiopathic. Hereditary forms, however, have been recognized in many countries and ethnic groups. Familial disease may present with an early onset and progress to premature OA [7], while in other instances it can be identical to sporadic disease [8]. CPPD can also be associated with a number of metabolic diseases including primary hyperparathyroidism [9], hereditary hemochromatosis [10], hypomagnesemia [11] and hypophosphatemia [12]. CPPD can develop in previously damaged joints in both juvenile arthritis [13] and dysplasias [14]. Chondrocalcinosis is more common in knees that have undergone meniscectomy than in contralateral nonoperated knees [15]. And CPP crystals are occasionally found in noninflammatory SF samples from knees with OA, where its significance is uncertain. The boundaries of CPPD are thus unclear.

**Pathogenesis**

Inorganic pyrophosphate (PPi) is produced endogenously, as it is not absorbed in the gut. Interestingly, both this process and the crystallization occur only in the extracellular cartilage matrix, as intracellular PPi is rapidly hydrolyzed by phosphatases. Several proteins take part in this process [16]:

- ANKH, is a transmembrane transporter which moves PPi out of the chondrocytes;
- Plasma cell glycoprotein-1, a form of nucleotide-pyrophosphate hydrolase that synthesizes PPi;
- Alkaline phosphatase, that splits and inhibits PPi.

Abnormal function of these proteins might lead to different anomalies in CPP formation. An increase in PPi formation by plasma cell glycoprotein-1 through an increased secretion of ATP has been reported as a response of the chondrocytes to mechanical stress [17]; this might explain the development of chondrocalcinosis in the knees, but not in other typical places such as the triangular ligament of the wrist or the pubic symphysis. A decrease in the activity of alkaline phosphatase – as in hypophosphatemia [18] – associates with an increase in PPi and CPP crystal formation. Different types of abnormal activity of ANKH/ANK have been reported. In mice, ANK mutation with a decreased function implies that less PPi is transferred to the extracellular space and the high inorganic phosphate:PPi ratio leads to basic calcium crystals (hydroxapatite) formation and deposition; these mice present with joint ankylosis and prominent osteophytosis [19]. Conversely, ANKH mutation leads to an oversecretion of PPi from the chondrocytes and an increase in CPP crystal formation [20]. ANKH is the only gene identified in hereditary cases of CPPD and different mutations have been found [21–24]. In a single study a relationship between a single nucleotide polymorphism of ANKH a nonheritable CPPD was found [25], but the role of these proteins in sporadic CPPD remains unclear.

As mentioned, CPP crystals form in the extracellular matrix of the fibrocartilage and hyaline cartilage, an area of poor vascularity. The passage of crystals to the SF seems to be required to induce inflammation. CPP crystals, as well as monosodium urate (MSU), are recognized by innate immune system cells as danger signals through a type of pattern-recognition receptor, the Nod-like receptors. The Nod-like receptor-P3 inflammasome was identified as the proteic complex involved in crystal-induced arthritis [26]. The activated cell will secrete recruiting and activating cytokines, where IL-1 seems to play a key role in the process: in murine models of both MSU and CPP crystal-induced inflammation, blockade of IL-1 correlates with a reduction in neutrophil recruitment and inflammatory signs in the peritoneal and joints [27,28]. As evident in clinical practice, this process of inflammation self-limits within a few days, but the mechanisms behind that self limitation remain unidentified. As with gout, CPP crystals in asymptomatic joints result in persistent subclinical inflammation, although the evidence comes from a single study [29].

Both anatomical and sonographic studies have shown that CPP crystals deposit in the midzone of the articular cartilage (Figure 1), but can also be present in tendons and ligaments (Figure 2). CPP crystals are a regular finding in the SF of inflamed joints, and it may be that some cartilage damage is required to allow crystals deeply placed in the cartilage to reach the joint space. In some types of familial CPPD [7], crystal deposition associates with a very early and disabling OA, which might suggest that crystals in the midzone of the cartilage prompt early cartilage damage. On the other hand, in a study on knees with radiological OA, the presence of chondrocalcinosis was not associated with an increased cartilage loss evaluated by MRI [30].

**Clinical presentations**

CPP crystal deposits tend to be asymptomatic. Given that chondrocalcinosis is frequently encountered in healthy elderly individuals, CPPD should not be too easily considered as a certain
cause of joint symptoms; the boundaries of CPPD disease are often difficult to establish.

Acute CPP crystal arthritis generally involves only one or a few appendicular joints and tends towards resolution even in the absence of treatment. Attacks tend to be separated by long asymptomatic, intercritical periods, but some patients have frequent attacks affecting the same or different joints each flare. This clinical phenotype was described while studying patients presumed to have an acute gouty arthritis; the term pseudogout was coined, and appeared particularly apt as signs and symptoms are frequently undistinguishable from those of true gout. Erythema and swelling may be prominent in superficial joints, but inconspicuous in deeper joints. Although attacks can be as severe as those of gout, the average attack takes longer to reach peak intensity and may be somewhat less intense. Acute episodes can involve any joint, including hips and sacroiliac joints; knee and wrist are the most common joints, but instances of first metatarsophalangeal joint inflammation due to CPP crystals are occasionally seen. Occasionally acute attacks can involve numerous joints. Acute attacks most often occur as isolated events in patients without other joint symptoms; on occasion they superimpose on patients with a persistent polyarthritis or with OA of several joints, raising the red flag, which uncovers the CPP crystal deposit. Severe inflammation of a large joint may be accompanied by fever. In some instances, fever may be the sole or predominant manifestation and the arthritis can pass undetected if a careful musculoskeletal examination is not routinely performed.

Attacks can be spontaneous or be triggered by diverse events such as hospitalization, intercurrent medical illnesses or surgery. A small study suggests that 9% of people with CPPD undergoing surgery and 24% with an intercurrent severe medical illness will develop an episode of acute arthritis – a number very similar to gout. Within surgeries, parathyroidectomy seems to be an especially frequent trigger attributed to the subsequent drop in serum calcium. Arthroscopic lavage in joints with pre-existing chondrocalcinosis has been estimated to provoke acute CPP crystal arthritis in 26% of cases, probably by promoting crystal shedding into the joint space. Hylurionate intra-articular injection has been repeatedly reported as a triggering factor. CPP crystal arthritis has also been recognized after knee arthroplasty. It must be highlighted that the presence of CPP crystals does not rule out infection. If a joint with CPP crystal deposits becomes infected, the crystals will remain. It is therefore crucial to culture the SF whenever an infection is suspected, independently of the crystal analysis findings.

Chronic CPP crystal inflammatory arthritis frequently affects one or a few joints (mono- or oligoarthritis) with special preference for the wrists and knees. Inflammation can be chronic and persistent but is more commonly migratory or fluctuating, classically described as subacute with superimposed flares. Acute phase reactants may be increased, as will the cellularity of the SF. An especially prompt search for crystals should be performed in patients with fluctuating symptoms. Identification of CPP crystal arthritis is key, as treatment may differ

Figure 1. Chondrocalcinosis in the knee. (A) Cadaveric specimen showing calcification in the medial meniscus (white arrowhead), medial femoral condyle (black arrowhead) and medial tibial plateau. (B) Faxitron radiograph of the same region demonstrating presence of radiodense material in the same locations. FC: Femoral cartilage; TC: Tibial cartilage. Reproduced with permission from [105].
from other types of inflammatory arthritis. Occasionally, the chronic arthritis presents as a quite symmetrical and persistent polyarthritis with prominent morning stiffness and elevated C-reactive protein and erythrocyte sedimentation rate which can easily be mistaken for RA; more asymmetric or large-joint presentations may suggest a spondyloarthropathy. CPPD is one of the key differential diagnoses in a polyarthritis of an elderly patient. Up to 10% can have rheumatoid factor positivity (albeit at low titers); care must be taken in these patients to differentiate true RA from chronic CPPD crystal arthritis. Radiographs differ from RA and typically exhibit chondrocalcinosis, fine subchondral bone sclerosis, epiphyseal geodes and prominent osteophytosis [40]. Crumbing erosions might be present in late CPPD disease, although they are not a feature of early disease [41]. Elderly patients with CPPD can also present as a polymyalgia rheumatica-like syndrome [42].

OA associated with sporadic CPPD is usually similar to OA without CPP crystals. Chondrocalcinosis does not seem to be associated to a worse outcome of OA in prospective studies [30]. Some hospital series have suggested that OA with CPPD may be characterized by:

- Atypical joint distribution including non-weight bearing joints (e.g., wrist, shoulder or glenohumeral joint);
- Atypical intra-articular distribution (e.g., radiocarpal compartment within the wrist);
- Prominent osteophytosis;
- Large and confluent subchondral cysts;
- Bone fragmentation and joint destruction.

OA of the trapezioscaphoid joints especially in the absence of first carpometacarpal abnormalities, suggests CPPD [43]. It is not unusual for patients with OA associated to CPP crystals to be diagnosed at the time of an episode of joint inflammation.

Acute and recurrent arthritis flares, chronic inflammatory polyarthritis and OA form a continuum within the spectrum of CPPD. Any patient can present with a variable combination of these phenotypes and they can occur at the same or at different time points.

The spine is increasingly recognized as a site of CPP crystal deposition. CPP crystals can deposit at the transverse ligament of the atlas, resulting in a characteristic computed tomography image known as the crowned dens. Local inflammation can produce sudden onset neck pain, fever and signs of meningeal inflammation. Even though severe symptoms are rare, radiographic evidence of involvement of their cervical spine has been demonstrated in around half the patients with CPPD [44]. Crystals can also deposit within the intervertebral discs – rarely resulting in an aseptic discitis [45] – in the interapophyseal joints or in the ligamentum flavum.

CPPD has also been involved – albeit more rarely – in other clinical presentations. Instances of rapid and severe joint destruction include several cases simulating a neuropathic arthropathy [46] and a rapidly destructive OA of the hip [47]. Occasional tumoral deposits have also been described, especially in periarticular tissues of

**Figure 2. Posterior cruciate ligament calcification.** (A) Posterior cruciate ligament calcification (black arrowhead) in a sagittal anatomic slice of a cadaveric specimen and (B) a faxitron imaging of the corresponding slice.

PCL: Posterior cruciate ligament.

Reproduced with permission from [105].
the temporomandibular joint or the hip \[48\]. These patients frequently lack radiologic chondrocalcinosis. Even though CPP crystals tend to deposit within the joint, deposits in tendons and enthesis occur, resulting in acute tendinitis or even in tendon rupture \[49\]. A few reports show that CPP deposits can occasionally deposit in nonmusculoskeletal structures such as the eye \[50\] or the mitral valve \[51\].

As reviewed, the clinical presentations of CPPD can be quite varied and can easily pass unsuspected. It is therefore a sensible approach to look for CPPD in all cases of undiagnosed inflammatory arthropathy, either intermittent or persistent, with or without associated OA \[4\].

**Diagnosis**

As EULAR recommendations highlight, definite diagnosis must be based on the identification of CPP crystals in a SF sample (or very occasionally from biopsied tissue) \[4\]. CPP crystals are parallel-epipeds of varying length and shape ranging from rhomboids to rod-shaped crystals. Only around one in five CPP crystals exhibit some degree of birefringence, and its intensity is less than MSU’s acicular crystals (Figure 3) \[52\]. When using a first order red compensator, CPP crystals show positive birefringence and therefore appear blue when the crystal’s long axis is parallel to the compensator’s long axis and yellow when perpendicular.

SF samples for analysis can be obtained either from inflamed or from asymptomatic joints \[29\]. Occasionally a small number of CPP crystals can be identified in a SF sample, frequently from osteoarthritic joints. The pathogenic meaning of the occasional CPP crystal is uncertain and it is currently unclear if a threshold number of crystals must be identified \[53\]. Although of uncertain clinical significance, CPP and MSU crystals can occur in the same joints. A small number of CPP crystals identified by cytocentrifugation have been seen in gouty SFs originating in joints with OA \[54\].

Several studies have assessed the reliability of CPP crystal identification \[55–58\]. It must be noted that in these studies, no independent verification of CPP crystals by a physicochemical technique has been performed but that the ‘gold standard’ was expert identification through optic microscopy. In the largest study to date, six observers with different experiences evaluated 143 unstained slides with MSU crystals, CPP crystals or no crystals \[59\]. Results were unsatisfactory with a moderate-to-low sensitivity and specificity for CPP crystals identification. Crystals were synthetically fabricated and then added to samples of SF obtained from patients. Data must be interpreted with care as synthetic crystals can be larger and more irregular in shape and large added crystals might remain outside the cell and not be phagocytosed. Of note, the most experienced observer had the lowest false-positive ratio but was the most likely to miss crystals at low concentrations, suggesting a greater reluctance to report occasional particles or equivocal findings. In a more recent study, a prior short training in crystal identification resulted in good or excellent sensitivity, specificity and reproducibility \[60\]. As with all operator-dependent techniques, the training of the observer and the adequateness of the visualization instrument are essential for the validity and usefulness of the technique.

Even though no direct data exists, the degree of adherence to the recommendation of diagnosing CPP crystal deposition by SF analysis appears limited. In both clinical practice and in published case series, chondrocalcinosis is commonly used as a surrogate marker. The validity of this equivalence however, is far from clear. In a study of over 800 menisci harvested from autopsies, 22% exhibited some type of calcific deposit \[61\]. Conventional x-rays were not available from these cadavers, but many were probably small enough as to pass undetected. Of those deposits large enough to identify their nature, only half were due to CPP crystals while the rest were due to brushite or hydroxyapatite. Thus, histological cartilage calcification is not equivalent to CPP crystal deposit.

Even though calcific cartilage deposits can be of varied nature, radiological ‘typical’ chondrocalcinosis might show reasonable specificity for CPPD. There is no clear description of what should be considered typical chondrocalcinosis on plain x-rays (Figure 4). Knee menisci

![Figure 3. Intracellular and extracellular polymorph calcium pyrophosphate crystals at x1000 magnification under ordinary light optic microscope.](image-url)
are amongst the most common calcification sites; chondrocalcinosis tends to occupy the inner two thirds of all four menisci [61]. Calcification within the joint hyaline cartilage appears thinner and more linear, and parallels the subchondral bone. At times calcification of joint capsules, synovium, tendons or bursa can accompany more typical cartilage deposits. In a study of 300 knees with varying degrees of OA, 51 showed radiological chondrocalcinosis [62]. CPP crystals were identified in the SF of 86% (all of the knees had at least one SF analysis). These data suggest that chondrocalcinosis on x-rays, although not pathognomonic, could have a reasonable specificity. More worrisome for the use of chondrocalcinosis as a surrogate marker is its lack of sensitivity. Detection of chondrocalcinosis in crystal-proven cases varies from 29 to 93% depending on the population and the number of joints examined [4]. Situations such as complex joints with superimposition of skeletal parts (e.g., spine, hip or tarsus) can complicate the identification of chondrocalcinosis. Also, with progression OA cartilage becomes thinner and eventually complete eburneation of the subchondral bone will occur. Since CPP crystals mainly form in the depth of the joint cartilage, its disappearance likely alters the radiological appearance and makes diagnosis more difficult. Interpretation of x-rays of joints with structural damage and cartilage loss has received little critical attention for the diagnosis of CPP crystal disease.

Ultrasound is a promising technique for the detection of chondrocalcinosis. Signs of CPP crystal deposit include hyperechoic deposits in the depth of hyaline joint cartilage, hyperechoic aggregates in accessible fibrocartilage structures (e.g., menisci and triangular ligament of the wrist), and linear intratendinous and paratenodinous calcifications [63]. In a recent study, ultrasound seems to be able to detect chondrocalcinosis in some patients without overt radiologic chondrocalcinosis [64].

As CPPD is a disease of the elderly, a search for secondary forms in patients under 55 years of age is recommended, especially if CPPD is florid and polyarticular. Screening for hyperparathyroidism, haemochromatosis and hypomagnesemia should be routinely performed in these patients. The relationship between hypothyroidism and chondrocalcinosis and the need for screening remains controversial [65–70]. Treatment of associated metabolic abnormalities has not been shown to affect or mitigate CPP crystal deposition or symptoms. Screening, however, allows early diagnosis of diseases that if left untreated can cause irreversible organ damage.

### Treatment

#### Crystal dissolution

The deposit of CPP crystals in the joint is responsible for the inflammatory features in CPPD. Therefore, the removal or dissolution of these crystals should be the mainstay of the management, as in gout [71]. But to date no treatment has proven effective in dissolving CPP crystals; various agents such as phosphocitrates [72], pyrophosphatase [73] or probenecid [74,75] have been tested in vitro with promising results but have failed in vivo testing. Magnesium carbonate was tested against placebo in a controlled, double-blind study [76], showing a tendency to improve the solubility of CPP crystals. However, no further studies have focused on this agent. Due to the inability to remove CPP crystals from the SF, the management of CPPD relies on controlling the resulting inflammation [77].

#### Inflammation control

**Conventional strategies**

In spite of being a troublesome rheumatic condition in our clinics and a main cause of acute arthritis in the elderly, the evidence for CPPD management relies mainly on clinical experience rather than on controlled trials, of which only a few have been published in the last decades.

Most of the patients with symptomatic CPPD will only develop isolated episodes of acute CPP...
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arthritides, so the management focuses on treating these episodes. NSAIDs, colchicine and glucocorticosteroids are commonly used, and patients frequently respond well. From clinical practice we know that NSAIDs are effective in CPP arthritis. To our knowledge, there are no formal studies of NSAIDs in this condition; despite this, they are recommended as one of the first-line treatments for acute CPP crystal arthritis [78,79].

Intra-articular injection of long-acting glucocorticoids (i.e., methylprednisolone or triamcinolone) is a fast and very effective approach in patients with mono- or oligo-articular attacks once coexisting infection (possible but unusual [80]) has been ruled out; the dose required has not been defined, but in gout small doses (such as 10 mg of triamcinolone in knees) can be enough [81]. Intramuscular or intraarticular glucocorticoids are also effective alternatives [82,83], especially for patients with polyarticular involvement.

The oral alkaloid agent colchicine in acute CPP arthritis seems effective in small studies [84]. But it is our personal impression that compared with gout, response to colchicine is not as good in acute flares, especially if therapy is delayed, and its use is limited by frequent adverse events when higher doses are used. In acute gouty attacks, low-dose colchicine (1.8 mg total over 1 h) proved as effective as higher doses (initial 1.2 mg, then 0.6 mg every 2 h up to the appearance of gastrointestinal toxicity or the resolution of the inflammation) but with significantly less frequent adverse events [85]. The reported data on colchicine in acute CPP arthritis shows a significant variability in the doses used, but no controlled trials have been published; the low-dose regime might be effective in CPP acute arthritis while preventing most of the adverse effects. Intravenous colchicine was assayed [86–89] but withdrawn due to relevant toxicity.

The majority of the patients with CPPD will present with isolated episodes of arthritis, so there is no need for maintenance therapy. But there is a subgroup that will require continuous therapy to prevent further episodes of inflammation because of very recurrent or persistent inflammatory features [77]. Further epidemiologic studies are needed to ascertain this proportion of patients.

Daily low doses of colchicine (0.5–1 mg daily) successfully reduced further acute attacks of arthritis and controlled persistent inflammation in small uncontrolled studies [90–92]. In a prospective randomized controlled trial [93] the addition of colchicine 0.5 mg twice daily to a scheme of intra-articular glucocorticoids plus oral piroxicam in patients with known knee OA and inflammatory signs found significantly better pain relief after 4 months of treatment. Interestingly, of the 39 patients they enrolled, around 75% had CPP crystals in the SF and 38% had chondrocalcinosis on x-rays. In the past, high-dose NSAIDs or high-dose glucocorticoids were used with the same purpose, but adverse events limit their use. Nevertheless, small doses of NSAIDs (i.e., naproxen 250 mg, indomethacin 25 mg daily) or glucocorticoids (prednisolone 5–7.5 mg daily) might be effective in preventing further attacks, and may be used if there are no contraindications. Strong evidence supporting these schemes is lacking and long-term treatment may be associated with side effects.

In patients with persistent symptoms, synoviorthesis with Yttrium-90 might be an option. This technique reduced pain and improved range of movements in 15 patients with chronic CPP arthropathy of the knee; however, CPP crystal count and x-ray findings did not change [94].

Immunosuppressive agents
Some patients with CPPD, especially those with polyarticular disease, may not respond to conventional treatments. Others do not tolerate these therapies, or these are simply contraindicated due to comorbidities (history of peptic ulcer or gastrointestinal bleeding, high blood pressure, coronary heart disease, chronic kidney disease or diabetes) common in the elderly patients. This subgroup – although not large – is troubling as persistent inflammation or very frequently recurring flares can lead to relevant disability. The chronic use of colchicine, NSAIDs or glucocorticoids should be carefully balanced against the potential side effects, and some patients may require a different approach.

Several years ago, Daniel McCarty pointed out that patients with chronic CPP arthritis, initially misdiagnosed with other types of inflammatory arthritis (i.e., RA), responded well to immunosuppressive agents [95]. Misdiagnosis is not unusual, bearing in mind the ability of CPPD to mimic other conditions and the low adherence to recommendations of SF analysis for crystal identification in all SF obtained from undiagnosed joints [4]. This suggests that some form of immunosuppressive therapy might be effective in patients with CPP crystal arthritis.

Antimalarial agents have been tested in patients with CPP arthritis [96]. Hydroxychloroquine 400 mg/day was evaluated in a double-blind placebo-controlled study in 36 patients with persistent arthritis and radiologic findings suggestive of CPPD. After 6 months, patients in the
hydroxychloroquine group showed a reduction in tender and swollen joint counts, without significant adverse events. In total, 85% of patients with no improvement in the placebo group improved after switching to hydroxychloroquine in an open extension of the study. Despite the need for further evaluation, antimalarials might be a successful choice in refractory CPP arthritis.

Methotrexate (MTX) seemed another promising agent for refractory CPP arthritis. In 2007, Chollet-Janin et al. reported five patients with chronic or very recurrent CPP arthritis, refractory to conventional treatments, who had been treated with MTX [97]. The patients showed an important reduction in attack frequency, joint counts and intensity of pain. Inflammatory markers returned to normal and no significant adverse events were noted. In three patients a tapering of the dose or the discontinuation of MTX led to a worsening of symptoms.

Conversely, Doan et al. reported three patients with CPP mono- or oligoarthritis who despite treatment with MTX showed no improvement [98]. We recently communicated our experience with MTX in refractory forms of CPP arthritis [99]. We retrospectively reviewed eight patients in whom several conventional agents showed no effect and were treated with MTX. Joint involvement was polyarticular in four patients, oligoarticular in three patients and one patient presented with very recurrent episodes of severe arthritis of the knee. Patients’ and physicians’ retrospective evaluation of the response to MTX was globally considered as satisfactory. Noteworthy, MTX was discontinued in two patients due to an increase in liver enzymes levels in one patient, and stomatitis and bone marrow aplasia in another patient, who successfully recovered with folinic acid.

Why MTX might work in CPPD is unclear, but its anti-inflammatory properties, rather than the immunomodulation, might be behind the effect in inflammatory arthritis. These seem mediated by an increased release of adenosine, a strong anti-inflammatory molecule, into the extracellular space [100]. MTX might be a promising agent for patients with uncontrolled forms of CPP arthritis, but data only come from retrospective case series. Moreover, we reported a serious adverse event with MTX. Further studies are highly desirable to assess efficacy and safety of MTX in CPPD. Currently, a randomized placebo-controlled trial with MTX in a crossover design is underway; disappointingly, a preliminary interim analysis has not shown a clear advantage of MTX [101].

In recent years, two case reports have suggested that the IL-1 inhibitor anakinra might be effective in patients with refractory forms of CPP arthritis [102,103]. Molto et al. [104] communicated three patients with persistent acute CPP arthritis and refractoriness to some of the conventional treatment; anakinra was effective in two of them with a quick resolution of the attack and pain relief. Given the key role of IL-1 in crystal-driven inflammation, further work on IL-1 inhibitors is warranted. But there are still many concerns which remain about effectiveness, safety and costs; thus, the position of IL-1 inhibitors in the management of CPPD currently remains unclear. In our review of the literature we found no reports about the use of other immunosuppressive or biologic agents.

Summary of management
No drug has been effective for the dissolution of CPP crystals from SF, so the management of CPPD relies on the control of the ensuing inflammation. As the majority of the patients will present with isolated episodes of acute monoarthritis, they will only require treatment during the acute flare. NSAIDs, glucocorticoids (i.e., systemic or intra-articular) or colchicine seem to be effective in this setting; patient characteristics, risk of adverse events and clinical setting will influence the choice. For patients with persistent or very recurrent CPP arthritis, low-dose daily colchicine is an appropriate option, but low-dose NSAIDs and glucocorticoids may be essayed instead. If these treatments are ineffective or contraindicated or if the patient does not tolerate the treatment, the use of antimalarials or MTX might be considered in selected and symptomatic patients. A few case reports show the successful use of IL-1 inhibitors in refractory cases. A very similar scheme for the management of CPPD has been suggested by other authors [79].

Management of CPPD-related OA
A subgroup of the patients with CPPD will develop OA in their joints, sometimes with some peculiar features. The management of CPPD-related OA should not differ from the primary OA [77], where patient education, reduction of mechanical stress of the joints and pain relief with conventional analgesia is the mainstay of the management. As a reported trigger of acute attacks, intra-articular hyaluronic acid is not recommended. If patients also present superimposed episodes of arthritis they should be specifically managed as previously mentioned. The development of this form of chronic arthropathy is probably related with the recurrent or persistent
inflammation, and the formation of the CPP crystals in the middle of the cartilage, as shown by ultrasound. Controlling the inflammation might prevent further chronic arthropathy, but to our knowledge this has not been formally evaluated.

- **CPPD-associated metabolic diseases.** Although the finding of CPPD may lead to the diagnosis of an underlying metabolic condition, especially in young patients, their prompt treatment seems to have no influence in CPPD, as chondrocalcinosis will not regress after parathyroidectomy, phlebotomies or magnesium replacement. As we mentioned previously, parathyroidectomy may induce acute attacks of CPP arthritis [9].

**Future perspective**

Although in its most characteristic presentations – such as acute knee arthritis – the disease related to the CPP crystal deposition is well defined, other less common clinical presentations have received little critical attention and the boundaries the disease remain unclear. Hopefully we will see further work aimed to:

- Clarify the spectrum of the disease in unequivocally diagnosed patients through CPP crystal identification;
- To gain understanding of the relationship between CPP crystals and OA (as cause and/or consequence);
- The role of radiologic chondrocalcinosis and ultrasound in both the diagnostic work-up and in better understanding the spread of the crystal deposits.

As the goal of dissolving CPP crystals seems currently unattainable, further work regarding the value of symptomatic treatments – especially regarding MTX and IL-1 inhibitors – in common phenotypes will probably be forthcoming. Further insight into whether adequate management of CPPD-related arthritis will affect OA progression would be of special interest.

**Financial & competing interests disclosure**

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### Executive summary

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<td>Further options for patients with frequently recurring or persistent inflammatory symptoms need to be investigated through randomized controlled trials.</td>
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</table>

### References

Papers of special note have been highlighted as:

† of interest

‡ of considerable interest


Sivera, Andres & Pascual

Shows how CPP (and monosodium urate) crystals can induce inflammation through the innate immune system and the activation of IL-1.

An excellent update about pathogenesis and pathophysiology of calcium pyrophosphate (CPP) crystals and CPPD.

An excellent update about pathogenesis and pathophysiology of calcium pyrophosphate (CPP) crystals and CPPD.

A review of the pathogenesis and pathophysiology of CPP crystals, focusing on their role in the innate immune system.

A comprehensive review of the pathogenesis and pathophysiology of CPP crystals, with emphasis on their role in joint inflammation.

A detailed review of the pathogenesis and pathophysiology of CPP crystals, highlighting their role in joint inflammation.

A thorough review of the pathogenesis and pathophysiology of CPP crystals, with a focus on their role in joint inflammation.

A comprehensive overview of the pathogenesis and pathophysiology of CPP crystals, emphasizing their role in joint inflammation.

A detailed review of the pathogenesis and pathophysiology of CPP crystals, with an emphasis on their role in joint inflammation.

An in-depth review of the pathogenesis and pathophysiology of CPP crystals, focusing on their role in joint inflammation.

A comprehensive review of the pathogenesis and pathophysiology of CPP crystals, with a focus on their role in joint inflammation.

A detailed overview of the pathogenesis and pathophysiology of CPP crystals, highlighting their role in joint inflammation.

A thorough review of the pathogenesis and pathophysiology of CPP crystals, with emphasis on their role in joint inflammation.

A comprehensive overview of the pathogenesis and pathophysiology of CPP crystals, focusing on their role in joint inflammation.

A detailed review of the pathogenesis and pathophysiology of CPP crystals, with an emphasis on their role in joint inflammation.
Calcium pyrophosphate crystal deposition


**Crystal identification is the recommended method for diagnosing CPPD. In this study, the sensitivity and specificity of the detected CPPD crystals in synovial fluid with a polarized compensated optic microscope seems encouraging after a short training period.**


Sivera, Andres & Pascual

97 This, along with Chollet-Janin et al. [97], were the first studies where immunosuppressive agents were tested in patients with refractory forms of CPPA, a troublesome group in clinical practice.