

# Diagnosis and Treatment of Calcium Pyrophosphate Deposition (CPPD) Disease: A Review

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**Abstract:** Calcium Pyrophosphate Dihydrate (CPPD) crystal-related arthropathies are a common cause of acute and chronic arthritis caused by the deposition of calcium pyrophosphate crystals in joints and soft tissues, resulting in inflammation and joint damage. They present with a wide spectrum of clinical manifestations and often present challenges to diagnosis and management as they commonly affect older co-morbid patients. The challenges are compounded by a lack of a well-defined description of CPPD. However, an international expert-driven process is underway to develop CPPD classification criteria. Treatment is also problematic as unlike gout, there are no agents available that decrease the crystal burden. Treatment options have often been extrapolated from gout treatment pathways without having extensive trials or a solid evidence base. It is hoped the new CPPD classification guidelines will contribute to large multicentre studies, with well-defined patient cohorts, which will facilitate the production of high-quality evidence to guide the management of this condition. Here, we discuss the barriers and facilitators in diagnosing and treating CPPD-related arthropathy.

**Keywords:** crystal arthropathy, calcium pyrophosphate dihydrate, CPPD

## Introduction

The “pseudogout syndrome” was first described by Kohn in 1962<sup>1</sup> and describes acute attacks of synovitis provoked by CPPD crystals. CPPD-related arthritis is the third most common inflammatory arthritis<sup>2</sup> and its prevalence increases with age.<sup>3</sup> CPPD crystal-related arthropathies can present with varied clinical syndromes which can be a barrier to diagnosis as heterogeneous presentations create diagnostic uncertainty. There are a variety of terms that are used to describe CPPD and its phenotypes which add to the confusion for clinicians, researchers, and patients. According to the European Alliance of Associations for Rheumatology (EULAR), there are at least four different clinical presentations including 1) asymptomatic CPPD; 2) osteoarthritis (OA) with CPPD; 3) acute CPP crystal arthritis; 4) chronic CPP inflammatory crystal arthritis.<sup>4</sup> There are also several others described in the literature including pseudo-polymyalgia rheumatica (pseudo-PMR), pseudo-neuropathic arthropathy, and tumoral CPPD. There is ongoing work on new classification criteria by an international data- and expert-driven process to develop CPPD classification criteria.<sup>5</sup> Treatment of acute CPPD relies on options used in gouty arthropathy and includes a variety of drugs including colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and interleukin-1 inhibitors. Chronic CPPD remains difficult to treat in an evidence-based manner, due to the lack of randomised controlled trials though there is some low-level evidence for hydroxychloroquine, methotrexate, colchicine and steroids. Here, we discuss the barriers to and facilitators of the diagnosis and treatment of CPP crystal-associated arthropathy.

## Clinical Phenotypes of CPPD

### Asymptomatic CPPD

Asymptomatic or lanthanic CPPD is that with no apparent clinical consequence. It may consist of isolated hyaline or fibrocartilage calcifications detected by plain radiographs (chondrocalcinosis), or osteoarthritis (OA) with CPP crystals

without classic acute CPPD episodes.<sup>6</sup> The prevalence of chondrocalcinosis varies from 7 to 10% in the sixth decade and shows equal sex distribution.<sup>7</sup> Radiographic chondrocalcinosis is commonly present in CPPD crystal deposition disease but is neither specific to CPP nor universally present in affected patients.<sup>8</sup> The knee is the most commonly affected joint, followed by wrists, hips, and symphysis pubis.<sup>9</sup> Despite being the most affected joint, knee radiograph alone is not a sufficient screening tool for chondrocalcinosis as it may be absent in the knee but present elsewhere.<sup>10</sup> More recent studies have shown a higher diagnostic accuracy with ultrasound.<sup>11</sup> Chondrocalcinosis is significantly associated with OA independent of age, but chondrocalcinosis and OA both increase independently with age.<sup>12</sup> Despite chondrocalcinosis being a common incidental finding on plain film radiographs, with one study showing a prevalence of 3.8% in patients over 50 years referred for knee radiograph for a variety of reasons, these patients have not been rigorously studied to see if they develop clinical arthritis over time at a greater frequency than the general population. However, patients with radiographic chondrocalcinosis are more likely to report joint complaints upon taking a complete history as compared to a control group of similar age without chondrocalcinosis.<sup>13</sup>

## OA with CPPD

A large proportion of patients with CPPD crystal deposition have an associated degenerative arthritis with an unusual distribution resembling OA. It typically involves the knees, wrists, metacarpophalangeal (MCP) joints, hips, shoulders, and ankles and presents with gradual onset of pain and slow progressive joint destruction. Inflammatory symptoms and signs such as morning stiffness and synovitis are lacking.<sup>14</sup> However, half of these patients will have superimposed attacks of acute CPP arthritis in addition to their chronic symptoms.<sup>15</sup> For patients with gradual onset of pain and slow joint destruction, especially when occurring in the knee, it can be challenging to differentiate it from primary OA. The distinguishing feature is that the medial compartment is more commonly involved in primary OA, resulting in a varus deformity. OA with CPPD, or the older term pseudo-osteoarthritis, is more likely to affect the lateral compartment and result in a valgus deformity.<sup>14</sup> Isolated patellofemoral osteoarthritis is also a common presentation. Increasing difficulty is posed when both CPPD and primary OA co-exist.

## Acute CPPD Arthritis/Pseudogout

Approximately 25% of patients with CPPD exhibit the classical “pseudogout” pattern of disease.<sup>8</sup> The patient typically presents with intermittent, acute, self-limiting, severe episodes of joint pain and swelling with associated redness and tenderness. Patients often have systemic manifestations including fever, leukocytosis and elevated erythrocyte sedimentation rate (ESR) and other acute-phase reactants.<sup>15</sup> Compared to true gout, acute CPP arthritis attacks may take longer to reach peak intensity, and symptoms may last as long as 120 days despite therapy.<sup>16</sup> Acute CPP arthritis is also more common in large joints. Knee, wrist, and MCP joints are the most affected sites, but any joint can be involved.<sup>6</sup> It presents typically as an acute monoarticular or oligoarticular arthritis, although migratory arthritis and polyarticular arthritis can also be observed.<sup>17</sup> Patients are usually asymptomatic in between acute flares. Synovial fluid analysis is the gold standard for diagnosis and assists in excluding acute CPP arthritis and septic arthritis, although the two can occasionally co-exist. Classic synovial fluid findings include rhomboid-shaped crystals that exhibit weakly positive birefringence or no birefringence under polarised light microscopy (PLM).

## Chronic CPP Crystal Arthritis

Chronic CPP crystal arthritis (previously referred to as pseudo-rheumatoid arthritis) affects approximately 25% of patients with CPPD.<sup>18</sup> It presents as a chronic, symmetrical, deforming polyarthritis. It commonly affects the MCP joints and wrists and can sometimes manifest with carpal tunnel syndrome, synovial thickening, localised oedema and flexion contractures of the hands/wrists.<sup>19</sup> Flares in this variant are often present with sequential joint involvement, and generally, it is less symmetric than that seen with true rheumatoid arthritis.<sup>18</sup> In addition, a further 10% of patients will have a positive rheumatoid factor (RF), given the increasing likelihood of elevated RF in the older population.<sup>15</sup> In this setting, aspiration of joint fluid and radiography will be imperative in establishing the correct diagnosis. The detection of erosive changes on radiographs differentiates RA from chronic CPP arthritis (where bony erosions are not commonly seen).<sup>20</sup>

## Pseudo-Polymyalgia Rheumatica (PMR)

Older patients with PMR features such as early morning stiffness and bilateral shoulder pain should also be given consideration for an atypical presentation of CPP arthritis. Involvement of proximal joints may be a feature of CPPD and has been reported in the literature.<sup>21</sup> It can be very challenging to differentiate “pseudo-PMR” from true PMR. The presence of tibiofemoral osteoarthritis, tendinous calcifications, and ankle arthritis may alert the clinician to the presence of CPPD in an elderly patient presenting with PMR manifestations.<sup>21</sup>

## Pseudo- Neuropathic Arthropathy

Some patients with CPPD exhibit a severe destructive monoarthritis that bears similarity to a neuropathic Charcot joint.<sup>22</sup> However, these patients have no neurologic abnormalities on examination yet present with a painful monoarthritis with radiographic destructive features.<sup>8</sup> Little is known about the natural history of this rare presentation. It is important for the clinician to differentiate between this entity and true neuropathic joint as joint replacement is not an option in the true neuropathic joint, whereas it may be in CPP crystal-associated arthropathy.

## Tumoral CPPD

Tumoral CPPD is also known as tophaceous CPPD and is characterised by accumulation of a tumour-like lesion consisting of foci of calcium deposits and chondroid metaplasia.<sup>23</sup> There are reported cases involving the temporomandibular (TMJ) joint, MCP joints, cervical spine, hips<sup>24</sup> and wrists.<sup>23</sup> Interestingly, this can occur without evidence of chondrocalcinosis in other joints. Those presenting with axial and TMJ involvement often have more pain than those with tumoral lesions in the extremities.<sup>25</sup> Patients with distal joint involvement more commonly have an asymptomatic presentation but may present similarly to acute gout.<sup>23</sup> It is important to recognize this rare form of CPPD crystal deposition disease and to identify the CPPD crystals in the calcified deposits to avoid misdiagnosis as a benign or malignant cartilaginous lesion.

## Associated Conditions

Previous studies showed almost 20% of chondrocalcinosis cases are accompanied by underlying (metabolic) disorders such as primary hyperparathyroidism, secondary hyperparathyroidism (common causes of which are chronic renal failure and vitamin D deficiency), hypomagnesaemia, hypophosphatasia, hemochromatosis, previous joint surgery, metabolic risk factors such as obesity and hypertension,<sup>26</sup> and chronic gout.<sup>27</sup> Intra-articular hyaluronate injection may also predispose to crystal formation by causing shedding of CPP crystals from the cartilage or synovial membrane,<sup>28</sup> however, this relationship is not entirely clear. Middle Eastern Pain Syndrome, a newly discovered disease characterised by vitamin D deficiency, secondary hyperparathyroidism and fibromyalgia, may also predispose to chondrocalcinosis due to the occurrence of secondary hyperparathyroidism in these patients.<sup>29</sup> Bartter's and Gitelman's syndromes may also be associated, likely due to the associated chronic hypomagnesaemia. In a recent study by Chotard et al, 79% of patients with Gitelman's Syndrome had evidence of chondrocalcinosis at least at one site, with the highest prevalence at the cervical spine (81.8%) followed by the knee (52.6%) and the wrist (50.9%).<sup>30</sup> In a patient with newly diagnosed acute CPP arthritis, particularly in those of younger age, evaluation should include measurement of serum calcium, ferritin, magnesium, phosphorus, alkaline phosphatase, and thyroid-stimulating hormone.

Hereditary haemochromatosis (HH) is associated with the full spectrum of CPPD presentations. It may be caused by the inhibitory action of iron on pyrophosphatases.<sup>18</sup> Haemochromatosis arthropathy exhibits more prevalent narrowing of the MCP joint spaces including the fourth and fifth digits in addition to the commonly affected second and third MCPs in classic CPPD.<sup>31</sup> Peculiar hook-like osteophytes on the radial aspect of the metacarpal heads, and less prevalent separation of the scaphoid and the lunate can also be observed in HH arthropathy. These findings should prompt evaluation of family history and measurement of serum ferritin although it is important to take into consideration that not all HH arthropathy will have concomitant CPP crystal deposition.

Previous joint trauma is also strongly associated with CPPD-related arthropathy. Similarly, previous joint surgery appears to have an association, with one study showing lateral meniscectomy was associated with 20% of patients exhibiting CC after more than 20 years, compared to only 4% of unoperated knees.<sup>32</sup>

The diverse clinical presentations of CPP-arthropathy often act as a barrier to establishing the correct diagnosis. To date, we are awaiting the outcome from a working group established to develop CPPD classification criteria.<sup>33</sup> Classification criteria will provide a system classifying clinical, imaging and laboratory features of patients with CPP-related arthropathy. This is important as identification by compensated PLM is frequently not possible because of availability and, even when available, has a high false-negative rate with inter-observer variability. The classification criteria will also identify patients to be included in clinical studies, enabling comparison of outcomes across studies and classifying clinical, imaging and laboratory features of this cohort.<sup>34</sup> Establishing diagnostic criteria in heterogeneous rheumatic diseases is an even more challenging task, and often classification criteria are used by proxy as a guide for diagnosis. Varied presentations mean that universal application of classification criteria should be used with caution and clinical acumen must also be regarded.

## Diagnosis

### Crystal Analysis

Synovial fluid aspiration and crystal analysis under compensated PLM remains the gold standard in facilitating diagnosis. While bright field microscopy will allow the identification of CPP crystals' characteristic morphology appearing as rhombuses, thin bars and parallelepipeds, compensated PLM additionally defines birefringence.<sup>35</sup> CPP crystals can often require meticulous scrutiny of the synovial fluid for correct detection as they often show no birefringence, can be found phagocytized, and can frequently be found inside vacuoles.<sup>35</sup> It often requires allocating additional time for careful examination of the sample to yield a diagnosis, as crystals can be sparsely distributed. Correct identification of CPP crystals in the synovial fluid of a suspected case is a major facilitator in reaching the correct diagnosis. However, it is important that CPP analysis is done by a sufficiently experienced clinician or laboratory scientist to avoid reporting a false-negative result. Studies to date have shown inconsistency in correct identification of CPP crystals when assessed by clinicians and laboratory scientists.<sup>36,37</sup> The dedication and training of the observers are significant factors, and lack of experience may be a barrier to diagnosis.

## Imaging Techniques

### Conventional X-Ray

The typical appearance of chondrocalcinosis with punctate and linear densities in hyaline and/or fibrocartilage is diagnostically helpful. The diagnosis of CPPD is strongly supported by the presence of chondrocalcinosis, however conventional radiography only detects 40% of clinically important CPPD.<sup>38</sup> The characteristic sites of such deposits include the articular cartilage of the knee, particularly the medial meniscus and the patellofemoral joint, the acetabular labrum of the hip, the pubic symphysis, the triangular fibrocartilage and lunotriquetral ligaments of the wrist and the spine where it may present at the cervico-occipital junction and the intervertebral discs. Diagnosis is straight-forward when dense, clear deposits are visible but can be challenging when the deposits are faint or atypical. CPPD also has many features of OA that tend to be in a symmetric distribution, but features atypical for primary OA include involvement of non-weight bearing joints or, in the hands, particularly the intercarpal and MCP joints.

While not the ideal screening tool, radiographs still provide important information and can assist in excluding other differential diagnoses. It may be a useful starting point to carry out screening with four radiographs: an anteroposterior (AP) view of both knees (preferably not standing), an AP view of the pelvis for visualization of the symphysis pubis and hips, and a posteroanterior (PA) view of each hand to include the wrists.<sup>15</sup> If these views show no evidence of crystal deposits, it is most unlikely that further study will prove fruitful.<sup>15</sup> Indeed, Ryan and McCarty proposed several diagnostic criteria which include diagnosis based on a combination of the described characteristic radiographic appearance<sup>39</sup> and identification of CPPD crystals in the synovial fluid.<sup>40</sup>

## Ultrasound

The era of ultrasound (US) has revolutionised screening peripheral joints.<sup>4,11</sup> In patients with acute mono-oligoarthritis, a targeted ultrasound scanning protocol shows great accuracy for the diagnosis of both gout and CPPD.<sup>11</sup> Radiographs have low sensitivity for the identification of CPP deposition, while synovial fluid analysis is not always performed, or CPP crystals if present may be overlooked contributing to underdiagnosis.<sup>41</sup> US allows highly sensitive and rapid detection of microcrystal aggregates in multiple anatomic regions. It is also non-invasive and can be used to guide joint aspiration at sites with only minimal fluid collections. The knee is the anatomic region with the highest probability of being positive for CPPD crystal aggregates.<sup>42</sup> The outcome measures in rheumatology working group (OMERACT), reported the overall diagnostic accuracy of US in identifying CPPD at the medial meniscus of the knee was 75% with a sensitivity of 91% and specificity of 59%.<sup>43</sup> OMERACT have also outlined ultrasound definitions for the diagnosis of CPPD at other sites to include the triangular fibrocartilage of the wrist, the acromioclavicular joint and the labrum of the hip, but these have lower intra-observer concordance amongst expert-ultrasonographers compared to the knee joint.<sup>44</sup> A recent study showed that a targeted US scanning protocol of the knees and wrists bilaterally plus the target joint showed a diagnostic accuracy of >90% for crystal arthritis in patients with acute mono/oligoarthritis.<sup>11</sup>

There have also been several studies comparing US and X-ray. Gutierrez et al compared US and conventional x-ray to identify CPPD when compared to a gold standard defined by the presence of synovial fluid CPP crystals detected by PLM in the affected joint. Meniscal chondrocalcinosis was detected by ultrasound in at least one knee in 90% of the patients with CPPD, compared to 83.7% with conventional radiography.<sup>45</sup> Another study comparing US and X-ray at the wrist joint showed US identification of CC in 93.7% of cases, while radiography identified CC in 53.1% of cases.<sup>46</sup> The sensitivity and specificity of US for the diagnosis of CPPD were 94% and 85%, respectively, and that for radiography were 53.1% and 100%, respectively, however patient numbers were small with 32 CPPD patients and 26 controls.<sup>46</sup> In the correct hands, US is a major facilitator in diagnosing CPPD. However, training and expertise are required to correctly identify CPP deposits when performed by the clinician at the time of clinical review.

## Computed Tomography and MRI

Computed Tomography (CT) is more accurate than conventional radiography, particularly for the axial skeleton and deep anatomic structures.<sup>47</sup> It is helpful in the diagnosis of crowned dens syndrome (CDS),<sup>48</sup> an under-recognised syndrome characterised by occipital pain and neck stiffness secondary to CPPD and can often manifest with raised inflammatory markers and fever.<sup>49</sup> However, it does expose the patient to ionising radiation and cannot be performed at the bedside. Furthermore, CT does not allow for differentiation between different crystal deposition diseases, for example, CPPD and basic calcium phosphate (BCP) crystals, however, newer emerging technology of dual emission CT (DECT) can discriminate differences in the composition of various crystals and can be color-coded. A recent study by Pascart et al has shown promising results, with sensitivity of DECT to discriminate between BCP and CPP calcifications of over 90% compared to Raman spectroscopic analysis as the gold standard for BCP detection.<sup>50</sup> Historically, MRI is generally considered to have limited utility in the diagnosis of CPPD as calcifications are poorly visualized in articular tissues.<sup>38</sup> There may be a role for high-field MRI, which has shown superiority over conventional MRI in detecting crystal deposits<sup>51</sup> but this is not used in practice when US and plain film radiographs have been studied in greater depth and are more accessible.

## Treatment

One of the biggest barriers in the treatment of CPPD is the paucity of randomised controlled clinical trials to objectively evaluate the currently used treatment options. In addition, no disease modifying treatments exist that reduce the CPP burden or prevent its deposition. Current therapy is aimed at reducing the acute inflammatory response and thereby lessening symptoms in affected patients. A variety of treatment options including colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids both systemic and intra-articular and interleukin-1 inhibitors have been inferred for use in CPP arthritis after success in treating gout.

## Colchicine/NSAIDs/Corticosteroids

Colchicine is recommended by EULAR in the treatment of acute CPPD, acknowledging that evidence is mainly extrapolated from gout treatment.<sup>52</sup> A regimen of 0.5 mg three or four times per day with or without a loading dose of 1 mg is recommended, predominantly on expert opinion.<sup>52</sup> There have been two small open-label studies, including a total of 21 patients that appeared to show reduced rates of disease flare and pain in patients who received colchicine.<sup>53</sup> It is less clear whether the use of colchicine for prophylaxis in acute CPPD is beneficial, but there is some evidence for its use. A study involving ten patients who were given 0.6 mg colchicine twice daily for one year reported less frequency of flares compared with one year without prophylaxis, with overall 90% reporting some level of benefit.<sup>54</sup> Similarly, NSAIDs are included in the EULAR treatment guidelines, with particular emphasis on considering NSAID-related side effects in an elderly patient population.<sup>52</sup> Astoundingly, there have been no published studies on the efficacy of NSAIDs in CPPD.<sup>53</sup> This is a barrier to treatment as clinicians are justifiably cautious given the extensive awareness of their many side effects and is it difficult to justify such treatment without adequate objective studies. With regard to corticosteroids, EULAR recommends a short tapering course of corticosteroids in acute CPPD, with a recommendation for joint aspiration and intra-articular corticosteroid injection which may be particularly useful for those with multiple comorbidities and contraindications to systemic corticosteroids or NSAIDs and oligoarticular involvement.<sup>52</sup> Again, a barrier to such treatment is the lack of robust evidence. However, one non-randomised controlled trial found that intra-articular steroids in hospitalised patients was associated with a quicker onset of relief compared with oral corticosteroids.<sup>55</sup> Although far from the ideal level of evidence, colchicine, NSAIDs and corticosteroids are regularly used in the treatment of acute CPPD, and most clinicians are comfortable in choosing one of these agents when acceptable low-level risk is present depending on individual patient characteristics.

## Other Agents for Acute CPPD

There is some evidence for the use of adrenocorticotrophic hormone (ACTH) and anti-interleukin 1 receptor antagonist anakinra in acute CPPD. One study looked at the use of ACTH in acute gout and CPPD, however only 5 CPPD patients were included, with the resolution of flare in CPPD occurring in an average of 4.2 days.<sup>56</sup> A recent systematic review included 11 studies that used anakinra for CPPD, with 74 patients in total.<sup>57</sup> Anakinra was used in both refractory disease (85.1%) and those with contraindications to standard treatments (23.0%). This review reported that a response to anakinra was seen in 80.6% of patients with acute CPPD and 42.9% of those with chronic CPPD.<sup>57</sup> While this research is welcomed and may facilitate justification of this agent in refractory patients, further research is needed to identify the optimal dose and duration of treatment, especially given its cost

## Treatment of Chronic CPPD

Similarly, in the treatment of chronic CPPD, the lack of adequately powered trials is a relative barrier to being able to prescribe with confidence. There are mixed results from studies pertaining to methotrexate. One randomised crossover trial examining the use of methotrexate reported no significant effect on disease activity,<sup>58</sup> however patient numbers were small at 26 which may have impacted the conclusions. An observational study<sup>59</sup> reported excellent outcomes in refractory CPPD with methotrexate use; however, only 10 patients were included and response was measured with visual analogue scale (VAS). There is some case series evidence for the use of tocilizumab, an anti-interleukin 6 receptor antibody in refractory CPPD.<sup>60</sup> After three months, patients reported vast improvement in VAS and this effect was sustained up to 10 months post-treatment. Hydroxychloroquine has been evaluated in one double-blind randomised crossover trial.<sup>61</sup> Patients were prescribed between 100 mg to 400 mg per day and at least a 30% reduction in the number of flares was seen in 76% of the treatment group versus 32% of the control group.<sup>61</sup> For chronic CPPD, EULAR recommends, in order of preference, oral NSAIDs (plus gastroprotective treatment if indicated) and/or colchicine (0.5–1.0 mg daily), low-dose corticosteroids, methotrexate and hydroxychloroquine.<sup>52</sup>

## Conclusion

There are many challenges in the diagnosis and treatment of CPPD arthropathy. Establishing the correct diagnosis is the first obstacle, but synovial fluid aspiration and examination under PLM remains a major facilitator to diagnosis. Including a white cell count with differential, gram stain, and fluid culture in this analysis is also invaluable to exclude other diagnoses, in particular infection. Despite being imperfect, x-ray and US remain the most useful imaging techniques in CPPD with the identification of chondrocalcinosis deposition in hyaline cartilage or articular cartilage being particularly useful findings. It is important to identify and treat any associated conditions including haemochromatosis, hyperparathyroidism, hypomagnesemia, and hypophosphatemia. Current therapeutics for CPPD arthritis lack robust evidence but is anticipated the new CPPD classification criteria from Tedeschi et al, will facilitate more clinical research on this common crystal arthropathy, with well-defined patient cohorts which will facilitate the production of high-quality evidence to guide the management of this condition in the future.

## Disclosure

The authors have reported no conflicts of interest in this work.

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