

# Overview on Prevalence, Etiology, and Management of Calcium Pyrophosphate Deposition (CPPD) Disease: Review article

Samirah Mohammed A Nasib \*, Raed Mohammed M Alkhudaiby

Internal medicine, Jeddah, Saudi Arabia

\*Corresponding author: Samirah Mohammed A Nasib, Email: [Sameeranaseeb@hotmail.com](mailto:Sameeranaseeb@hotmail.com), Phone no.: +966 53 521 5002

## ABSTRACT

**Background:** Calcium pyrophosphate deposition disease (CPPD) is a crystal arthropathy caused by the deposition of calcium pyrophosphate crystals in joints and soft tissues, resulting in inflammation and joint damage. Asymptomatic CPPD, osteoarthritis with CPPD, acute CPPD crystal arthritis (formerly pseudogout), and chronic CPPD crystal inflammatory arthritis are all clinical manifestations of CPPD. Aging, trauma, and osteoarthritis are all established risk factors for CPPD.

**Objective:** Our review article discusses several elements of CPPD. It goes through how CPPD can develop as various types of arthritis, which can be symptomatic or asymptomatic. **Methods:** PubMed, Google Scholar, and Science Direct were scoured for information on Arthritis, CPPD, Etiology of CPPD and Management of CPPD. The authors also reviewed the relevant literature, however only the most recent or comprehensive studies from 2000 to 2023 were included. Documents written in languages other than English have been disregarded because translation resources are inadequate. Unpublished articles, oral presentations, conference abstracts, and dissertations were not included because they were not considered to be part of major scientific projects. **Conclusion:** They occur with a wide range of clinical symptoms and can provide diagnostic and treatment issues. It is the third most prevalent kind of inflammatory arthritis. The clinical picture and radiographic/laboratory data are used to make a diagnosis. The detection of CPP crystals in synovial fluid is the gold standard for diagnosing CPPD. CPP crystals cause inflammation, resulting in articular tissue injury. The standard tests utilized in the diagnostic workup are briefly discussed. The origin of the sickness, traditional and novel approaches for the treatment of CPPD are discussed. Although being one of the most prevalent types of inflammatory arthritis, CPPD has received little attention, and evidence-based treatment guidelines are limited.

**Keywords:** Calcium pyrophosphate deposition disease (CPPD), Calcium pyrophosphate crystal, Arthritis, Chondrocalcinosis, Inflammation, NSAIDs.

## INTRODUCTION

Calcium pyrophosphate deposition disease (CPPD) is a kind of crystal deposition arthropathy that affects the synovium and per-articular tissues [1]. The term "pseudogout syndrome" was initially used by Kohn in 1962 to refer to acute synovitis attacks brought on by crystals caused by the illness CPPD [2]. CPPD-related arthritis is the third most frequent inflammatory arthritis, with an increasing frequency with age [3]. Various terminology are used to characterize the various manifestations of CPPD. Asymptomatic to acute or chronic inflammatory arthritis are possible clinical presentations. CPPD crystal-related arthropathies can present with a variety of clinical symptoms, which can make diagnosis difficult due to diagnostic ambiguity, which further confuses doctors, researchers, and patients [4].

According to the European Alliance of Rheumatology (EULAR), there are at least four clinical presentations: 1- Asymptomatic CPPD, 2-OA with CPPD, 3- Acute CPP crystal arthritis and 4-Chronic CPP inflammatory crystal arthritis. Pseudo-polymyalgia rheumatic (pseudo-PMR), pseudo-neuropathic arthropathy, and tumoral CPPD are among the others documented in a literature. An international data and expert-driven effort is now working on new classification criteria to establish CPPD classification criteria. While CPP disease is defined as arthritis induced by calcium pyrophosphate (CPP)

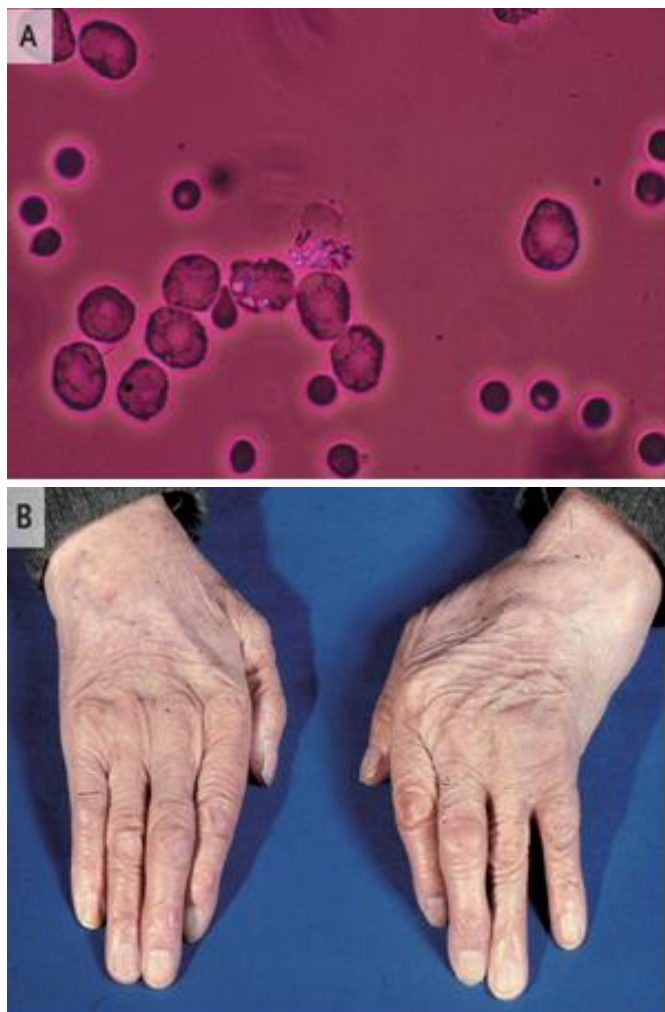
crystals (Figure 1A) and chondrocalcinosis (CC) has been defined as cartilage calcification determined by imaging or histological techniques. While, CC is most usually caused by CPP crystals, it is not limited to this illness and may present as a coincidental discovery or coexist with structural alterations that mimic OA [5, 6].

High blood calcium levels and alterations in the cartilage matrix have been linked to CPPD. Both the etiology of CPPD and the mechanism of crystal deposition's beginning are mostly unknown and hotly discussed in the literature. Idiopathic, metabolic, genetic, and posttraumatic CPPD causes can be divided into four groups. Hemochromatosis, hyperparathyroidism, hypophosphatemia, hypomagnesaemia, and hypothyroidism are all associated with an increased incidence of calcium pyrophosphate deposition. Despite efforts to identify a cause, the majority of cases with CPPD remain idiopathic. This illness has not yet been linked to gender, weight, or lifestyle, despite being somewhat more frequent among white people, but it has been linked to age (figure 1B), osteoarthritis, gout, hyperparathyroidism, and metabolic illnesses such as hemochromatosis and hypomagnesaemia [7]. The pathogenic significance of calcium-containing crystals, such as CPPD and basic calcium phosphate, is unclear and contentious [8]. Yet, clinical and experimental findings suggest that these crystals might cause microcrystalline

stress on synoviocytes and chondrocytes, leading to osteoarthritis aggravation [9].

As a result, the treatment of CPPD and its related clinical symptoms is still primarily relied on professional consensus judgment. Acute CPPD treatment is based on gouty arthropathy alternatives and involves a number of medicines such as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and interleukin-1 inhibitors. Chronic CPPD is difficult to treat evidence-based due to a paucity of randomized controlled studies, while hydroxyl-chloroquine, methotrexate, colchicine, and steroids have some low-level evidence [10].

This article describes calcium pyrophosphate deposition disease, as well as the genesis, prevalence, and therapeutic options for the management and therapy of CPPD. It also explains inter-professional solutions for enhancing care coordination in patients with calcium pyrophosphate deposition illness.



**Fig.1:** Calcium pyrophosphate deposition (CPPD). A: Using polarized light microscopy, rhomboid birefringent calcium pyrophosphate (CPP) crystals can be detected in this synovial fluid sample collected from a patient with acute CPP crystal arthritis of the wrist. B: A CPPD patient's hands reveal edema in the left wrist and the third proximal interphalangeal joint of the left hand [11].

**Etiology:** Calcium pyrophosphate deposition disease is thought to be caused by an imbalance in pyrophosphate production and pyro phosphatase levels in diseased cartilage. Pyrophosphate interacts with calcium to create CPP, which accumulates in the synovium and surrounding tissues. Many comorbidities have been linked to CPPD. Hyperparathyroidism was found to have the most favorable correlation with CPPD in several investigations, followed by gout, osteoarthritis, rheumatoid arthritis, and hemochromatosis. It is also connected with osteoporosis, hypomagnesaemia, chronic renal disease, and calcium supplementation. Calcium pyrophosphate deposition is thought to activate the immune system, resulting in inflammation and additional soft tissue damage [12].

**Prevalence:** The majority of people with acute calcium pyrophosphate deposition arthritis are above the age of 65 years. Thirty to fifty percent of the patients are beyond the age of 85 years. A cross-sectional research of 2,157 CPPD cases in US veterans found a point prevalence of 5.2/1000, with an average age of 68 years and 95% male predominance. CPPD is uncommon in people under the age of 60. According to a large cross-sectional investigation, the general population has a 4% crude prevalence of radiographic chondrocalcinosis. According to an Italian population study of the elderly, CPP crystal arthritis is the third most frequent inflammatory rheumatic condition, with a frequency of 0.42%. In Europe and the United States, CPPD illness appears to afflict 4 to 7% of the adult population. The epidemiology of CPPD is still poorly known, in part because substantial investigations with clinically relevant CPPD are lacking. Prevalence studies, for example, have frequently relied only on radiographic evidence of chondrocalcinosis. Chondrocalcinosis is likely to identify only around 40% of individuals with clinically significant CPPD illness, and it is especially difficult to observe on radiography in patients with substantial cartilage loss. Chondrocalcinosis, on the other hand, can occur in people who do not have arthritis and is made up of a non-CPP mineral, typically di-calcium phosphate di-hydrate. The bulk of research on the prevalence and comorbidities of CPPD are small, underpowered, or depend only on a radiological description of the condition [13, 14].

#### **Clinical presentations of CPPD:**

The precipitation of CPP crystals in joint connective tissues such as fibrocartilage or hyaline cartilage and synovial membrane causes CPPD-related arthropathies. They might be asymptomatic or show as various clinical symptoms. The term "CPPD" was coined by the European League Against Rheumatism (EULAR) to encompass all phenotypes of calcium pyrophosphate occurrences [5].

**Acute CPP crystal arthritis:** The most well-known kind of CPPD illness is acute CPP crystal arthritis (or pseudo-

gout). Patients usually have an abrupt onset of mono-articular or oligo-articular arthritis. Warmth, erythema, and swelling in and around the afflicted joint characterize the inflammatory response to CPP crystals, and the clinical presentation is sometimes indistinguishable from acute gouty arthritis or septic arthritis. The pattern of joint involvement, together with other results, may give a valuable signal regarding the occurrence of acute CPP crystal arthritis. The most often implicated joint is the knee, followed by the wrist and acute podagra in the first metatarsophalangeal joint is uncommon. Acute CPP crystal arthritis frequently causes systemic symptoms such as fevers, chills, and constitutional symptoms. Unlike acute gouty arthritis attacks, which normally last a few days to a week, acute CPPD disease bouts can last weeks or months. Acute CPP crystal arthritis accounts for roughly 25% of cases [15].

**Asymptomatic Chondrocalcinosis:** Chondrocalcinosis is a pathological calcification of cartilage that is commonly encountered in the elderly (> 80 years) and those with a history of joint trauma. Asymptomatic chondrocalcinosis is typically discovered on an accidental X-ray in a symptom-free patient. In general, it has little clinical importance. However, according to a survey, individuals with radiographic chondrocalcinosis are more likely to report joint symptoms when compared to a control group of same age who do not have chondrocalcinosis [16].

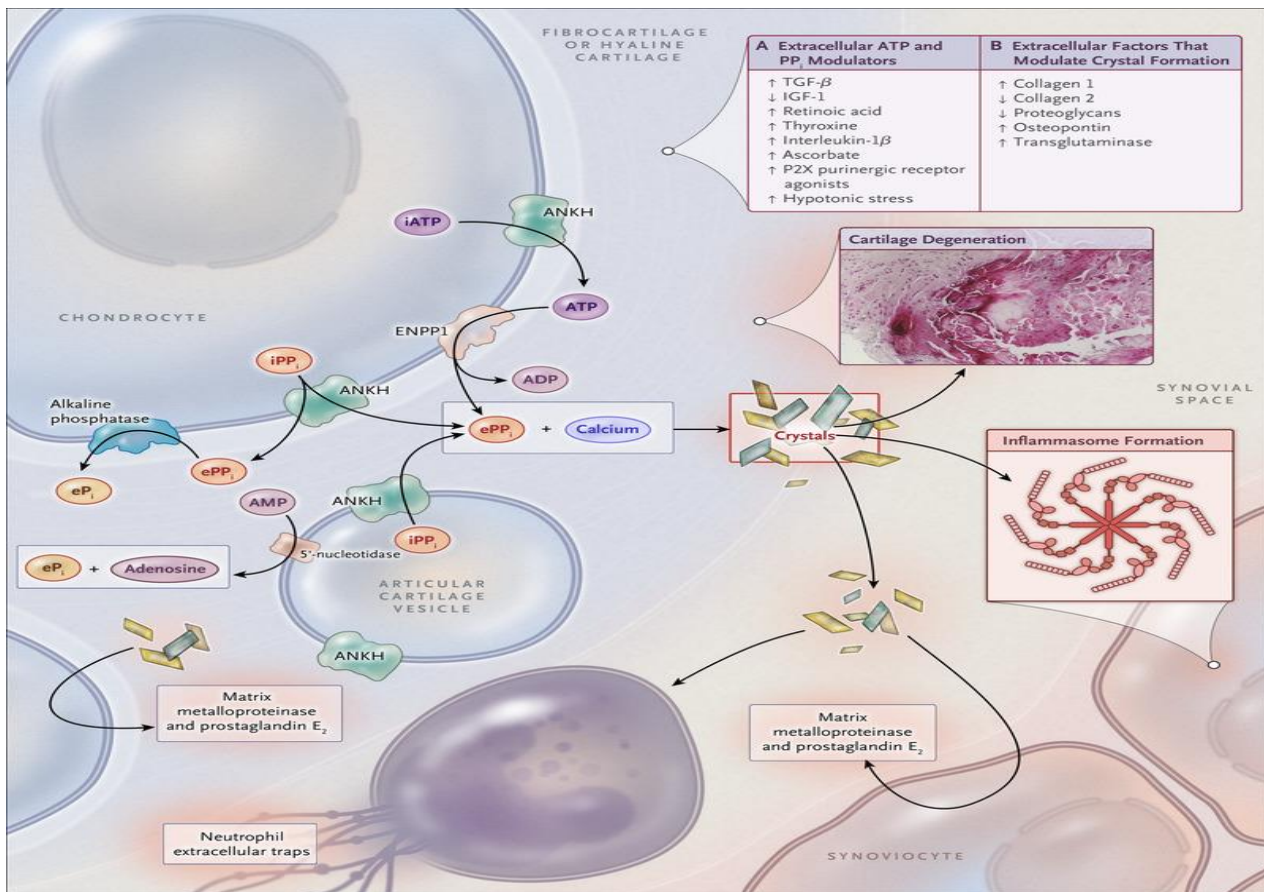
**Chronic CPP Crystal Inflammatory Arthritis:** There are numerous clinical manifestations of chronic CPP crystal arthritis. The majority of individuals suffer from poly-articular arthritis, which is similar to osteoarthritis. Flares of inflammatory signs and symptoms, as well as extremely severe articular destruction, generally distinguish this osteoarthritis-like arthritis from conventional osteoarthritis. The involvement of joints such as the glen-humeral joint, the wrist, and the meta-carp-phalangeal joints, which are seldom affected by normal osteoarthritis, should raise the possibility of CPPD illness. A less common type of poly-articular CPPD illness is similar to rheumatoid arthritis. Individuals with this illness have chronic inflammatory arthritis affecting both major and small joints. Flares in this phenotypic variation of CPPD illness frequently affect joints in a sequential manner, and involvement is less symmetric than in rheumatoid arthritis. McCarty calculated that the chronic degenerative poly-articular type of CPPD illness accounts for nearly 50% of patients [17].

**Pseudo-OA:** On the origin of pseudo-OA, two competing ideas have been offered. It is unclear if primary OA predisposes to the formation of CPPD or CPP crystals trigger the process by causing joint injury. CPP crystal deposition is detected in injured joint cartilage in advanced stages of OA. It commonly affects the knee, meta-carp-phalangeal (MCP) joints, wrist, and shoulder.

Current research has shown the existence of another sort of crystal in OA cartilage termed basic calcium phosphate (BCP), which is unique to OA, hence, their presence can prove this specific form of CPPD. It has been discovered that the concentration of BCP crystals corresponds closely with the severity of OA, consequently, medicines targeting BCP crystals can produce promising effects [18]. Several clinical manifestations of CPPD sickness that are less prevalent have been identified. CPP crystals are frequently seen in spinal tissues such as intervertebral discs and spinal ligaments. Crowned dens syndrome is characterized by CPP crystal deposition around the C2 vertebra and presents as abrupt severe neck pain, fever, and elevated levels of inflammatory markers. This illness is frequently misdiagnosed as meningitis or sepsis. CPP crystals have also been linked to a severe degenerative arthritis comparable to neurotropic (Charcot's) arthropathy. Tumoral deposits of CPP crystals occur infrequently in soft tissues, where they can cause significant tissue damage and may be misdiagnosed as malignancies. Chondrocalcinosis is found in an unknown number of people who do not have clinical arthritis [11].

#### **Pathogenesis of CPPD Disease:**

Calcium pyrophosphate crystal formation is mostly dependent on the presence of extracellular inorganic pyrophosphate (PPi), which is primarily generated by chondrocytes in the joints. Extracellular PPi is created largely by two mechanisms. The first mechanism is the ankylosing protein, which a membrane transporter, transports intracellular PPi across the chondrocyte membrane. The second is degradation of ATP into AMP and PPi by nucleoside triphosphate pyro-phosphohydrolase ecto-enzymes present on chondrocyte plasma membranes and matrix vesicles in cartilage matrix. Many variables have been discovered to influence chondrocytes' synthesis of extracellular PPi. The transforming growth factor- $\beta$  (TGF- $\beta$ ) is a powerful activator of extracellular PPi. TGF- $\beta$ -induced extracellular PPi synthesis is inhibited by intracellular growth factor-1 (IGF-1). Cartilage intermediate layer protein, which prevents IGF-1 from suppressing TGF- $\beta$ , has been reported to rise with age in cartilage tissue. Patients with OA may have elevated PPi levels due to chondrocyte insensitivity to IGF-1, resulting in CPPD deposition in OA-damaged joints. Alkaline phosphatase (ALP) and inorganic pyro phosphatases hydrolyze PPi to form inorganic phosphate. Hypophosphatase, a congenital disorder caused by an ALPL mutation, causes an excess of inorganic pyro phosphatases to accumulate. Excess iron in hemochromatosis inhibits ALP, resulting in an excess of inorganic pyro-phosphatase. Similarly, Mg works as a cofactor for the ALP enzyme, and its absence causes an excess of inorganic pyro-phosphatase to accumulate (Figure 2) [19, 20].



**Fig.2:** Pathophysiological Features of CPPD Disease [11].

**Familial CPPD:**

Although most CPPD illness is sporadic, several families with preterm or severe CPPD have been recorded across the world. CPPD illness in individuals under the age of 60 should initiate a search for similarly affected family relatives. Remarkably, five patients with afflicted relatives were included in the initial reports of CPPD sickness in Hungary. Chondrocalcinosis occurs in the majority of afflicted individuals prior to the beginning of clinical degenerative arthritis, indicating that CPP crystals have a causal role in joint destruction. Two genetic loci have been linked to familial CPPD. Mutations at the CCAL2 locus on chromosome 5p result in an autosomal dominant pattern of inheritance (due to a gain of function of the ANKH protein) and lend credence to ANKH's role in the etiology of CPPD illness. The CCAL1 locus on chromosome 8 has yet to be completely identified. In a family with early-onset osteoarthritis and chondrocalcinosis, a gain-of-function mutation in the TNFRSF11B (osteoprotegerin) gene was recently reported [11].

**Diagnosis:**

**Crystal Analysis:** Under compensated PLM, synovial fluid aspiration and crystal analysis remain the gold standard for assisting diagnosis. Although brilliant field microscopy can identify the typical shape of CPP crystals, such as rhombuses, thin bars, and parallelepipeds,

compensated PLM may also characterize birefringence. CPP crystals, which frequently show no birefringence, can be detected phagocytized, and are frequently found inside vacuoles, can necessitate rigorous examination of synovial fluid for proper diagnosis. Since crystals might be poorly dispersed, more time is sometimes required for detailed analysis of the sample to obtain a diagnosis. The proper identification of CPP crystals in a suspected case's synovial fluid is a crucial aid in establishing the right diagnosis. Nevertheless, to prevent reporting a false-negative result, CPP analysis must be performed by a suitably skilled clinician or laboratory scientist. To date, studies have revealed variability in the proper identification of CPP crystals by doctors and laboratory scientists. The observers' devotion and training are important elements, and a lack of experience may be a barrier to diagnosis [21].

**Conventional X-Ray (Imaging Techniques):** The characteristic appearance of chondrocalcinosis with punctate and linear densities in hyaline and/or fibrocartilage aids in diagnosis. The presence of chondrocalcinosis substantially supports the diagnosis of CPPD, nevertheless, standard radiography only identifies 40% of clinically significant CPPD. The articular cartilage of the knee, particularly the medial meniscus and the patella-femoral 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, are typical sites of such deposits. When deposits are dense and distinct, diagnosis is simple, however, when deposits are faint or aberrant, diagnosis might be difficult. Many of the characteristics of CPPD are asymmetric in nature, but traits uncommon for primary OA include involvement of non-weight bearing joints or, in the hands, notably the inter-carpal and MCP joints. While not the ideal screening technique, radiographs nonetheless give useful information and can help to rule out alternative possibilities. Screening using four radiographs may be a good beginning point: an anteroposterior (AP) view of both knees (ideally not standing), an AP image of the pelvis for visibility of the symphysis pubis and hips, and a posteroanterior (PA) view of each hand to include the wrists. If these views show no indication of crystal formations, further research is unlikely to be productive. Indeed, Ryan and McCarty provided numerous diagnostic criteria, including diagnosis based on a combination of the typical radiographic appearance and CPPD crystal detection in synovial fluid <sup>[10]</sup>.

**Ultrasound (Imaging Techniques):** The age of ultrasonography (US) has transformed the screening of peripheral joints. A targeted ultrasonic scanning technique for the diagnosis of gout and CPPD in individuals with acute mono-oligoarthritis showed high accuracy. Radiographs have limited sensitivity for detecting CPP deposition, and synovial fluid analysis is not frequently conducted, therefore CPP crystals, if present, may be missed, contributing to under-diagnosis. The US enables the very sensitive and quick identification of microcrystal aggregates in a variety of anatomic areas. It is also non-invasive and can be utilized to direct joint aspiration in low-fluid-collection areas. The knee is the anatomic location with the highest likelihood of CPPD crystal aggregates. According to the outcome measures in rheumatology working group (OMERACT), the overall diagnostic accuracy of US in detecting CPPD at the medial meniscus of the knee was 75%, with a sensitivity of 91% and a specificity of 59%. OMERACT has also defined ultrasound criteria for the diagnosis of CPPD at additional locations, including the triangular fibrocartilage of the wrist, the acromioclavicular joint, and the hip labrum, however they exhibit worse intra-observer concordance among professional ultrasonographers than the knee joint. A recent study found that in individuals with acute mono/oligoarthritis, a targeted US scanning procedure of the knees and wrists bilaterally plus the target joint had a diagnosis accuracy of > 90% for crystal arthritis. Many investigations comparing US and X-ray have also been conducted. Gutierrez & colleagues compared US and conventional x-ray to a gold standard established by the presence of

synovial fluid CPP crystals identified by PLM in the afflicted joint to diagnose CPPD. Ultrasound revealed meniscal chondrocalcinosis in at least one knee in 90% of CPPD patients, compared to 83.7% with conventional radiography. Another research comparing US and X-ray at the wrist joint found that US correctly detected CC in 93.7% of instances, whereas radiography correctly identified CC in 53.1% of cases. The sensitivity and specificity of US for the diagnosis of CPPD were 94% and 85%, respectively, and for radiography were 53.1% and 100%, respectively, despite the fact that the patient numbers were limited, with 32 CPPD patients and 26 controls. In the right hands, US may be a huge help in diagnosing CPPD. Nevertheless, when conducted by the physician during clinical evaluation, knowledge and competence are necessary to appropriately identify CPP deposits <sup>[10]</sup>.

**Computed Tomography (CT) and MRI:** CT is more accurate than traditional radiography, especially for the axial skeleton and deep anatomic regions. It aids in the diagnosis of crowned dens syndrome (CDS), an under-recognized illness characterized by occipital discomfort and neck stiffness owing to CPPD, which can frequently be accompanied by elevated inflammatory markers and fever. It does, however, expose the patient to ionizing radiation and cannot be conducted at the patient's bedside. Furthermore, CT does not distinguish between different crystal deposition diseases, such as CPPD and basic calcium phosphate (BCP) crystals. However, a newer emerging technology known as dual emission CT (DECT) can distinguish differences in the composition of various crystals and can be color-coded. A recent study found that DECT had a sensitivity of over 90% to distinguish between BCP and CPP calcifications when compared to Raman spectroscopic analysis, the gold standard for BCP identification. MRI has traditionally been thought to be of little use in the diagnosis of CPPD because calcifications in articular tissues are difficult to see. Although high-field MRI has demonstrated advantage over conventional MRI in identifying crystal deposits, it is seldom used in practice since US and plain film radiography have been researched in more depth and are more accessible <sup>[10]</sup>.

**Other imaging techniques:** Additional imaging modalities, both in the research phase and not often utilized to examine joints, may contribute to our diagnostic arsenal in CPPD. A study of diffraction-enhanced synchrotron imaging (DEI) in cadaveric knee joints was recently published by **Li et al.** <sup>[22]</sup>. This approach is based on radiographic technology that uses x-ray refraction and scatter rejection features that traditional radiography does not have, resulting in extremely detailed pictures of articular cartilage. While, these excellent investigations were conducted at a synchrotron facility and this approach is not currently viable in real patients, this technology eloquently illustrates chondrocalcinosis.

When modified for human usage, similar approaches might be valuable in diagnostics [23].

#### **Risk Factors and Associated Conditions:**

CPPD illness is definitely an ageing disease, and it is uncommon in persons under the age of 60. Chondrocalcinosis is seen in 44% of people over the age of 84 in radiographic exams of the knee, pelvis, and wrist; the frequency increases with each decade above 60. Prior joint trauma is also a substantial risk factor for CPPD. This relationship is most seen in the knee meniscus. According to one study, chondrocalcinosis occurred decades after meniscectomy in 20% of the knees treated with surgery, compared to just 4% of the contralateral knees not treated with surgery. CPPD is frequently seen in the setting of osteoarthritis. Because the clinical manifestations of CPPD illness and osteoarthritis coincide, diagnostic mimicry may explain part of the connection. While osteoarthritis and CPPD illness are both quite frequent in the elderly, co-occurrence through coincidence may explain the link. Yet, because there is significant evidence that CPP crystals have a negative effect on articular tissues, it is evident that CPP crystals aggravate cartilage injury and are likely to induce such damage. The latter theory is supported by studies of familial CPPD disease in which crystal formation precedes joint degeneration, as well as the co-occurrence of radiographic and clinical features of CPPD disease and osteoarthritis in joints that are normally spared in osteoarthritis, such as the metacarpophalangeal, radio carpal, and glen-humeral joints. A number of metabolic disorders are well-known risk factors for CPPD illness. In individuals with hypophosphatemia, a congenital illness characterized by low functional levels of alkaline phosphatase, CPPD disease develops from a high ratio of inorganic pyrophosphate to phosphate ions. Hyperparathyroidism is firmly linked to CPPD illness. While hyperparathyroidism changes calcium metabolism, the persistence of CPPD illness years after hyperkalemia has been corrected implies a complicated connection between both disorders. Hemochromatosis is also significantly linked to CPPD and may be produced by iron's inhibitory influence on pyro phosphatases or by elevated parathyroid hormone levels in cartilage. Hypomagnesaemia is also a risk factor for CPPD illness, and the Gitelman's variation of Bartter's syndrome is thought to be caused by hypomagnesaemia. Magnesium improves CPP crystal solubility and functions as a cofactor for pyro phosphatases [11].

CPP crystals have been seen in the synovial fluid [24] of up to 5% of gout patients, supporting the concept that both illnesses share shared local and systemic risk factors. Since arthritis may be the presenting symptom in individuals younger than 60 years old with CPPD illness, testing and evaluation for all of these related metabolic conditions is recommended. We propose iron

investigations, which include measuring iron, transferrin, and ferritin levels, as well as blood calcium, alkaline phosphatase, and parathyroid hormone levels. Acute CPPD episodes are common in the setting of acute sickness, joint damage, or the postoperative phase, notably following Para thyroidectomy or hip fracture repair [25].

There are no documented dietary correlations with CPPD. A number of drugs can cause acute CPP crystal arthritis. Although this relationship is somewhat debatable, intra-articular hyaluronan preparations may cause acute CPP crystal arthritis. Loop diuretics, granulocyte-macrophage colony-stimulating factor, and pamidronate are also probable correlations. Since inorganic pyrophosphate is a powerful regulator of normal and pathologic mineralization, patients with CPPD illness may have various modest signs of defective tissue mineralization. Patients with familial CPPD illness have elevated amounts of inorganic pyrophosphate in their lymphocytes and skin fibroblasts, indicating a systemic condition. **Abhishek et al.** [26] discovered that individuals with non-familial chondrocalcinosis had lower cortical bone mineral density and greater rates of vascular and soft-tissue calcification than those without.

#### **Management:**

**Interventions and treatment options:** The basic aims of CPPD treatment are to reduce inflammation and prevent acute flares. Asymptomatic chondrocalcinosis patients should not be treated. Exercise, weight loss, and the use of joint support devices can help CPPD patients with concomitant arthritis minimize joint stiffness and preserve mobility.

**Conventional drugs for treatment and prevention of acute flares related to CPPD:** Clinical investigations suggest treating acute CPPD arthritis episodes in the same manner as real gout is treated. Joint aspiration is used to decrease pressure within the joint in rare circumstances of considerable swelling and discomfort; it has both diagnostic and therapeutic significance. Non-pharmacological treatments such as applying cold packs and resting can help temporarily reduce pain and swelling. Anti-inflammatory medicines such as NSAIDs and glucocorticoids continue to be the basis of therapy. They can stop acute episodes and reduce pain on rare occasions, but they cannot change the course of the disease. Colchicine is still the standard medication for avoiding recurring bouts of acute flares [18].

**Non-steroidal Anti-inflammatory Drugs (NSAIDs):** To decrease inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin are administered in low dosages. If an acute flare is not treated, the symptoms might continue much longer. NSAIDs work by inhibiting an enzyme known as cyclooxygenase (COX), which is essential in the formation of inflammatory chemicals known as

prostaglandins. Low-dose NSAIDs not only stop the present attack but also assist to lessen the incidence of future acute flares. However, despite their usefulness, NSAIDs are widely recognized for several potential adverse effects and medication interactions, and it is thus suggested that they be discontinued as soon as the pain decreases. Long-term NSAID usage can cause kidney damage and peptic ulcers, which can be avoided by monitoring renal function (blood creatinine) and prescribing proton pump inhibitors (PPIs). In individuals who are at high risk of upper GI bleeding and renal or hepatic failure, NSAIDs should be avoided [18].

**Corticosteroids:** When NSAIDs and colchicine are contraindicated, corticosteroids (CS) are the medication of choice [1]. CS are extremely effective and fast-acting; results can be seen within 24 hours of starting medication. It is given orally, intravenously, or intramuscularly. In senior patients with many comorbidities, an intra-articular route is recommended because to its localized effect and greater tolerance, although an intra-articular CS is only beneficial when arthritis is oligo-articular, affecting one or two joints. Oral steroids, such as prednisone or methylprednisolone, are most effective in individuals with severe poly-articular episodes. Long-term usage of oral steroids is usually linked with several systemic adverse effects such as weight gain, recurrent infections owing to immunosuppression, acne, muscular weakness, anxiety, and osteoporosis. Oral CS can potentially worsen pre-existing diabetes by causing hyperglycemia. Intramuscular triamcinolone injection was found to be an effective therapy for 14 individuals who presented with an acute flare of pseudo-gout in a prospective investigation. Consequently, when NSAIDs are contraindicated and joint involvement is poly-articular, an intramuscular steroid injection might be regarded an acceptable alternative treatment in individuals with an acute flare of CPPD [27].

**Colchicine:** Colchicine (COL) has been shown to work like a charm in averting acute flares. It operates by interfering with the polymerization of microtubules, which is required for neutrophil migration to the site of inflammation, as well as inhibiting the assembly of the inflammasome complex. Since COL is very caustic when delivered intravenously and its extravasation can cause irritation and tissue necrosis, it is best administered orally. Nevertheless, in the event of acute gastritis, when NSAIDs and oral colchicine should be avoided, intravenous colchicine pre-diluted with 0.9% NaCl has been shown to be as effective [28].

#### **Other treatment considerations:**

Some patients do not react to the typical medications listed above. As a result, various disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and hydroxyl-chloroquine, as well as other medications, have been evaluated to treat refractory instances of CPPD

arthritis based on small-scale randomized controlled studies.

**Methotrexate:** While the mechanism of action of methotrexate (MTX) in the treatment of CPPD is unknown, it is thought to be due to its anti-inflammatory and immunosuppressive effects. Because of its immunosuppressive properties, MTX is especially beneficial in pseudo-rheumatic presentations and poly-articular arthropathies with repeated acute bouts. A research on five individuals revealed that it had anti-inflammatory properties. Their acute CPPD was resistant to standard therapy, which included NSAIDs and steroids. Low-dose MTX (5-20 mg/week) effectively decreased pain, joint swelling, and blood levels of inflammatory biomarkers. Another observational research on ten patients found that MTX was effective in treating acute inflammation in individuals with treatment-resistant CPPD who were not responding to conventional therapy [18, 29].

#### **Interleukin-1 Receptor Antagonists (Anakinra):**

Anakinra is an IL-1R antagonist that has been shown to be effective in auto-inflammatory illness. It is administered as a daily subcutaneous injection of 100 mg. Anakinra has been used to treat acute CPP crystal arthritis in many case studies. A recent systematic literature analysis revealed 76 individuals who had anakinra treatment, the majority of them had recurring acute CPP arthritis. All patients were noted as being intolerant or not responding well to traditional therapy. The vast majority (68.9%) were given a three-day course of therapy. A total of 21.6% were treated for 5-9 days, while 9.5% were treated for 30-365 days. Physician-reported effectiveness was obvious, with C-reactive protein (CRP) levels reduced in 73% of patients and physician VAS improved in 70.3% of instances. These trials were entirely retrospective, non-blinded, and had no comparison arm, putting them at a high risk of bias. However, anakinra is a viable treatment choice for people with refractory CPPD. To better characterize the best dose and duration of anakinra in the treatment of CPPD, more randomized controlled trials with well-defined illness populations are required. When it comes to treating and preventing acute CPP arthritis flares, oral NLRP3 inflammasome inhibitors like dapansutrile constitute a potentially developing class of medicines. Dapansutrile revealed an acceptable safety profile and effectiveness in lowering target joint pain in individuals with acute gout flares in an open-label, dose-adaptive, proof-of-concept phase 2a study. In theory, such medicines might be used to treat and prevent acute CPP arthritis. Because they are administered orally rather than subcutaneously, these medications would have an advantage over anakinra. Future research should look on the use of oral NLRP3 inhibitors in the treatment of crystal arthritis, especially acute CPP arthritis [30].

**Magnesium:** A double-blind, placebo-controlled randomized clinical trial (RCT) on magnesium carbonate in individuals with chronic CPPD arthropathy found that it reduced joint pain and stiffness. In vitro investigations have revealed that magnesium (Mg) may solubilize CPP crystals while also inhibiting their crystal formation. Apart from that, Mg can be administered as a supplement in individuals with CPPD caused by Mg insufficiency [31].

**Hydroxychloroquine:** Hydroxychloroquine (HCQ) is an anti-malarial medication that may also be used as an adjuvant. Various mechanisms of action for HCQ in the context of CPPD therapy have been proposed, all of which indicated its capacity to immune-modulate and decrease inflammation. HCQ inhibits T-cell activation and lowers the production of different cytokines (interleukin-1, interleukin-6 and tumor necrosis factor-alpha). It has also been shown in animal studies to suppress the activity of matrix metallo-protease. In a six-month double-blind experiment, HCQ was proven to be effective especially for chronic CPPD-related arthropathies [30].

**Hyaluronan:** Sodium hyaluronan is a visco-supplement that has been authorized for the treatment of OA. It is a naturally occurring synovial fluid component that permits bones to glide easily against each other. When traditional medications fail to enhance joint mobility and function, hyaluronan is injected intra-articularly to promote joint mobility and function. In general, it is well tolerated by patients with no side effects. Nevertheless, some individuals have been observed to suffer acute pseudo-septic arthritis hours after receiving hyaluronic acid injections [18, 29].

**Radiosynovectomy:** A modest double-blind, self-controlled research with 15 patients with bilateral knee CPPD included radiation synovectomy. Participants were given yttrium-90 with CS (triamcinolone hexacetonide 20 mg) intra-articularly in one knee and saline plus CS in the contralateral control knee. At 6 months, there were significant decreases in pain, inactivity stiffness, joint line soreness, and effusion in the treated knees compared to controls. Another small research of 49 individuals, 26 of whom were allocated to the treatment arm, looked at synovial destruction by laser irradiation. The comparator arm was given diclofenac by mouth. Response was defined as a pain reduction of 60-100% in 69.2% of the treatment group and 60.8% of the diclofenac group. The diclofenac group experienced gastrointestinal adverse effects, but the radiation synovectomy group experienced none [30].

**Surgery:** Pseudo-neuropathic arthropathy, in particular, may benefit from the surgical replacement of injured joints with a prosthesis (arthroplasty) to cure the deformity [18, 29].

#### **Prophylaxis against recurrent attacks:**

Colchicine, at 0.6 mg twice daily, may be beneficial as a preventive medication in individuals with recurrent

pseudo-gout bouts. Those who have three or more episodes per year may benefit from prophylactic medication. If gastrointestinal discomfort or diarrhea occur, a dosage reduction to 0.6 mg once daily, or every other day, may be beneficial. Oral NSAIDs with gastro protective therapy can also be explored. In individuals with renal insufficiency or liver illness, both NSAIDs and colchicine should be administered with care [32].

#### **FUTURE DIRECTIONS:**

This prevalent type of arthritis has received little attention in the medical community around 55 years after its original report. Diagnostic difficulties lead to under-diagnosis, but more importantly, there is a scarcity of specialized and effective treatments for afflicted people. Although no proven disease-modifying drugs are available, we can improve patient outcomes by carefully diagnosing CPPD illness with a complete synovial fluid investigation and initiating suitable treatment measures [11].

#### **CONCLUSION**

CPPD is an umbrella name for all clinical subgroups of CPP crystal-related arthropathies. Because industrialized nations' demography are ageing, the incidence and prevalence of CPPD are projected to rise. Acute mono-arthritis is the most prevalent manifestation, however individuals can also present with OA and rheumatoid arthritis. CPPD arthritis can be related with metabolic and endocrine problems. The initial hurdle is determining the accurate diagnosis, however synovial fluid aspiration and evaluation under PLM remains a vital aid in diagnosis. The detection of CPP crystals in microscopy is used to diagnose CPPD. Despite their limitations, x-ray and US remain the most relevant imaging tools in CPPD, with chondrocalcinosis accumulation in hyaline cartilage or articular cartilage being particularly important results. Approaches to treatment are based on clinical experience and, in most situations, extrapolated from gouty arthritis. If CPPD is linked to an underlying condition, specialized treatment should be initiated. NSAIDs, CSs, and COL are still the mainstay medications for treating acute pseudo-gout, however they have been shown to be less effective in treating chronic instances. Because no particular therapeutic method has been established to yet that can change the condition or stop CCP crystal production, larger-scale research investigations and clinical trials on additional possible medications are needed.

#### **REFERENCES**

1. **Rosales-Alexander JL, Balsalobre Aznar J, Magro-Checa C (2014):** Calcium pyrophosphate crystal deposition disease: diagnosis and treatment. *Open Access Rheumatol.*, 6: 39-47.
2. **Mccarty J, Kohn N , Faires J (1962):** The significance of calcium phosphate crystals in the synovial fluid of arthritic patients. The " pseudogout syndrome" I. Clinical aspects. *Annals of Internal Medicine*, 56 (5 Part 1): 711-737.



3. **Musacchio, E, Ramonda, R, Perissinotto, E, Sartori, L, Hirsch, R, Punzi, L, Crepaldi, G (2011):** The impact of knee and hip chondrocalcinosis on disability in older people. The ProVA Study from northeastern Italy. *Annals of the rheumatic diseases*, 70 (11): 1937-1943.
4. **Bencardino J , Hassankhani A (2003):** Calcium pyrophosphate dihydrate crystal deposition disease. *Seminars in musculoskeletal radiology*, 7 (3): 175–185. <https://doi.org/10.1055/s-2003-43228>
5. **Zhang W, Doherty M, Bardin T, Barskova V, Guerne P , Jansen T , Pascual E (2011):** European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Annals of the rheumatic diseases*, 70 (4): 563-570. doi:10.1136/ard.2010.139105
6. **Tedeschi S , Pascart T, Latourte A, Godsave C, Kundakci B, Naden R , Abhishek A (2022):** Identifying potential classification criteria for calcium pyrophosphate deposition disease: item generation and item reduction. *Arthritis Care & Research*, 74 (10): 1649-1658.
7. **Abhishek A (2014):** Calcium pyrophosphate deposition. *British Journal of Hospital Medicine*, 75 (4): C61-C64.
8. **Gamon E, Combe B, Barnetche T, Mouterde G (2015):** Diagnostic value of ultrasound in calcium pyrophosphate deposition disease. A systematic review and meta-analysis. *RMD open*, 1 (1): e000118.
9. **Tanikawa H, Ogawa R, Okuma K, Harato K, Niki Y, Kobayashi S, Nagura T (2018):** Detection of calcium pyrophosphate dihydrate crystals in knee meniscus by dual-energy computed tomography. *Journal of Orthopaedic Surgery and Research*, 13: 1-6.
10. **Cowley S, McCarthy G (2023):** Diagnosis and Treatment of Calcium Pyrophosphate Deposition (CPPD) Disease: A Review. *Open access rheumatology: research and reviews*, 15: 33–41. <https://doi.org/10.2147/OARRR.S389664>
11. **Rosenthal A , Ryan L (2016):** Calcium Pyrophosphate Deposition Disease. *The New England journal of medicine*, 374 (26): 2575–2584. <https://doi.org/10.1056/NEJMra1511117>
12. **Zamora E, Naik R (2023):** Calcium Pyrophosphate Deposition Disease. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK540151/>
13. **Neame R , Carr A , Muir K, Doherty M (2003):** UK community prevalence of knee chondrocalcinosis. Evidence that correlation with osteoarthritis is through a shared association with osteophyte. *Annals of the rheumatic diseases*, 62 (6): 513-518.
14. **Ramonda R, Musacchio E, Perissinotto E, Sartori L, Punzi L, Corti M , Crepaldi G (2009):** Prevalence of chondrocalcinosis in Italian subjects from northeastern Italy. The Pro. VA (PROgetto Veneto Anziani) study. *Clin Exp Rheumatol.*, 27 (6): 981-4.
15. **Masuda I, Ishikaw A, Koichi R (1988):** Clinical features of pseudogout attack. a survey of 50 cases. *Clinical Orthopaedics and Related Research*®, 229: 173-181.
16. **Ellman M , Levin B (1975):** Chondrocalcinosis in elderly persons. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 18 (1): 43-47.
17. **McCarty D (1974):** Diagnostic mimicry in arthritis-patterns of joint involvement associated with calcium pyrophosphate dihydrate crystal deposits. <https://bestpractice.bmj.com/topi...>
18. **Iqbal S , Qadir S, Aslam H et al. (2019):** Updated Treatment for Calcium Pyrophosphate Deposition Disease: An Insight . *Cureus*, 11(1): e3840. doi:10.7759/cureus.3840
19. **Joshi A, Siva C (2018):** Magnesium disorders can cause calcium pyrophosphate deposition disease: A case report and literature review. *European journal of rheumatology*, 5 (1): 53–57. <https://doi.org/10.5152/eurjrheum.2017.16116>
20. **Whyte M (1994):** Hypophosphatasia and the role of alkaline phosphatase in skeletal mineralization. *Endocrine reviews*, 15 (4): 439-461.
21. **Berendsen D, Neogi T, Taylor W , Dalbeth N, Jansen T L (2017):** Crystal identification of synovial fluid aspiration by polarized light microscopy. An online test suggesting that our traditional rheumatologic competence needs renewed attention and training. *Clinical rheumatology*, 36: 641-647.
22. **Li J, Wilson N, Zelazny A, Meyer J, Zhong Z, Muehleman C (2013):** Assessment of diffraction-enhanced synchrotron imaging for cartilage degeneration of the human knee joint. *Clinical Anatomy*, 26 (5): 621-629.
23. **Miksanek J, Rosenthal A (2015):** Imaging of calcium pyrophosphate deposition disease. *Current rheumatology reports*, 17 (3): 20. <https://doi.org/10.1007/s11926-015-0496-1>
24. **Jaccard Y , Gerster J , Calame L (1996):** Mixed monosodium urate and calcium pyrophosphate crystal-induced arthropathy. A review of seventeen cases. *Revue du Rhumatisme (English ed.)*, 63 (5): 331-335.
25. **Harato K, Yoshida H (2015):** Pseudogout at the knee joint will frequently occur after hip fracture and lead to the knee pain in the early postoperative period. *Journal of Orthopaedic Surgery and Research*, 10 (1): 1-4.
26. **Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M (2014):** Association between low cortical bone mineral density, soft-tissue calcification, vascular calcification and chondrocalcinosis.a case-control study. *Annals of the Rheumatic Diseases*, 73 (11): 1997-2002.
27. **Roane D , Harris M , Carpenter M , Finger D , Jarek M , Alloway J , Drehmer T (1997):** Prospective use of intramuscular triamcinolone acetonide in pseudogout. *The Journal of Rheumatology*, 24 (6):1168-1170.
28. **Zhang W, Doherty M, Pascual E, Barskova V, Guerne P , Jansen T , Bardin T (2011):** EULAR recommendations for calcium pyrophosphate deposition. Part II: management. *Annals of the rheumatic diseases*, 70 (4): 571-575.
29. **Romera M (2002):** Effect of intraarticular hyaluronate injections in chondrocalcinosis: comment on the article by Martens. *Arthritis & Rheumatism*, 46 (3): 847-847
30. **Stack J, McCarthy G (2021):** Calcium pyrophosphate deposition (CPPD) disease - Treatment options. *Best practice & research. Clinical rheumatology*, 35 (4): 101720. <https://doi.org/10.1016/j.berh.2021.101720>
31. **Doherty M, Dieppe P (1983):** Double blind, placebo controlled trial of magnesium carbonate in chronic pyrophosphate arthropathy. *Annals of the Rheumatic Diseases*, 42 (1): 106.
32. **Ivory D, Velázquez C (2012):** The forgotten crystal arthritis: calcium pyrophosphate deposition. *Missouri medicine*, 109 (1): 64–68.