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Treatment of calcium pyrophosphate crystal deposition disease: a mini-review

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Abstract

Calcium pyrophosphate crystal deposition disease is a prevalent and impactful form of crystal arthropathy. It usually targets the large joints of the extremities, significantly affecting daily life. Progression of this disease, commonly observed in older individuals and often mistaken for septic arthritis, osteoarthritis, or several rheumatic conditions, remains poorly understood. The disease can present in various forms, from asymptomatic to severe joint deformity. The primary goal of treating this disease is to firmly control inflammation, prevent joint deformities, and decisively stop attacks. Medications used to treat the disease include anti-rheumatic drugs such as non-steroidal anti-inflammatory drugs, oral, intramuscular, or intra-articular steroids, hydroxychloroquine, colchicine, methotrexate, and interleukin-1 receptor antagonists. Radiosynovectomy is a radioactive technique that effectively targets and eliminates inflamed synovium. This article highlights the importance of awareness and early intervention to manage this condition effectively.

Keywords

Calcium pyrophosphate crystal deposition disease, acute arthritis, crystals, osteoarthritis, treatment

Introduction

Calcium pyrophosphate crystal deposition disease (CPPD) is one of the common crystal arthropathies [1]. This arthropathy affects the knees, wrists, ankles, elbows, toes, shoulders, hips, and, rarely, the temporomandibular joints and spine [1–3]. The prevalence of the disease increases with age, with an average of 15% between the ages of 65–74 and an average of 45% over the age of 85 [4].

The cause of the CPPD remains unclear. The disease starts with the formation of calcium pyrophosphate (CPP) crystals in the pericellular matrix of cartilage. The resulting CPP crystals activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, which initiates the inflammatory response. Additionally, CPP crystals directly affect chondrocytes and synoviocytes by modulating metalloproteinases. Additionally, CPP crystal deposits in articular cartilage may alter the mechanical properties of the joint and cause joint damage [5]. Understanding CPP-induced inflammation at the molecular level is important to encourage the search for more effective treatments targeting inflammation [6]. Metabolic diseases such as hyperparathyroidism, hemochromatosis, hypophosphatemia, hypomagnesemia, and hypercalcemia can lead to an acceleration of CPPD. Chondrocalcinosis may be seen in Gitelman's syndrome due to hypomagnesemia [7].

Examination of synovial fluid with direct and polarized light microscopy is useful in the diagnosis of CPPD. CPP crystals are rhomboid or rod-shaped, 1–20 μm in size, weakly positive birefringent crystals under polarized light microscopy. These crystals are found in the synovial fluid or tissue of the affected joint [1, 8]. In cases where synovial fluid analysis is not possible, radiological examinations gain importance.

The European League Against Rheumatism (EULAR) has defined the term "CPPD" to encompass all phenotypes [3]. Acute CPPD arthritis (pseudogout) presents with intermittent, self-limiting joint pain, swelling, and tenderness. The buildup of CPP crystals in articular cartilage and the synovial membrane leads to an inflammatory response. Acute CPP stands out as a prevalent cause of inflammatory monoarthritis or polyarthritis among older individuals. Attacks occur suddenly, as in gout, but are not as severe as in gout. Compared to an acute gout attack, attacks may last longer despite treatment [9]. Patients may remain asymptomatic between these attacks. Surgeries or serious medical illnesses such as cerebrovascular disease or myocardial infarction may trigger acute arthritis [10]. Acute CPP crystal arthritis is more common in women, and attacks most often occur in the knee and wrist [4, 11].

Chronic CPP crystal inflammatory arthritis is a less severe form of acute arthritis and typically manifests as inflammatory oligoarthritis or polyarthritis. Patients complain of pain, mild swelling, and morning stiffness. The disease is mostly bilateral and symmetrical. In some cases, a chronic arthritis flare can last for months, resulting in significant joint deformation [10]. It is essential to include this condition in the differential diagnosis of chronic inflammatory joint diseases among older adults.

When CPPD is found in a joint with osteoarthritic changes, it is called osteoarthritis with CPPD. It is most commonly seen in the knee. In primary osteoarthritis, the medial compartment is more frequently involved and causes varus deformity. In osteoarthritis associated with CPPD, the lateral compartment is predominantly affected and is directly linked to a valgus deformity. It is uncertain whether osteoarthritis increases the risk of developing CPPD or if CPP crystals trigger joint damage [9].

The pseudo-rheumatoid arthritis variant of CPPD, though less common, often masquerades as rheumatoid arthritis, leading to frequent misdiagnoses. Patients with pseudo-rheumatoid arthritis typically present with polyarticular joint pain, swelling, and morning stiffness (especially the proximal interphalangeal joint and metacarpophalangeal joint). Joint involvement is symmetrically distributed, and levels of acute-phase proteins are elevated. Low-titer rheumatoid factor (RF) positivity is seen in 10% of cases, further increasing diagnostic confusion. Classical rheumatoid arthritis can be distinctly identified from pseudo-rheumatoid arthritis through the presence of elevated levels of RF and the more specific anti-cyclic citrullinated peptide (CCP) antibodies [12].

Pseudo-neuropathic arthropathy is a rare and significant subtype of CPPD-related arthropathy that demands further investigation. The clinical and radiological features of pseudo-neuropathic arthropathy closely resemble those of neuropathic Charcot joint, resulting in significant joint damage over a relatively short period [13]. Crowned dens syndrome (CDS) is a rare and interesting condition resulting from pseudogout at the atlantoaxial junction. CPPD or calcium hydroxyapatite deposition around the dens causes distinct and often challenging clinical symptoms. Neck pain, fever, and malaise seen in patients require differential diagnosis with many diseases [14].

Treatment options for CPPD

Treatment focuses on reducing inflammation and lessening attack frequency and severity due to CPPD [15, 16]. Many agents used in the treatment of CPPD are also used in the treatment of gout, symptomatic osteoarthritis, and rheumatoid arthritis. The primary objective in treating gout, a notable form of crystal arthropathy, is to eliminate the accumulation of monosodium urate crystals or to ensure their dissolution. To accomplish this, effective strategies must be implemented to maintain serum uric acid levels within a targeted range. On the other hand, unlike in gout, treatment methods for CPPD do not directly target the crystals [8, 17]. The CPPD arthritis treatment guideline was published by EULAR in 2011, before the use of biological agents in treatment [18]. Surgery may occasionally become essential, particularly in cases of soft tissue damage or when there is a significant loss of cartilage or instability in the joint. These circumstances often require a more decisive approach to restore function and alleviate discomfort [19]. Surgical removal of chondrocyte calcification is not a recommended method; however, successful outcomes can be obtained through arthroplasty in patients with severe joint deformation [18].

Patients with asymptomatic chondrocalcinosis do not require treatment. However, it is crucial to effectively address any underlying condition associated with CPPD [1, 3].

Treatment of acute CPPD arthritis

In treatment planning, it is crucial to thoroughly evaluate the patient's medical history, any accompanying diseases, the number of affected joints, and the suitability of joint injections. This comprehensive approach helps provide personalized and effective care [19]. After ruling out septic arthritis, managing joint inflammation can be effectively achieved through non-pharmacological methods like joint immobilization, compression, and cold application.

Joint aspiration and intra-articular corticosteroid injection are strongly recommended for patients experiencing acute CPP arthritis that affects one or two joints [15]. For large joints, triamcinolone acetonide (40–80 mg) can be mixed with 1 or 2 mL of lidocaine. For smaller joints, lower doses of corticosteroid preparations may be used. After the injection, pain and swelling typically lessen within 8 to 24 hours. However, if there is no improvement after 48 to 72 hours or if inflammation develops in new joints, oral anti-inflammatory medications may be required [18]. Another scenario where oral anti-inflammatory medications are essential is for patients who are unable to receive joint injections. If more than two joints are affected, intra-articular steroid injections are not suitable. It is essential to utilize anti-inflammatory medications, specifically nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids, to effectively manage inflammation [18].

According to EULAR guidelines, NSAIDs are deemed effective for treating acute CPPD arthritis and are also recommended for prophylaxis based on expert consensus. While these medications are commonly used for treating gout, randomized controlled trials (RCTs) have yet to assess their effectiveness specifically for CPPD. Any NSAID can be used, as there is no evidence indicating that any particular NSAID is more effective than another. Both traditional NSAIDs and selective COX-2 inhibitors are strong and effective options that should be considered for pain management. Side effects such as gastrointestinal discomfort and deteriorating kidney function are quite rare with short-term treatment, making it a safe and effective option for many patients. The use of NSAIDs in elderly patients with CPPD is often restricted due to several concurrent health conditions. These include renal insufficiency [particularly when the estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m^2], active duodenal or gastric ulcers, heart failure, uncontrolled hypertension, NSAID allergies, and ongoing treatment with anticoagulants. When initiating treatment for an exacerbation, NSAID therapy effectively alleviates pain and mitigates inflammation. It's recommended to discontinue NSAIDs just 1–2 days after clinical symptoms have resolved. For most acute attacks, a 1–2 week course of NSAIDs is often all that is needed for effective relief [4, 18, 20]. Gastroprotective measures should also be kept in mind in the treatment of CPPD.

EULAR strongly recommends using colchicine for managing acute CPP crystal arthritis, supported by expert opinion. Colchicine functions by disrupting the polymerization of microtubules. While the exact mechanism remains unclear, in vitro studies have demonstrated that the expression of interleukin-1β (IL-1β) induced by CPP and monosodium urate crystals can be reduced [18, 21, 22]. Colchicine treatment should begin within 24 hours of flare onset. Administration should be done orally, as intravenous use can cause irritation and tissue necrosis due to extravasation [23, 24]. For treating acute CPP crystal arthritis, 0.5 mg of colchicine is recommended three to four times daily [18]. Colchicine commonly causes gastrointestinal side effects like diarrhea, abdominal pain, vomiting, and nausea. However, patients on low doses may experience these symptoms much less frequently [25]. Serious toxicities, including peripheral neuropathy, cytopenia, rhabdomyolysis, myopathy, hepatic failure, and severe skin rash, are consistently rare in patients taking colchicine for short durations.

Avoid colchicine in patients with renal or hepatic insufficiency, especially when used with drugs that inhibit cytochrome P450 3A4 (CYP3A4) or P-glycoprotein (P-gp) transporters. Healthcare providers must carefully review patients' medical histories and current medications before prescribing statins with colchicine, as this combination can lead to serious complications like myopathies and rhabdomyolysis [19, 22, 26].

If NSAIDs, colchicine, or intra-articular corticosteroid injections are not appropriate, systemic corticosteroids may be used. Prednisone, or another equivalent oral corticosteroid, is typically prescribed at a dose of 30–50 mg once daily until the flare-up subsides. The dose is then gradually reduced for about 10–14 days. Typically, a response to oral corticosteroids is observed within 2 to 3 days; however, the response may take longer if multiple joints are affected [3, 19]. Corticosteroids must be used cautiously in patients with heart failure, uncontrolled hypertension, or glucose intolerance. Parenteral corticosteroids are given in doses equivalent to the recommended oral dose for patients who cannot take oral medications [27]. As parenteral therapy, a single dose of 60 mg triamcinolone acetonide can be administered intramuscularly [28].

Adrenocorticotropic hormone analogs may be used as an alternative in the treatment of acute CPP arthritis in patients in whom corticosteroids, NSAIDs, and colchicine are contraindicated. In a compelling retrospective study on synthetic ACTH for treating acute CPP arthritis, 13 out of 14 patients reported substantial pain relief within just 24 hours. Only one patient needed a second dose the next day, highlighting the effectiveness of this treatment option for rapid pain management [29].

Anakinra is an interleukin-1 (IL-1) receptor antagonist administered as a daily subcutaneous injection of 100 mg, and it is the preferred biological medication for patients who are unresponsive to other treatments [30]. Research has indicated that CPP crystals lead to a downregulation of the natural IL-1 receptor antagonist (IL-1Ra), which results in heightened IL-1 activity. This change causes an increase in cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and various chemokines [31]. A three-day treatment regimen is the standard protocol for effectively managing acute attacks [32]. In a systematic literature review, 74 patients with CPPD, who had conditions unresponsive to standard treatments or had contraindications, received treatment with anakinra. Among these patients, 68.9% underwent a 3-day treatment regimen. A total of 21.6% of patients were treated for 5–9 days, and 9.5% for 30–365 days. A good clinical response was observed in 80.6% of patients with acute CPP arthritis with anakinra treatment, with significant improvement in clinical and laboratory parameters [30]. Anakinra treatment remains a good option for patients with refractory CPPD. A retrospective study of patients with acute CPP arthritis determined that anakinra was effective in alleviating pain for 79% of patients after they received two to four doses [33]. Dumusc et al. [34] conducted a definitive double-blind, randomized trial that effectively compared the efficacy of anakinra and prednisone in treating 15 patients with CPPD. The study indicated that anakinra has a quicker onset of action than prednisone, suggesting it may be a more appropriate option for patients with comorbidities. Additional RCTs are necessary to more accurately determine the optimal dose and duration of anakinra for treating CPPD. There are currently no RCTs demonstrating the efficacy and safety of the IL-1 inhibitors, rilonacept and canakinumab, for treating acute CPPD arthritis.

Refractory acute CPPD disease is uncommon. Acute flare-ups typically subside within 7 to 14 days. However, if treatment is not initiated promptly, it may be challenging to resolve the attack. If symptoms fail to improve as anticipated, it is essential to assess the patient's adherence to treatment. Consider exploring alternative medications and investigating other possible causes of acute arthritis, including infections, to ensure comprehensive care [3, 17]. Prophylactic treatment may be recommended for patients who experience frequent acute exacerbations (≥ 3 attacks per year). Research shows that oral colchicine shows promise in significantly reducing the frequency of exacerbations in patients with CPPD. This finding highlights its potential as a valuable treatment option for those affected by this condition [17, 23]. Colchicine (0.5 or 0.6 mg twice daily) is recommended as prophylaxis. Dosage may be reduced in intolerant patients. Low-dose colchicine has been shown to reduce the exacerbation rate from 3.2/patient/year to 1/patient/year [19]. A small prospective cohort study conducted in Spain involving 12 patients found that the average number of attacks of acute CPP crystal arthritis decreased from 9.3 attacks per year to 2.4 attacks per year after one year of treatment with oral colchicine at a dose of 1 mg daily [35]. Prophylaxis alone fails to deliver satisfactory results with colchicine; consider incorporating NSAIDs as an alternative or complementary treatment to enhance therapeutic effectiveness [3, 10]. Low-dose corticosteroids may be used for prophylaxis in patients who are unresponsive to both NSAIDs and colchicine or who have contraindications to both. For patients who do not respond to or cannot take these medications, anti-IL-1 therapy is a viable alternative. Daily or alternate-day doses can be administered as maintenance therapy for those with frequently relapsing or refractory arthritis [32]. Prophylaxis treatments should be continued until no acute CPP crystal arthritis flares have occurred for at least two years. Due to limited data, methotrexate (MTX) is not recommended as a prophylactic treatment [32, 36].

Treatment of chronic CPPD arthritis

Patients with chronic CPPD arthritis may exhibit ongoing joint inflammation symptoms that could be mistaken for rheumatoid arthritis. In such cases, long-term use of the lowest effective dose of an NSAID, such as naproxen at 250 to 500 mg taken twice daily, may help in managing symptoms. It is essential to take into account the patient's age, any existing health conditions, and the medications they are currently taking. Other compelling treatment options include low-dose oral corticosteroids, such as colchicine or prednisone, which should be taken at a maximum dose of 7.5 to 10 mg per day [19, 32]. The increasing prevalence of corticosteroid side effects in the elderly constitutes a significant obstacle to their use in the management of chronic CPPD in this age group [17]. Many patients require combination treatments to control the disease. Hydroxychloroquine (HCQ) inhibits the activity of T cells, reducing the release of various cytokines such as IL-1, IL-6, and TNF-α. A double-blind, RCT evaluated HCQ's efficacy in CPPD, involving 19 patients on HCQ and 17 on a placebo. The HCQ dosage starts at 100 mg each day, and it is escalated to a maximum of 400 mg daily for individuals who do not show a response. Seventy-six percent of the treatment group and thirty-two percent of the placebo group showed improvement in inflamed joints. During the open-label phase of the study, it was observed that 85% of patients who initially received a placebo and subsequently switched to HCQ demonstrated a positive response to the treatment. This finding underscores the potential effectiveness of HCQ in improving patient outcomes [3, 37].

MTX is a structural analog of folate and is one of the older disease-modifying anti-rheumatic drugs (DMARDs). It works as an inhibitor of adenosine release, as in rheumatoid arthritis [38].

The role of treatment for CPPD arthritis is still uncertain, as studies have yielded mixed results. A retrospective cohort study of 5 patients with refractory CPPD arthritis demonstrated a strong and favorable response to MTX, affirming its effectiveness as a viable option for managing this difficult condition [38]. However, in a double-blind, randomized study of 26 patients with recurrent or persistent chronic CPPD arthritis, no significant clinical or laboratory differences were found in the treatment response of the MTX and placebo groups [39]. MTX and HCQ were recommended as treatment options in the 2011 EULAR guidelines [3]. There is currently insufficient data to support the use of MTX for treating CPPD; however, more studies are necessary to definitively evaluate this inexpensive, safe, and well-known therapy among rheumatologists.

In a systematic review, Cipolletta et al. [30] reported a 42.9% response rate to anakinra in chronic CPP arthritis. While the limited number of patients in this single report poses challenges for definitive conclusions, all studies included in the analysis suggest that anakinra is effective in preventing new flares of chronic CPP arthritis. Susceptibility to serious infections is the most important problem with the use of anakinra. It can be used alone or in combination with low-dose corticosteroids. Longer-acting IL-1 inhibitors, such as canakinumab and rilonacept, are likely to be beneficial for CPPD; however, their effectiveness has not been studied yet. It's essential to prioritize research in this area to confirm its potential advantages.

The report on recurrent CPPD attacks in a patient with rheumatoid arthritis, who was treated with etanercept, clearly indicates that distinct inflammatory pathways are involved in both CPPD and rheumatoid arthritis [40]. In treating CPPD arthritis, TNF-α blockers appear to have a minor effect, whereas IL-1 inhibitors appear to have a more significant role.

Tocilizumab is an effective monoclonal antibody that specifically targets the IL-6 receptor. Case series and reports have documented the experience with tocilizumab in treating CPPD. The largest case series comprised 11 patients, with seven having been previously treated with anakinra. Of these patients, seven had chronic CPP inflammatory arthritis, and four suffered from recurrent attacks of acute CPP crystal arthritis. Tocilizumab was given through monthly intravenous or weekly subcutaneous administration. After three months, the median global assessment visual analogue scale (VAS) dropped significantly from 60 to 15 (P = 0.006), demonstrating that the treatment efficacy was successfully maintained through a ten-month follow-up. However, an increased infection rate was reported. The overall findings suggest that Tocilizumab cannot be considered effective in CPPD, but it may be a promising drug and deserves further evaluation. In managing chronic CPPD disease, one must consider the increased risk of infection, particularly in elderly individuals [41].

In the treatment of CPPD, glycosaminoglycan polysulfate (GAGP) is one of the drugs investigated, but there is not enough data regarding its effectiveness. A prospective study was undertaken to assess the effectiveness of intra-articular GAGP in a group of 12 patients suffering from CPPD. This investigation included individuals with bilateral knee involvement. GAGP was administered to the most severely affected joint, with the contralateral joint serving as a control. A notable decrease in pain and enhancement in joint mobility were observed during the 1-year follow-up. During the follow-up period, acute arthritis was observed in four treated joints and nine control joints [42].

The effectiveness of intra-articular hyaluronic acid in patients with CPPD arthritis is still debated. There have been reports of CPPD arthritis cases triggered by hyaluronic acid injections [43, 44].

Magnesium supplements are recommended as a potential treatment for CPPD, irrespective of baseline magnesium levels. In a double-blind, placebo-controlled study with 38 patients, the treatment group received 30 mEq of magnesium carbonate daily for 6 months. A notable reduction in pain scores, joint swelling, and tenderness was observed in the magnesium carbonate group [45]. Magnesium is believed to enhance the solubility of CPPD crystals. Further investigation is necessary to clarify magnesium's role in CPPD treatment [46].

Radiosynovectomy is an innovative radioactive technique designed to effectively eliminate inflamed synovium. It offers significant benefits, particularly for patients suffering from CPPD due to hemophilia, making them ideal candidates for this remarkable treatment. In a double-blind study assessing the effectiveness of radiation synovectomy, 15 patients with bilateral knee CPPD were involved. In this study, intra-articular yttrium-90 (5 mCi) combined with triamcinolone hexacetonide (20 mg) was administered to one knee, while saline combined with triamcinolone hexacetonide (20 mg) was administered to the other knee. At six months, treated knees showed significant reductions in pain, stiffness, tenderness, and swelling compared to the control group [47].

High levels of free inorganic phosphate in chondrocyte extracellular matrix promote calcium crystal formation. Employing pharmacological agents like probenecid, phosphocitrate (PC), and polyphosphate

(polyP) to lower free phosphate levels may prevent the formation of calcium pyrophosphate (CPP) crystals [48]. Probenecid is believed to prevent CPPD crystal growth by inhibiting TGF beta-1, a crucial stimulator of the nucleotide triphosphate pyrophosphohydrolase (NTPPPH) enzyme that is necessary for pyrophosphate synthesis. PC has been demonstrated to be a strong anti-mineralizing agent in an animal model, potentially helping to reduce calcium deposits; however, there is no available data regarding its effectiveness in humans [49]. PolyP is another agent that can dissolve CPPD crystals and has the potential to inhibit local mineralization. However, the effects of these agents remain theoretical and require confirmation [10]. To effectively identify evidence-based treatment strategies for CPPD, it is essential to conduct well-designed RCTs. Oral NLRP3 inhibitors, PC, and nucleotide pyrophosphatase/phosphodiesterase (NPP1) inhibitors are potential therapeutics worthy of further investigation in CPPD.

Conclusions

CPPD arthritis refers to various clinical subsets of CPP crystal-associated arthropathies. The goal of treatment is to reduce inflammation and lessen the frequency and severity of symptoms caused by CPPD.

NSAIDs, corticosteroids, and colchicine remain standard treatments for acute CPPD; however, their effectiveness decreases in chronic cases. In cases where standard treatments are ineffective, biologic therapies like anakinra and tocilizumab may be options to consider (Table 1) [50].

Table 1. Current drugs used in the treatment of calcium pyrophosphate deposition disease and their indications

Nonsteroidal anti-inflammatory drugs	In the treatment and prevention of flare-ups
Steroids	Effective during flares, especially in multiple joint involvement. Intramuscular steroids are applied to those who cannot take oral steroids. Intra-articular steroids are used for cases of mono or oligoarticular involvement.
Colchicine	It can be used in combination with NSAIDs in the treatment of flares. It is also effective in the prophylaxis of flares.
Methotrexate	This drug is recommended for situations where conventional medications have failed to control attacks or when their use poses potential risks.
Hydroxychloroquine	It is effective in treating chronic arthropathies associated with CPPD.
Interleukin-1 receptor antagonist (anakinra)	It is preferred in cases where conventional drugs cannot be used or in diseases that cannot be managed with conventional drugs.

Levels of Evidence 5 for Therapeutic Studies: Expert opinion without explicit critical appraisal or based on physiology bench research or “first principles”. CPPD: calcium pyrophosphate crystal deposition disease; NSAIDs: nonsteroidal anti-inflammatory drugs. The table was adapted with permission from [50]. © 2019 Iqbal et al.

Abbreviations

CPP: calcium pyrophosphate

CPPD: calcium pyrophosphate crystal deposition disease

EULAR: European League Against Rheumatism

GAGP: glycosaminoglycan polysulfate

HCQ: hydroxychloroquine

IL-1: interleukin-1

IL-6: interleukin-6

MTX: methotrexate

NLRP3: NOD-, LRR- and pyrin domain-containing protein 3

NSAIDs: nonsteroidal anti-inflammatory drugs

PC: phosphocitrate

polyP: polyphosphate

RCTs: randomized controlled trials

RF: rheumatoid factor

TNF-α: tumor necrosis factor-alpha

Declarations

Author contributions

EA: Conceptualization, Methodology, Supervision, Writing—review & editing. HB: Validation, Writing—original draft. Both authors read and approved the submitted version.

Conflicts of interest

Both authors declare that they have no conflicts of interest.

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References

1. Pascart T, Filippou G, Lioté F, Sirotti S, Jauffret C, Abhishek A. Calcium pyrophosphate deposition disease. Lancet Rheumatol. 2024;6:e791–804. [DOI] [PubMed]
2. Kwon K, Seok H, Lee J, Kim M, Kim S, Park H, et al. Calcium pyrophosphate dihydrate deposition disease in the temporomandibular joint: diagnosis and treatment. Maxillofac Plast Reconstr Surg. 2018;40:19. [DOI] [PubMed] [PMC]
3. Zhang W, Doherty M, Bardin T, Barskova V, Guerne P, Jansen TL, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70:563–70. [DOI] [PubMed]
4. McCarthy GM, Dunne A. Calcium crystal deposition diseases – beyond gout. Nat Rev Rheumatol. 2018; 14:592–602. [DOI] [PubMed]
5. Williams CJ, Rosenthal AK. Pathogenesis of calcium pyrophosphate deposition disease. Best Pract Res Clin Rheumatol. 2021;35:101718. [DOI] [PubMed]

6. Franchi L, Warner N, Viani K, Nuñez G. Function of Nod-like receptors in microbial recognition and host defense. Immunol Rev. 2009;227:106–28. [DOI] [PubMed] [PMC]
7. Ham Y, Mack H, Colville D, Harraka P, Savige J. Gitelman syndrome and ectopic calcification in the retina and joints. Clin Kidney J. 2021;14:2023–8. [DOI] [PubMed] [PMC]
8. Yavorskyy A, Hernandez-Santana A, McCarthy G, McMahon G. Detection of calcium phosphate crystals in the joint fluid of patients with osteoarthritis - analytical approaches and challenges. Analyst. 2008; 133:302–18. [DOI] [PubMed] [PMC]
9. Ivory D, Velázquez CR. The forgotten crystal arthritis: calcium pyrophosphate deposition. Mo Med. 2012;109:64–8. [PubMed] [PMC]
10. Rosales-Alexander JL, Aznar JB, Magro-Checa C. Calcium pyrophosphate crystal deposition disease: diagnosis and treatment. Open Access Rheumatol. 2014;6:39–47. [DOI] [PubMed] [PMC]
11. Yates KA, Yoshida K, Xu C, Lyu H, Norvang V, Solomon DH, et al. Acute Calcium Pyrophosphate Crystal Arthritis Flare Rate and Risk Factors for Recurrence. J Rheumatol. 2020;47:1261–6. [DOI] [PubMed] [PMC]
12. Resnick D, Williams G, Weisman MH, Slaughter L. Rheumatoid arthritis and pseudo-rheumatoid arthritis in calcium pyrophosphate dihydrate crystal deposition disease. Radiology. 1981;140:615–21. [DOI] [PubMed]
13. Lomax A, Ferrero A, Cullen N, Goldberg A, Singh D. Destructive pseudo-neuroarthropathy associated with calcium pyrophosphate deposition. Foot Ankle Int. 2015;36:383–90. [DOI] [PubMed]
14. Oka A, Okazaki K, Takeno A, Kumanomido S, Kusunoki R, Sato S, et al. Crowned Dens Syndrome: Report of Three Cases and a Review of the Literature. J Emerg Med. 2015;49:e9–13. [DOI] [PubMed]
15. Flood R, Stack J, McCarthy G. An Update on the Diagnosis and Management of Calcium Crystal Disease. Curr Rheumatol Rep. 2023;25:145–51. [DOI] [PubMed] [PMC]
16. Parperis K, Papachristodoulou E, Kakoullis L, Rosenthal AK. Management of calcium pyrophosphate crystal deposition disease: A systematic review. Semin Arthritis Rheum. 2021;51:84–94. [DOI] [PubMed]
17. Stack J, McCarthy G. Calcium pyrophosphate deposition (CPPD) disease – Treatment options. Best Pract Res Clin Rheumatol. 2021;35:101720. [DOI] [PubMed]
18. Zhang W, Doherty M, Pascual E, Barskova V, Guerne P, Jansen TL, et al. EULAR recommendations for calcium pyrophosphate deposition. Part II: management. Ann Rheum Dis. 2011;70:571–5. [DOI] [PubMed]
19. Voulgari PV, Venetsanopoulou AI, Drosos AA. Recent advances in the therapeutic management of calcium pyrophosphate deposition disease. Front Med (Lausanne). 2024;11:1327715. [DOI] [PubMed] [PMC]
20. Ho KY, Cardosa MS, Chaiamnuay S, Hidayat R, Ho HQT, Kamil O, et al. Practice Advisory on the Appropriate Use of NSAIDs in Primary Care. J Pain Res. 2020;13:1925–39. [DOI] [PubMed] [PMC]
21. Leung YY, Hui LLY, Kraus VB. Colchicine—Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45:341–50. [DOI] [PubMed] [PMC]
22. Spilberg I, McLain D, Simchowitz L, Berney S. Colchicine and pseudogout. Arthritis Rheum. 1980;23: 1062–3. [DOI] [PubMed]
23. Tabatabai MR, Cummings NA. Intravenous colchicine in the treatment of acute pseudogout. Arthritis Rheum. 1980;23:370–4. [DOI] [PubMed]
24. Nashel DJ. Intravenous administration of colchicine. Arthritis Rheum. 1981;24:1215–6. [DOI] [PubMed]
25. Abhishek A, Tedeschi SK, Pascart T, Latourte A, Dalbeth N, Neogi T, et al. The 2023 ACR/EULAR classification criteria for calcium pyrophosphate deposition disease. Ann Rheum Dis. 2023;82: 1248–57. [DOI] [PubMed] [PMC]
26. Stack J, Ryan J, McCarthy G. Colchicine: New Insights to an Old Drug. Am J Ther. 2015;22:e151–7. [DOI] [PubMed]

27. Hodgens A, Sharman T. Corticosteroids. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [PubMed]
28. Roane DW, Harris MD, Carpenter MT, Finger DR, Jarek MJ, Alloway JA, et al. Prospective use of intramuscular triamcinolone acetonide in pseudogout. J Rheumatol. 1997;24:1168–70. [PubMed]
29. Daoussis D, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. ACTH as first line treatment for acute calcium pyrophosphate crystal arthritis in 14 hospitalized patients. Joint Bone Spine. 2014;81: 98–100. [DOI] [PubMed]
30. Cipolletta E, Matteo AD, Scanu A, Isidori M, Battista JD, Punzi L, et al. Biologics in the treatment of calcium pyrophosphate deposition disease: a systematic literature review. Clin Exp Rheumatol. 2020; 38:1001–7. [PubMed]
31. Altomare A, Corrado A, Maruotti N, Cici D, Cantatore FP. The role of Interleukin-1 receptor antagonist as a treatment option in calcium pyrophosphate crystal deposition disease. Mol Biol Rep. 2021;48: 4789–96. [DOI] [PubMed] [PMC]
32. Andrés M, Sivera F, Pascual E. Therapy for CPPD: Options and Evidence. Curr Rheumatol Rep. 2018; 20:31. [DOI] [PubMed]
33. Desmarais J, Chu C. Utility of Anakinra in Acute Crystalline Diseases: A Retrospective Study Comparing a University Hospital with a Veterans Affairs Medical Center. J Rheumatol. 2019;46:748–50. [DOI] [PubMed]
34. Dumusc A, Maldonado BP, Benaim C, Zufferey P, Aubry-Rozier B, So A. Anakinra compared to prednisone in the treatment of acute CPPD crystal arthritis: A randomized controlled double-blinded pilot study. Joint Bone Spine. 2021;88:105088. [DOI] [PubMed]
35. González T, Gantes M. Colchicine and pseudogout. Arthritis Rheum. 1982;25:1509–10. [DOI] [PubMed]
36. Pascual E, Andrés M, Sivera F. Methotrexate: should it still be considered for chronic calcium pyrophosphate crystal disease? Arthritis Res Ther. 2015;17:89. [DOI] [PubMed] [PMC]
37. Rothschild B, Yakubov LE. Prospective 6-month, double-blind trial of hydroxychloroquine treatment of CPDD. Compr Ther. 1997;23:327–31. [PubMed]
38. Chollet-Janin A, Finckh A, Dudler J, Guerne P. Methotrexate as an alternative therapy for chronic calcium pyrophosphate deposition disease: an exploratory analysis. Arthritis Rheum. 2007;56: 688–92. [DOI] [PubMed]
39. Finckh A, Carthy GMM, Madigan A, Linthoudt DV, Weber M, Neto D, et al. Methotrexate in chronic-recurrent calcium pyrophosphate deposition disease: no significant effect in a randomized crossover trial. Arthritis Res Ther. 2014;16:458. [DOI] [PubMed] [PMC]
40. Josefina M, Ana CJ, Ariel V, Silvio AA. Development of pseudogout during etanercept treatment. J Clin Rheumatol. 2007;13:177. [DOI] [PubMed]
41. Latourte A, Ea H, Frazier A, Blanchard A, Lioté F, Marotte H, et al. Tocilizumab in symptomatic calcium pyrophosphate deposition disease: a pilot study. Ann Rheum Dis. 2020;79:1126–8. [DOI] [PubMed]
42. Sarkozi AM, Nemeth-Csoka M, Bartosiewicz G. Effects of glycosaminoglycan polysulphate in the treatment of chondrocalcinosis. Clin Exp Rheumatol. 1988;6:3–8. [PubMed]
43. Disla E, Infante R, Fahmy A, Karten I, Cuppari GG. Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection. Arthritis Rheum. 1999;42:1302–3. [DOI] [PubMed]
44. Luzar MJ, Altawil B. Pseudogout following intraarticular injection of sodium hyaluronate. Arthritis Rheum. 1998;41:939–40. [DOI] [PubMed]
45. Doherty M, Dieppe PA. Double blind, placebo controlled trial of magnesium carbonate in chronic pyrophosphate arthropathy. Ann Rheum Dis. 1983;42:106–7. [PMC]
46. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: A new challenge. World J Nephrol. 2012;1:151–4. [DOI] [PubMed] [PMC]

47. Doherty M, Dieppe PA. Effect of intra-articular yttrium-90 on chronic pyrophosphate arthropathy of the knee. Lancet. 1981;2:1243–6. [DOI] [PubMed]
48. Cowley S, McCarthy G. Diagnosis and Treatment of Calcium Pyrophosphate Deposition (CPPD) Disease: A Review. Open Access Rheumatol. 2023;15:33–41. [DOI] [PubMed] [PMC]
49. Cheung HS, Kurup IV, Sallis JD, Ryan LM. Inhibition of calcium pyrophosphate dihydrate crystal formation in articular cartilage vesicles and cartilage by phosphocitrate. J Biol Chem. 1996;271: 28082–5. [DOI] [PubMed]
50. Iqbal SM, Qadir S, Aslam HM, Qadir MA. Updated Treatment for Calcium Pyrophosphate Deposition Disease: An Insight. Cureus. 2019;11:e3840. [DOI] [PubMed] [PMC]