Nonpharmacologic and Pharmacologic Management of CPP Crystal Arthritis and BCP Arthropathy and Periarticular Syndromes

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INTRODUCTION

Calcium crystal arthritis, including calcium pyrophosphate deposition (CPPD) and basic calcium phosphate (BCP) arthropathies and tendinitis, are common, underrecognized causes of arthritis and musculoskeletal pain for which there are few effective therapies. This article defines these syndromes, briefly describes existing diagnostic challenges, and discusses available and emerging management strategies for CPPD and BCP-associated musculoskeletal syndromes. These entities are considered separately although there is considerable overlap in the populations they affect and, in arthritis, both types of crystals may be simultaneously present in a single joint.1

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CPPD

Clinical Presentation and Epidemiology

CPPD comprises a clinically heterogeneous group of arthritides caused by the presence of calcium pyrophosphate (CPP) crystals in articular tissues (Fig. 1). CPP crystals produce a vigorous inflammatory response under certain conditions but are also present in noninflammatory settings. For example, CPP crystals were seen in 20% of unselected samples of cartilage and synovium examined at the time of knee replacement for osteoarthritis (OA). The presence of CPP crystals is often suggested by the finding of chondrocalcinosis on radiographs of affected joints. Chondrocalcinosis typically appears as finely stippled lines of calcification in fibrocartilages such as menisci (Fig. 2), or outlines the bony contours in hyaline articular cartilage (Fig. 3).

The most commonly recognized clinical manifestation of CPPD is an acute inflammatory monoarthritis or oligoarthritis resembling gout. In acute CPPD (formerly known as pseudogout), the affected joint is erythematous and swollen, and synovial fluids can be inflammatory. The knee is the most commonly affected joint in acute CPPD. CPPD also presents as a chronic noninflammatory arthritis similar to OA, although it often affects joints rarely affected in typical OA, such as shoulders, wrists, metacarpophalangeal joints, and ankles. Patients with CPPD may or may not have intermittent episodes of inflammation in these areas. Polarticular chronic inflammatory involvement in CPPD may resemble rheumatoid arthritis. Unusual presentations of CPPD similar to those of neuropathic arthropathy have also been described. Although tophaceous deposits of CPPD are unusual, they can be particularly symptomatic in the axial skeleton.

Advanced age is the major risk factor for CPPD, and idiopathic CPPD is unusual in patients younger than 60 years of age. Familial forms of CPPD are well-described. CPPD also occurs in association with a small number of metabolic diseases, including hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypophosphatasia. The association between CPPD and other common comorbidities such as diabetes, renal disease, and hypothyroidism, require further study for confirmation.

Diagnostic Modalities

Because the clinical picture of CPPD may resemble other forms of arthritis, much of the challenge in management of CPPD lies in making an accurate diagnosis. The radiographic finding of chondrocalcinosis is suggestive but not diagnostic of the disease. Isolated chondrocalcinosis developing after meniscal tears in the knee is well-described and is of uncertain clinical significance. In addition, CPP crystals are often

Fig. 1. CPPD crystals seen under polarizing light microscopy. These crystals appear as weakly positive birefringent rhomboidal crystals.
seen in synovial fluids of joints without radiographically apparent chondrocalcinosis. Indeed, in histopathologic studies, chondrocalcinosis was present in only about 37% of subjects with articular CPP crystals. ²

Diagnostic criteria for CPPD were proposed by Ryan and McCarty. ⁹ Although the presence of rhomboidal, positively-birefringent crystals in synovial fluid (see Fig. 1) is relied on to confirm this diagnosis, the presence of severe OA with an unusual distribution in addition to key radiographic findings may strongly suggest CPPD. ⁹ CPP crystals in synovial fluids can be difficult to identify because they are often quite small and only weakly birefringent. ¹⁰ Accurate and reproducible identification of CPP crystals in synovial fluid samples requires some expertise and careful thorough examinations of the samples. ¹¹

Studies including plain radiography, ultrasonography, and advanced imaging techniques such as CT and MRI scans can be suggestive of CPPD. In addition to chondrocalcinosis (see Figs. 2 and 3), CPPD is suggested by radiocarpal or patellofemoral predominant joint space narrowing, large or numerous subchondral cysts, severe progressive joint degeneration with bony collapse and fragmentation, variable osteophyte formation, tendon calcification, and unusual axial skeleton involvement. ⁹ The increasing use of musculoskeletal ultrasound as a readily available bedside technique provides an additional diagnostic tool for crystal arthritis. The double contour sign may correlate with radiographic chondrocalcinosis and small bright objects in synovial fluid

![Fig. 2. Radiographic chondrocalcinosis. Dense deposits of CPPD are seen in this knee radiograph in the fibrocartilage of the meniscus.](image)

![Fig. 3. Radiographic chondrocalcinosis. Dense deposits of CPPD are seen outlining the contours of the articular cartilage in this knee radiograph.](image)
may reflect clusters of CPP crystals. Ultrasound may be a useful screening tool to prompt studies that are more specific and may assist in more accurate and successful arthrocentesis. MRI is relatively insensitive to CPP deposits and presents particular difficulties in distinguishing tears and calcium deposits in menisci. CT scanning more effectively identifies calcified deposits but is not commonly used to image painful joints.

TREATMENT STRATEGIES

CPPD lacks a clear cause and thus has no mechanistically targeted therapies. In addition, this field suffers from a paucity of randomized control trials of any commonly used therapies. Consequently, many of the treatment paradigms for CPPD lack a sound evidence base.

Causal Influences in Therapy

Although there is still much to learn about the pathogenesis of CPPD, it can be conceptualized in three stages. In the first stage, CPP crystals develop in the pericellular matrix of articular cartilage. It is known that overproduction of the anionic component of the crystal, pyrophosphate (PPi), is required for CPP crystals to be generated and that PPi in CPPD is analogous to the urate anion in gout. Less is known about the influence of calcium levels and the extracellular matrix changes that are necessary for the generation of CPP crystals. Probenecid may block PPi production by chondrocytes through its actions on the progressive ankylosis gene product commonly known as ANK. ANK is a putative PPi transporter. Magnesium is a cofactor for PPi degrading enzymes and correction of low levels may increase PPi hydrolysis and reduce levels of PPi available for crystal formation. Drugs that increase alkaline phosphatase may also reduce PPi levels. Ongoing work to understand PPi transport and the role of ANK in CPPD will ultimately result in novel therapies that block PPi production; however, at present, no therapies are available that clearly interfere with this stage of the disease. The presence of mineralized matrix likely alters cartilage biomechanics and may initiate or accelerate articular damage during this early phase.

In the next phase of this disease, CPPD crystals are mined or released from the cartilage surface and may elicit an inflammatory response through innate immune pathways as well as by interacting with other inflammatory cells. Colchicine and anti-inflammatory medications, particularly those targeted at interleukin (IL)-1β, may be useful in this phase of the disease. During the third phase of disease, crystals accelerate cartilage degeneration through mechanical strain and wear, and through other actions on articular chondrocytes and synoviocytes. Although no therapies are currently available to affect crystal interactions with cells, work in vitro with phosphocitrate suggests the crystal–articular cell interaction may represent a rich source of potential therapeutic targets.

This section discusses the current recommendations for management of CPPD. An excellent review of CPPD management strategies based on a consensus from experts across Europe was recently published that summarizes the commonly used medications for CPPD and clearly identifies multiple areas needing further study.

Acute CPPD

Acute CPPD is treated in a similar manner to acute gouty arthritis. The mainstays of pharmacologic therapy are intraarticular corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), and colchicine. The relative effectiveness of these therapies
has not been studied and, typically, therapeutic decisions are based on the safety of these interventions in the context of individual patient comorbidities and preferences of the provider. There is some evidence supporting the effectiveness of intraarticular corticosteroid injections in acute CPPD. Oral colchicine is also commonly used, but has not been well studied. Because the dose recommendations for acute gout have dramatically changed the way colchicine is used, studies of similar low-dose short-term regimens in acute CPPD are warranted. The use of NSAIDs in acute CPPD is extrapolated from the gout literature but advanced patient age and common comorbidities in CPPD patients often increase the risk of these drugs. Oral corticosteroids have seen a resurgence in use for crystal arthropathies in general. The IL-1β inhibitor, anakinra, has been useful in some patients with acute CPPD. A recent case series of 16 subjects who were otherwise refractory and intolerant of other treatments describes anakinra treatment of CPPD. The mean number of injections was 15 (±42.9) and relapse occurred in one-third. Most subjects had a good response, but certainly the cost and side effects of this and similar medications may limit their widespread use. Similarly, canakinumab, an IL-1β inhibitor with a different mechanism of action than anakinra that has been tested in clinical trials for acute gout, may also have some efficacy in CPPD.

Nonpharmacologic therapies are often used adjunctively in CPPD but, again, have not been rigorously compared with other therapies. Arthrocentesis, with or without lavage, may reduce the burden of both crystals and inflammatory mediators and would logically improve symptoms. Heat, ice, and rest may be useful and pain medications including narcotics may be indicated for short-term relief. Complementary or alternative treatments such as green tea polyphenols may eventually be useful based on their antiinflammatory effects in vitro.

**Chronic Inflammatory CPPD**

The chronic inflammatory form of CPPD with either a polyarticular inflammatory presentation or an OA-like presentation with episodic inflammation can be particularly challenging to treat. These patients often suffer from frequent attacks and may have significant pain between attacks of inflammation. NSAIDs may help in those patients able to tolerate them. Systemic corticosteroids are also used and may be effective, despite serious long-term side effects. There is some weak evidence to support the use of long-term low-dose oral colchicine, although its current cost makes this option more difficult for many patients. Long-term corticosteroids, despite the high risk of side effects, are necessary in some patients. There is some evidence supporting the use of methotrexate in patients with recurrent inflammatory attacks and scattered case reports using IL-1β blockade. Less evidence supports the use of hydroxychloroquine, magnesium, probenecid, or other long-term antiinflammatory strategies.

If a single or a few large joints are involved in chronic CPPD, joint replacement may be helpful. A recent report suggests similar outcomes in unicompartmental knee arthroplasty in those with and without radiographic chondrocalcinosis. Heat, ice, and physical therapy to maintain strength and flexibility in the muscles and soft tissues around the joints may also be useful adjuncts.

** Chronic Noninflammatory CPPD **

Chronic noninflammatory CPPD is typically managed with similar strategies used for the treatment of OA. The mainstays of pharmacologic therapy for OA include intraarticular corticosteroids, acetaminophen, NSAIDs, and pain medications. Acetaminophen or NSAIDs, as tolerated, are first-line therapies for patients whose joint involvement precludes use of intraarticular corticosteroids. Hyaluronan injections...
are relatively contraindicated in CPPD because acute crystal arthritis has been associated with their use.\textsuperscript{35} Colchicine may be useful in some patients with OA, but has not been well studied in chronic noninflammatory CPPD. Some patients may require more aggressive pain regimens, including narcotics. Whether recently approved therapies for OA such as duloxetine would be helpful in this form of CPPD is not-known. Emerging strategies include drugs that block nerve growth factor,\textsuperscript{36} which may soon be available for patients suffering from OA and may have some efficacy in CPPD. Heat, ice, and physical therapy are useful adjunctive strategies for some patients. Joint replacement surgery can be effective long-term treatment of large joint involvement.

**Summary of CPPD**

In summary, therapies are borrowed from acute gout, rheumatoid arthritis, and OA to manage various forms of CPPD. This underscores the need for more specific and effective pharmacologic therapies for CPPD. It is hoped that an improved understanding of the cause of CPPD will lead to the development of novel treatments or preventive strategies that interfere with the early stages of this disease before extensive joint damage occurs. Careful attention to diagnosis and large population-based studies of risk factors and current treatment patterns will provide an improved evidence base on which to make treatment decisions.

**TREATMENT OF BCP-DEPOSITION DISEASES**

BCP crystals deposit in a variety of diseased tissues, including musculoskeletal tissues: cartilage, synovial fluid, and periarticular structures. Three principal forms of BCP in joint fluids have been identified by Fourier transform infrared spectroscopy as hydroxyl-substituted apatite, octacalcium phosphate, and tricalcium phosphate.\textsuperscript{37} The role of BCP crystals in causing disease in these tissues, although unproven, is suggested by clinical observations and in vitro studies. This section summarizes the available treatment strategies for combating the pathologic processes associated with BCP crystal deposits in tendons and joints.

**Acute Calcific Tendinitis**

Acute calcific tendinitis typically occurs around the shoulder joint, where it may present with acute severe pain, associated with large radiographically apparent calcific deposits (Fig. 4). It has been described in the hands and feet, as well as the shoulder. The cause of calcific tendinitis remains unclear.

Standard conservative treatment of acute calcific tendinitis involves treatment with NSAIDs, exercises, and injections. IL-1\textbeta inhibition has also seemed effective in a small open label series of five subjects treated with anakinra for 3 consecutive days.\textsuperscript{38} For those cases refractory to standard treatment, several physical modality options exist. Ultrasound therapy is considered part of standard traditional conservative management providing short-term improvement in symptoms (but not long-term improvement at 9 months) and associated with no changes in the size of calcifications\textsuperscript{39} compared with sham treatment.

Newer approaches to treatment are available. Extracorporeal shock wave therapy (ESWT) involves application of 0.06 to 0.55 mJ/mm\textsuperscript{2} at 1000 to 6000 impulses per session to the calcified area. Conscious sedation or intravenous analgesia may be necessary for this procedure, which is often painful. The largest study of ESWT compared high-energy level with low-energy level and with sham shock waves. The design incorporated concomitant physiotherapy.\textsuperscript{40} Both high-energy and low-energy ESWT
directed at the areas of calcification improved pain and shoulder function while reducing size of calcific deposits compared with placebo. Subjects receiving high-energy treatment fared better than those receiving low-energy therapy. A recent systematic review indicates a level of evidence B for this intervention. Side effects included erythema at the site of treatment and hematomas. Conscious sedation is especially desirable in those with ongoing acute symptomatology before the shockwave treatment. One form of ESWT, termed radial shock wave therapy, delivers pneumatic instead of ultrasound impulses. This mode of delivery seems to be less painful and equally effective.

Needling of tendon calcifications, also known as barbotage, has long been used for treatment of acute calcific tendinitis, often in combination with lavage. The rationale is that needling may decrease intratendon pressure and lavage removes some of the particulate matter that is inciting inflammation. For instance, an open study of fluoroscopic needling with saline lavage resulted in improvement in symptoms and a 50% decrease of radiographic calcium deposit size 6 months after procedure. Interpretation of these results and those of most needling studies is complicated by the subjects having received intralesional or bursal glucocorticoid injections at the conclusion of the lavage procedure. Similarly, a longer term 1-year follow-up of ultrasound-guided needling, lavage, and steroid injection indicated an 89% complete or near complete resolution of calcifications and 91% of subjects had substantial improvement of symptoms and clinical findings. Other case series have described similar outcomes for ultrasound-guided needling, lavage, and injection. To assess the impact of the needling and lavage versus that of the steroid injection, a study compared glucocorticoid injection into the subacromial bursa alone with the combination of needling-lavage-subacromial injection. Significantly more improvement was noted in the combination therapy than in the subacromial bursa injection alone. Needling and lavage added significant benefit to injection alone. Refinements to the

Fig. 4. Calcific tendinitis. A round radiodense deposit of calcium is seen in the supraspinatus tendon of this shoulder radiograph.
needling and lavage approach have been identified. Two-needle lavage (one for inflow another for outflow) has been advocated and specifics of methodology have been recently reviewed. Using warm saline solution lavage improves calcium deposit reduction, shortens the procedure time, and diminishes the frequency of bursitis after lavage compared with the use of lavage with room temperature saline. Another “needling” technique is mesotherapy, defined as the intermittent injection of drugs into painful tissues. In a randomized controlled study, EDTA treatment was tested. Forty patients received mesotherapy weekly with an EDTA-containing solution along with interval pulsed-mode sonotherapy with an EDTA-containing sonographic gel 5 days weekly for 3 weeks. The comparator group of 40 subjects received injections not containing EDTA and sham ultrasound without EDTA and with the ultrasonic generator turned off. The EDTA treatment group had significant improvement in pain and shoulder function and a remarkable decrease in calcification at 4 weeks compared with the control group.

Nonoperative treatments are usually successful. When surgery is necessary for refractory calcific tendinitis of the rotator cuff, debridement and concomitant subacromial decompression by acromioplasty is often advocated. However, a study comparing debridement alone with debridement plus subacromial decompression suggests that debridement alone is preferable.

**Acute Calcific Periarthritis of the Hand**

Acute calcific periarthritis of the hand presents in much the same way as local infection, gout, acute CPPD, or palindromic rheumatism attacks. BCP crystals are noted in aspirates. It is typically a disease of premenopausal women and involves the hand, although identical attacks may occur in the feet. Periarticular calcifications are often radiographically subtle. Its course is self-limited but recurrences are common. Treatment with either corticosteroid injection or NSAIDs has been described and either is thought to be effective. No controlled studies or large series of treatment are available due to its rarity and self-limited nature.

**BCP-Associated Arthropathies**

**Milwaukee shoulder syndrome**

The best characterized, but not the most common, form of joint disease associated with BCP deposition is the Milwaukee shoulder syndrome (MSS), comparable in many respects with the previous descriptions of cuff-tear arthropathy (Fig. 5). This syndrome is a noninflammatory enzyme-driven destruction of articular structures, including articular cartilage and rotator cuff tendons, accompanied by large effusions. The unifying feature of MSS is the presence of BCP crystals in the joint fluid. One-half of affected patients have coexistent CPP crystals and one-half have involvement of joints other than the glenohumeral joints, notably the knees. Standard treatment has involved use of NSAIDs, analgesics, physical therapy, and intraarticular injections of glucocorticoids. Randomized controlled studies that validate this approach are lacking. The paucity of therapeutic studies of MSS results in part from lack of convenient assays for detecting and quantifying BCP crystals in joint fluids. Use of magnesium supplementation is anecdotal but may be helpful for BCP disease or the frequently attendant CPPD. In the authors’ clinic, repeated arthrocentesis with glucocorticoid injection seems to relieve pain and decrease effusions in some individuals but has not increased function. Other investigators have suggested treatment with tidal irrigation. In the latter study, subjects with advanced radiographic changes fared less well than those with minor radiographic changes. Potentially, this treatment’s efficacy depends on the removal of BCP crystals from joints that do not yet have
extensive damage. When conservative strategies fail, surgical outcomes may be extrapolated from the literature surrounding the closely related entity of cuff tear arthropathy. Reverse total shoulder arthroplasty seems to have better outcomes than hemiarthroplasty.59,60

Musculoskeletal involvement with BCP crystals: targeting the crystals. The next approach?
Ultimately, successful treatment of the above conditions may necessitate either preventing crystal deposition or blocking the harmful biologic effects. A rationale for targeting BCP crystals in future approaches to treatment is provided below.

BCP Crystals Are Linked to Degenerative Joint Processes
BCP crystals have been uniformly detected in osteoarthritic hyaline cartilages removed from hip or knee joints at the time of arthroplasty.2,61 In these studies, hyaline cartilage BCP deposits were not visible on standard preoperative radiographs but could be seen using digital-contact radiography on the surgical specimens. The degree of cartilage calcification correlated with the severity of OA both on preoperative radiographs and by histology of operative specimens. Markers of chondrocyte hypertrophy were prominent in the pathologic specimens. Control cartilage specimens from subjects undergoing amputation for malignancies did not contain BCP deposits, albeit the few control subjects were generally younger than the OA subjects. Thus, cartilage BCP deposits are intimately linked to advanced OA of sufficient severity to require joint replacement. These findings confirm and extend those of a previous study of cartilage calcification in consecutive postmortem knees, which also noted a correlation between presence of calcium phosphate mineral and histologic severity of OA.62 Joint fluid studies also indicate frequent detection of BCP crystals in specimens taken from osteoarthritic joints.1

In Vitro Effects of BCP Crystals Suggest a Role in Inflammation and Degenerative Processes
In general, calcium-containing crystals elicit numerous biologic responses that may lead to tissue injury and inflammation. Among the responses are synthesis and

Fig. 5. MSS. Note the severe cartilage loss evidenced by the loss of glenohumeral joint space, subchondral sclerosis, and global joint degeneration in this radiograph from a patient with MSS.
release of several proteases. Proteases, including matrix metalloproteinases 1, 3, 8, 9, and 13, are released after exposing cells to BCP crystals. At the same time these crystals down-regulate tissue inhibitor of metalloproteinase. BCP crystals also elicit release of prostaglandin E2 and IL-1β from fibroblasts. Nitric oxide production was enhanced in cells exposed to other calcium-containing crystals and will likely increase with BCP exposure. BCP crystals are also mitogens, which results in proliferation of tissues such as synovium, increasing the cell population that may secrete proteases and cytokines. The usefulness of targeting crystal formation and blockade of calcium crystal downstream effects has been tested in an animal model. The Hartley guinea pig model of OA features intraarticular BCP formation. Treatment of these animals with phosphocitrate, which blocks growth of BCP crystals and their biologic effects, attenuated the degenerative process in this animal model of OA.

Summary of BCP-related Diseases

Current treatment approaches to BCP-related diseases differ little from the treatment of coexistent OA or tendon disease. However, specific procedures (vide supra) improve outcomes in patients with calcific tendinitis refractory to standard treatments. Promising avenues for ameliorating the pathologic effects of BCP crystals include use of magnesium, possible use of colchicine, and phosphocitrate compounds. Each of these can block crystal formation and/or biologic effects of calcium-containing crystals. Further studies would be facilitated by more convenient and standardized methods of identifying BCP crystals in biologic specimens, which would enable a more precise identification of the target population.

SUMMARY

In conclusion, calcium-containing crystals are commonly associated with painful musculoskeletal syndromes. A better understanding of why and how these crystal deposits occur, the use of more accurate diagnostic modalities, and randomized controlled trials of available therapies will lead to the development of more specific and effective management strategies for patients with these conditions.

REFERENCES


