Exploration of Musculoskeletal Diseases

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Calcium pyrophosphate deposition (CPPD) disease: a review of pathophysiology, clinic and diagnosis

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Academic Editor: Jürgen Braun, Ruhr Universität Bochum, Germany
Received: March 18, 2025 **Accepted:** July 21, 2025 **Published:** August 11, 2025

Cite this article: Dilek G, Kalcık Unan M, Nas K. Calcium pyrophosphate deposition (CPPD) disease: a review of pathophysiology, clinic and diagnosis. Explor Musculoskeletal Dis. 2025;3:100799. https://doi.org/10.37349/emd.2025.100799

Abstract

Calcium pyrophosphate deposition (CPPD) disease represents a crystal-induced arthropathy characterized by the deposition of calcium pyrophosphate dihydrate crystals within the articular joints and adjacent soft tissues. The manifestation of CPPD can present in a variety of clinical forms, including acute pseudogout episodes, chronic inflammatory arthritis, a variant associated with osteoarthritis, and the "crowned dens" syndrome; alternatively, it may be identified incidentally during radiological assessments. The condition is predominantly observed in individuals aged over 60 years, with its incidence escalating in correlation with advancing age. The presence of CPP crystals activates the innate immune response, subsequently eliciting an inflammatory cascade. Among the mechanisms implicated in this inflammatory process are the activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3) inflammasome, and the secretion of matrix metalloproteinases. The elevation of pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, and pro-IL-1β exacerbates the inflammatory state within the affected joint. Although there is a marginally higher prevalence of CPPD in females, this gender disparity is not deemed statistically significant. CPPD may also manifest in younger and middle-aged populations, necessitating vigilance regarding potential metabolic disorders or hereditary conditions in such cases. The diagnosis of CPPD is predominantly established through a combination of clinical assessment and imaging modalities. The definitive diagnostic criterion involves the identification of CPP crystals in synovial fluid utilizing polarized light microscopy. Clinically, CPPD can be misdiagnosed as rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), infectious arthritis, and other crystal-related arthropathies. The recently developed classification criteria by ACR/EULAR in 2023 are intended to enhance the precision of diagnosis. This review seeks to encapsulate the pathophysiology, clinical presentation, and diagnostic approaches related to CPPD disease, informed by contemporary literature.

Keywords

Calcium pyrophosphate deposition (CPPD), crystals, inflammatory arthritis

Introduction

Calcium pyrophosphate deposition (CPPD) disease was first described in the 1960s and is a disease that affects mainly the elderly population today. Its prevalence is reported to be between 4–7% among individuals aged over 60 years. In addition to advancing age, osteoarthritis (OA) represents a significant risk factor for the development of CPPD. However, the precise etiology remains elusive, it is postulated that antecedent joint injuries and surgical interventions may contribute to its onset [1]. Furthermore, genetic abnormalities and metabolic disorders, including hemochromatosis, primary hyperparathyroidism, hypomagnesemia, and hypophosphatasia, have been identified as additional factors associated with CPPD [2]. There exists a potential genetic susceptibility in CPPD patients who manifest symptoms at a younger or middle age. The condition can precipitate episodes of inflammatory arthritis that are characterized by pain, functional impairment, elevated temperature, and edema in the involved joint, or it may present asymptomatically. This ailment, colloquially referred to by designations such as crystal arthropathy, chondrocalcinosis, and pseudogout, was formally classified as CPP crystal arthritis by EULAR in 2011 [3]. In accordance with the nomenclature established by EULAR, the term CPPD serves as an umbrella designation for CPP crystals. Chondrocalcinosis is defined as radiographic evidence of cartilage calcification. Clinically, CPPD disease is categorized into four distinct classifications: asymptomatic CPPD, CPPD associated with OA, acute CPPD crystal arthritis, and chronic CPPD inflammatory arthritis [3]. In 2023, ACR/EULAR developed classification criteria for CPPD disease [4]. This review aspires to encapsulate the pathophysiological mechanisms, clinical manifestations, and diagnostic approaches for CPPD disease, drawing on recent scholarly literature. We searched PubMed and Google Scholar for articles and reviews in English. A literature search was done on PubMed using keywords including “CPPD”, cartilage calcification, crystal arthritis, inorganic pyrophosphate (PPi), and search for clinical studies, clinical trials, reviews, and meta-analyses.

Pathophysiology

Inflammation and arthritis stem from the immune response triggered by the accumulation of CPP crystals. The inflammatory mechanism shares similarities with that observed in gouty arthritis, which involves monosodium urate. Nevertheless, CPP crystals tend to aggregate in fibrocartilage and hyaline articular cartilage and may also be observed extrajointally as a consequence of cartilage metaplasia [2]. In this section, the crystallization of CPP and the cellular mechanisms underlying the inflammatory response will be examined.

PPi metabolism and formation of CPP crystals

CPP crystals arise within enzyme-rich vesicles located in the pericellular matrix of chondrocytes within the extracellular milieu of synovial fluid. These vesicles are designated as articular cartilage vesicles (ACVs). ACVs are enriched with the enzymes nucleotide pyrophosphohydrolase (NTPPH) and tissue nonspecific alkaline phosphatase (TNAP), which are implicated in the biosynthesis of CPP crystals. Inorganic phosphate (Pi) is characterized by its low energy state and comprises a singular phosphate ion (PO_4^{3-}). It plays a pivotal role in cellular energy transfer and is an integral component of the structure of adenosine triphosphate (ATP). PPi is composed of two phosphate groups linked by a high-energy bond ($P_2O_7^{4-}$). It is essential for the biosynthesis of ribonucleic acid (RNA) and deoxyribose nucleic acid (DNA). PPi undergoes hydrolysis to yield Pi via an enzymatic reaction. An imbalance between PPi and Pi within the cellular environment presents a significant risk factor for the crystallization of CPP, with an elevated extracellular PPi (ePPi) ratio being instrumental in the precipitation of CPP crystals. In the context of synovial fluid, PPi is present in both fibrocartilage and hyaline cartilage [1]. Extracellular ATP serves as the primary precursor of PPi synthesized by chondrocytes, with its production being modulated by the enzyme ectonucleotide

pyrophosphatase/phosphodiesterase 1 (ENPP1). Chondrocytes subjected to mechanical stress exhibit an elevated synthesis of ATP, which concomitantly enhances the production of PPi. The ePPi generated by chondrocytes acts as an inhibitor of calcium mineralization. The accumulated ePPi interacts with calcium ions to facilitate the formation of CPP crystals [2]. TNAP is integral to the hydrolysis of ATP, adenosine diphosphate (ADP), and adenosine monophosphate (AMP) while concurrently modulating Pi levels through the hydrolysis of PPi to Pi. Ecto-5'-nucleotidase (CD73) facilitates the hydrolysis of AMP to Pi, and its deficiency is correlated with an elevation in TNAP enzyme activity (Figure 1). Transforming growth factor-beta (TGF-β), growth factors, and cytokines significantly influence the synthesis of PPi. TGF-β initiates the production of PPi by upregulating the expression levels of ENPP1 and the PPi transport regulator [progressive ankylosis protein (ANKH)]. Furthermore, TGF-β contributes to the augmentation of PPi, exhibiting effects analogous to those of epidermal growth factor (EGF) [2]. It is widely recognized that mutations in the *ANKH* gene, which are situated within the locus located on chromosome 5p, designated as the CCAL2 locus, correlate significantly with joint deterioration. The ANKH protein functions as a transmembrane protein and is hypothesized to enhance extracellular CPP crystal formation by facilitating the passage of PPi across the cellular membrane in the context of CPPD disease [2]. ACVs are small vesicles found in the pericellular matrix of the articular cartilage. These vesicles carry enzymes for ATP and PPi metabolism and play a role in CPP crystal formation by affecting cartilage mineralization [2].

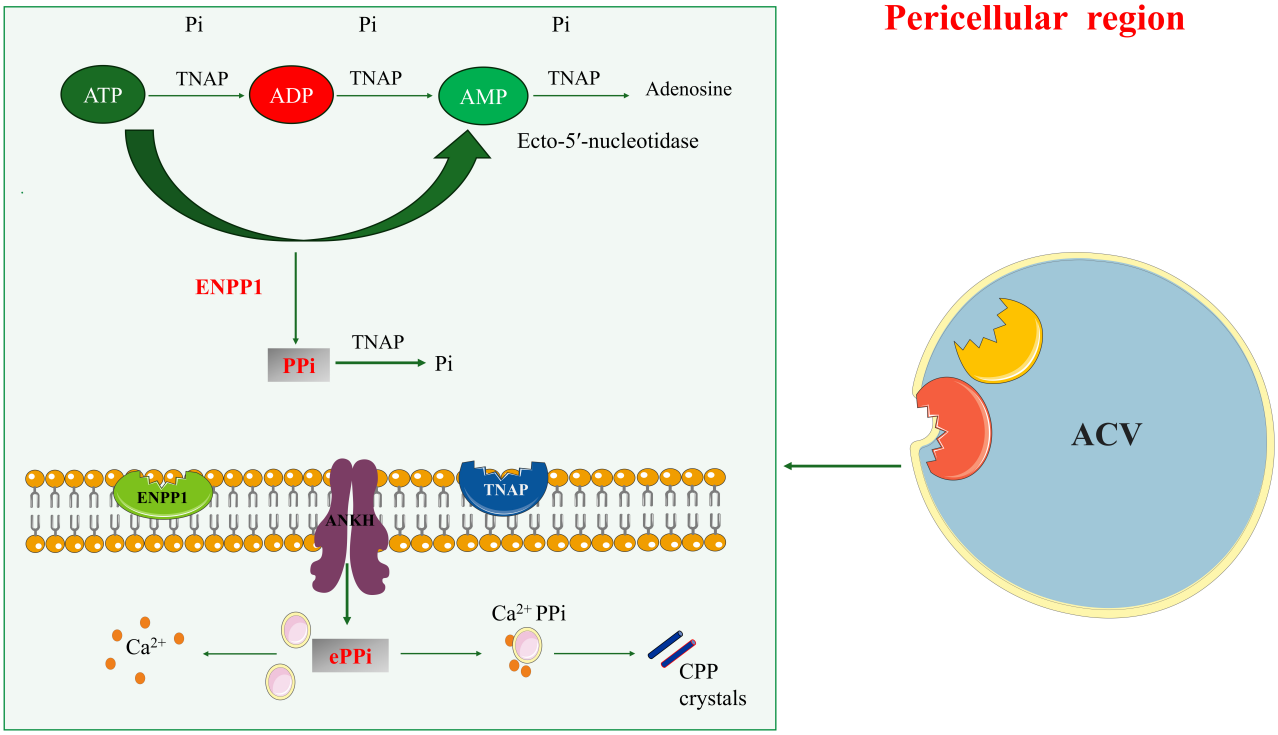

Figure 1. Formation mechanism of CPP crystals. ACV are membrane-bound vesicles located within the pericellular matrix of chondrocytes. This specific region serves as the site for the crystallization of CPP. The enzyme TNAP facilitates the hydrolysis of ATP, ADP, and AMP while also modulating the levels of Pi through the hydrolysis of PPi into Pi. The enzyme CD73 catalyzes the conversion of AMP to Pi. ENPP1 is involved in the hydrolytic conversion of ATP to yield PPi. The ANKH protein is instrumental in regulating the efflux of PPi from the cellular environment. In conjunction with ePPi and calcium minerals, it contributes to the formation of CPP precursors within the pericellular matrix. ACV: articular cartilage vesicle; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ANKH: progressive ankylosis protein; ATP: adenosine triphosphate; CD73: ecto-5'-nucleotidase; CPP: calcium pyrophosphate; ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1; ePPi: extracellular PPi; Pi: inorganic phosphate; PPi: inorganic pyrophosphate; TNAP: tissue nonspecific alkaline phosphatase. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

CPP crystal-induced inflammatory pathway

CPP crystals elicit a stimulation of the innate immune system, subsequently provoking an inflammatory response. Chondrocytes serve as the repository for CPP crystals within the pericellular matrix vesicles. Indeed, the synthesis of PPi by chondrocytes constitutes a normal physiological process. When the

equilibrium between Pi and PPi is perturbed in favor of PPi, the formation of CPP crystals occurs, potentially leading to the development of CPPD, which may manifest as arthritis [2]. Two types of crystals have been detected in the synovial fluid of CPPD patients. They have been described as monoclinic (needle-shaped) and triclinic (rectangular rods). Small size (due to easier phagocytosis) and monoclinic crystals (larger area to interact with inflammatory mediators) have been reported to be more inflammatory [5]. It is known that CPP crystals stimulate synovial fibroblasts, activate the release of matrix metalloproteinase-8 (MMP-8) and interleukin-6 (IL-6), and cause inflammation [6]. CPP crystals activate synovial cells by direct phagocytosis or by interaction of the cell membrane and crystals [7]. Macrophages play an active role in synovial inflammation. Phagocytosis of insoluble CPP crystals by macrophages causes lysosomal rupture, release of reactive oxygen species (ROS) in the body, potassium release, ATP release, an increase in nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3), and activation of the inflammasome complex [8]. NLRP3 is sensitive to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and activates caspase-1. Caspase-1 initiates the inflammatory cascade by increasing IL-1β production [9]. The inflammatory cytokine that is the major cause of the inflammatory process is IL-1β. In addition, CPP crystals activate the inflammasome via nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) and trigger the release of IL-1β [10, 11]. Nevertheless, CPP crystals possess the capacity to directly activate Toll-like receptors (TLRs), predominantly TLR2 and TLR4, as well as nucleotide-binding oligomerization domain-like receptors (NLRs) located on the cellular membrane, thereby instigating an inflammatory reaction through the activation of NF-κB [9]. The engagement of CPP crystals with the cellular membrane culminates in the activation of intracellular signaling cascades, including extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 MAPK, c-Jun N-terminal kinase (JNK), and other MAPKs, along with the induction of genes that facilitate the activation of transcription factors such as activator protein 1 and NF-κB. The secretion of IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and pro-IL-1β is significantly augmented [5] (Figure 2). CPP crystals have also been reported to cause inflammation via neutrophil extracellular traps (NETs) formation [6].

Epidemiology

The epidemiological CPPD disease exhibits a significant correlation with variables such as age, sex, genetic susceptibility, and the presence of comorbid conditions. Nevertheless, given that the diagnosis of CPPD is primarily established through radiological methods, the acquisition of epidemiological data is inherently influenced by the specific radiological techniques employed and their implementation. According to existing literature, the incidence of CPPD in both Europe and North America has been documented to be approximately 7–13% in individuals around the age of 60. Furthermore, it has been noted that the prevalence of this condition escalates to 50% in individuals over the age of 80, with no discernible differences observed between genders [9]. An extensive cohort study of veterans in the United States reported a prevalence of CPPD of 5.2/1,000, a mean age of 68, and a male predominance [12]. Although radiological knee chondrocalsinosis was reported as 7% in adults in cohort studies, it was stated that this rate could increase to 10.4% when pelvis and knee radiographs were evaluated and to 13.7% when hand radiographs were added to the evaluation [13]. Ultrasonography (US) and computed tomography (CT) modalities exhibit superior sensitivity in the identification of chondrocarcinoma prevalence, which may be augmented through the application of these diagnostic techniques. A recent investigation revealed that the prevalence of CPPD in adults presenting with knee pain was documented at 9.7% in hyaline cartilage and 22.4% in fibrocartilage when assessed via US. Furthermore, within the same research endeavor, the prevalence rates were ascertained to be 23.3% in hyaline cartilage and 46.7% in fibrocartilage among patients aged 80 years and older [14]. In patients who underwent spinal trauma, chondrocalcinosis was reported in CT scans at the sternoclavicular joint (17.2%) and at the anterior, posterior, or lateral atlanto-axial joint (12.5%) [15]. The prevalence of acute or recurrent CPPD attacks is unclear. A hospital-based study in the US reported an annual incidence of 11.4% of patients with acute CPPD [16]. In 102 patients with acute CPPD reported in Korea, the recurrence of CPPD attacks was reported as 19% within 46 weeks [9].

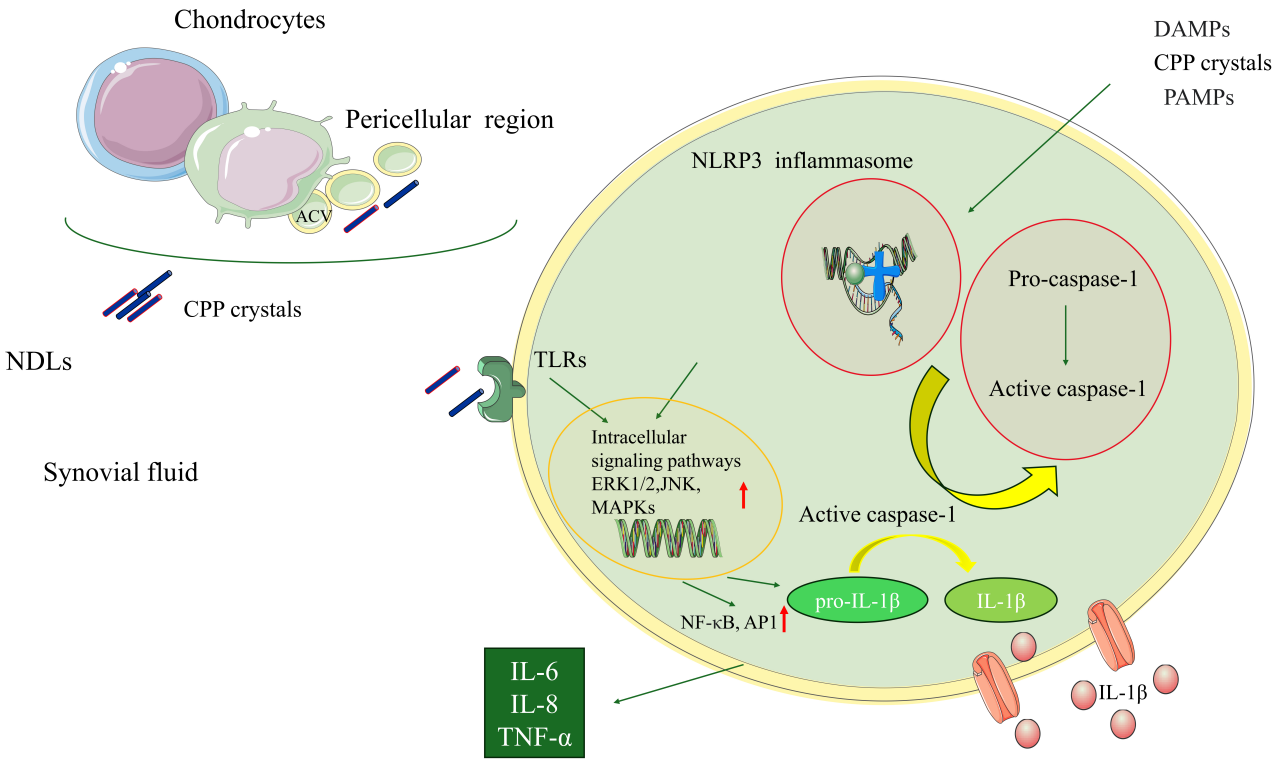

Figure 2. Mechanism of inflammation caused by CPP crystals. CPP crystals possess the capability to directly activate the immune system through TLRs situated on the cellular membrane. The stimulation of TLRs and NLRs within the cellular environment leads to the activation of ERK1/2, p38, and JNK proteins, which subsequently enhance intracellular signaling pathways. The release of pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, and pro-IL-1β is augmented as a consequence of the activation of NF-κB and AP1. Following phagocytosis, CPP crystals stimulate the formation of the NLRP3 inflammasome complex within the cytosolic compartment. This process leads to the proteolytic conversion of pro-caspase-1 into its active form, caspase-1, which then facilitates the maturation of pro-IL-1β into its active form, IL-1β. The cytokines IL-1β, IL-6, IL-8, and TNF-α, once released from the cell, contribute to the inflammatory processes occurring within the synovial fluid. ACV: articular cartilage vesicle; AP1: activator protein 1; CPP: calcium pyrophosphate; DAMPs: damage-associated molecular patterns; ERK1/2: extracellular signal-regulated kinases 1 and 2; IL-6: interleukin-6; JNK: c-Jun N-terminal kinase; MAPKs: mitogen-activated protein kinases; NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3; NLRs: nucleotide-binding oligomerization domain-like receptors; PAMPs: pathogen-associated molecular patterns; TLRs: Toll-like receptors; TNF-α: tumor necrosis factor-alpha. Image adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

CPPD disease risk factors

Age constitutes the principal risk factor for CPPD. Given that OA is a pathological condition whose prevalence escalates with advancing age, it is posited that a frequent correlation exists between OA and CPPD. Empirical studies utilizing the US have indicated that both the leukocyte count and the prevalence of synovitis are significantly elevated in patients with CPPD in comparison to those with OA. It is hypothesized that the presence of CPPD may expedite the deterioration of OA. Furthermore, it has been documented that secondary OA predominantly manifests in the scaphotrapeziotrapezoid joint as a consequence of CPPD [17]. Previous joint trauma increases the risk of CPPD. It has been reported that the prevalence of CPPD increases, especially in patients who have undergone meniscus surgery [12]. A case-control study reported that knee joint malalignment, such as varus deformity, was a risk factor for the development of CPPD at an early age [18].

Gitelman syndrome represents a renal tubular disorder characterized by a deficiency in magnesium levels. Magnesium functions as an inhibitor of the TNAP enzyme, which catalyzes the hydrolysis of PPi to Pi. This deficiency leads to the accumulation of CPP, particularly within the axial skeleton. Furthermore, chronic renal insufficiency exacerbates the likelihood of CPPD. Additional conditions such as primary hyperparathyroidism, hereditary hemochromatosis, hypophosphatasia, familial hypocalciuric hypocalcemia, and a range of other metabolic disorders are also recognized as being associated with CPPD [12].

In a particular investigation, it was documented that 30% of individuals afflicted with hemochromatosis exhibited chondrocalcinosis, and it was noted that this condition demonstrated a positive correlation with serum age, ferritin, and parathyroid hormone concentrations [19].

Genetic factors

Although familial CPPD attributable to genetic predisposition is infrequently observed, instances of polyarticular involvement and disease manifestation prior to the age of 55 may occur in affected individuals. Empirical data suggest that mutations in the *ANKH* gene, along with other genetic loci such as CCAL1, are correlated with familial chondrocalcinosis. Furthermore, there exists substantiation that mutations within the *ANKH* gene augment the production of ePPi, and this genetic alteration has been implicated in familial CPPD. A research investigation conducted in the United Kingdom identified the E490del mutation in the *ANKH* gene as being associated with chondrocalcinosis and the onset of premature OA [20]. The human homeostatic iron regulatory protein (*HFE*) gene mutation has been reported to be associated with CPPD with polyarticular involvement [21]. Mutations in the *TNFRSF11B* gene, which encodes osteoprotegerin (OPG), have been found to be associated with OA-associated chondrocalcinosis [22].

It is imperative that serum calcium, ferritin, magnesium, phosphorus, alkaline phosphatase, and thyroid-stimulating hormone assessments be requisitioned for patients diagnosed with CPPD at a relatively early age, taking into account the concomitant conditions that may coexist. Furthermore, should the situation warrant, these individuals ought to be evaluated for potential genetic mutations.

CPPD clinical presentations

CPP crystals accumulate in the cartilage and fibrocartilage in the joint tissue, and these crystals are also seen in the synovium. CPP crystals may continue to exist asymptomatically, or they may appear in various clinical forms. EULAR has classified the clinical forms of CPPD under 4 main headings [23]:

1. Asymptomatic CPPD: Asymptomatic CPPD is characterized by the lack of observable clinical manifestations. The accumulation of CPP crystals within the joints may be identified incidentally through various imaging modalities. The wrist is the most commonly affected joint after the knee [24]. Chondracalcinosis is reported to occur at a rate of nearly 50% in people over the age of 80.
2. Acute CPPD: Acute crystal-induced arthritis may manifest as monoarticular, oligoarticular, or polyarticular conditions. It is predominantly observed in the context of knee and wrist arthropathies. Additionally, involvement of the ankle, elbow, shoulder, and metacarpophalangeal (MCP) joints is also reported. Various triggers such as trauma, acute infectious processes, pharmacological interventions (including thiazide and loop diuretics, proton pump inhibitors, bisphosphonates, and chemotherapeutic agents), as well as predisposing factors, can precipitate episodes of this condition [25]. Clinical acute synovitis presents with symptoms such as increased temperature, swelling, and stiffness. Acute arthritis can be confused with gouty arthritis, septic arthritis, and rheumatoid arthritis (RA). Involvement sites, laboratory tests, and anamnesis may be important in differential diagnosis [26]. In contrast to gouty arthritis, CPPD disease predominantly impacts the knee joints, and systemic manifestations are observed with greater frequency. Arthrocentesis may be required, particularly for the purpose of differentiating between septic arthritis and other conditions. The duration of acute arthritis episodes in CPPD may exceed that observed in gouty arthritis. Typically, individuals remain asymptomatic in the interictal periods between episodes [23]. Crowned dens syndrome is a rare condition; it can be seen in 5% of CPPD. Cervical pain, stiffness, and acute phase elevation are observed. It can be confused with meningitis and infective spondylodiscitis. Crowned-shaped calcification of the odontoid process is seen. Case series in the literature have generally reported cases over the age of 70 [27]. In elderly people, proximal joint involvement may produce a pseudo-polymyalgia rheumatica (PMR)-like clinical picture [28].

3. CPPD and OA: Structural changes are seen as a result of crystals triggering inflammation within the joint. Joint space narrowing can also be seen in atypical locations for OA. MCP joints, wrists, ankles, shoulders, and elbows may be affected [29]. Also defined as pseudo-OA. Basic calcium phosphate (BCP) crystals are more associated with OA and are directly proportional to structural damage. Chondrocalcinosis may or may not be present in the affected joint. Cysts and osteophytes are often detected on imaging. CPPD can cause structural damage similar to Charcot arthropathy. Bilateral structural damage is seen in the ankle joints. The absence of diabetes or neuropathy and the detection of chondracalcinosis on imaging are important for the diagnosis of CPPD [29]. In an extensive cross-sectional investigation assessing the correlation between OA and chondrocalcinosis, it was determined that knee OA exhibited a significant association with chondrocalcinosis in all remote joints, ankle OA was correlated with chondrocalcinosis in both the knee and MCP joints, and MCP OA demonstrated an association with chondrocalcinosis in the wrist region. Conversely, in the same investigation, no significant relationship was established between hip OA and chondrocalcinosis in the aforementioned distant joints [30].
4. Chronic CPPD: It shows oligoarticular or polyarticular involvement with inflammation. CRP and sedimentation elevation are nonspecific, and differential diagnosis should be made from RA and other inflammatory arthritis. CPPD polyarthritis tends to be less symmetrical than RA. CPP crystals can cause chondroid metaplasia by forming tumor-like calcium deposits, the temporomandibular joint (TMJ), MCP joints, hips, wrists, and cervical spine are most affected [31].

The Outcome Measures in Rheumatology (OMERACT) study group, focusing on CPPD, initiated a research program with the objective of establishing a fundamental domain set for CPPD, founded on the clinical classifications delineated by the EULAR for CPPD, and systematically reviewed 112 clinical investigations conducted pertaining to CPPD. The findings from the review indicated that 47 (42%) of the clinical studies incorporated CPPD in conjunction with OA, 24 studies addressed acute CPPD, and 7 studies focused on chronic CPPD as the principal clinical manifestation. The predominant clinical symptoms documented in the article were joint pain and functional impairment [32].

Differential diagnosis

In the differential diagnosis of CPPD, other crystal arthropathies, OA, PMR, RA, and septic arthritis should be considered. CPPD disease is more common with acute inflammatory attacks than OA. In infectious arthritis, systemic symptoms accompany it, and it is more common in the monoarticular form. Joint fluid culture, cell count, Gram staining, and serological tests are helpful in diagnosis [33]. Acute CPPD arthropathy may be misidentified as RA, and it is not uncommon for both conditions to coexist in patients. A cross-sectional investigation examining the prevalence of CPPD among various rheumatological disorders revealed a significantly elevated incidence of CPPD in patients with seropositive RA in comparison to those with seronegative RA. The findings indicated that a substantial proportion of individuals received a preliminary diagnosis of RA. Furthermore, the research indicated that patients diagnosed with both CPPD and RA exhibited advanced age compared to those diagnosed solely with RA, alongside a notable predominance of females within this cohort. In this study, chondrocalcinosis was identified in all subjects presenting with RA and CPPD, with the wrist joint being the most commonly affected site; additionally, the frequency of OA was ascertained to be elevated in patients with both RA and CPPD at the 2–3 MCP joints when juxtaposed with individuals diagnosed with isolated CPPD [34]. Hydroxyapatite deposition disease (HADD) encompasses the deposition of calcium hydroxyapatite (CHA) and BCP crystals. CHA is predominantly observed in conditions such as calcific tendonitis, peritendinitis, bursitis, and pathological calcification. BCP crystal arthritis is characterized by inflammation in the periarticular region, whereas CPP crystal deposition results in intraarticular inflammation [35].

Diagnosis

CPPD disease can manifest through a spectrum of phenotypic expressions. It may present as acute inflammatory arthritis, chronic arthritis, crowned dens syndrome, or PMR-like symptoms. The disease can

exhibit mono-oligoarticular and polyarticular involvement. It may be misdiagnosed as other forms of inflammatory arthritis, meningitis, or infectious diseases. As with any medical condition, a comprehensive assessment of the patient's history, thorough physical examination, and laboratory analyses are imperative, and a differential diagnosis must be performed with respect to other inflammatory arthropathies. Imaging modalities are instrumental in the diagnostic process. The definitive diagnostic approach for CPPD is synovial fluid analysis.

In 2023, the American College of Rheumatology and the European League Against Rheumatism established classification criteria for CPPD. The initial criteria necessitate at least one instance of joint swelling, elevated temperature, and pain, while the definitive exclusion criteria require that findings can be accounted for by conditions other than CPPD. The qualifying criteria include the presence of crowned dens syndrome and the identification of CPP crystals in the affected joint. The new criteria, which encompass four clinical, one laboratory, and three imaging domains, stipulate that a score of 56 or higher is indicative of CPPD disease. Within this classification framework, factors such as being over 60 years of age, experiencing a characteristic arthritic episode, demonstrating evidence of CPP through imaging, and having a significant number of peripheral joints affected are more strongly associated with CPP. It has been indicated that diagnostic methods such as US, dual-energy CT (DECT), and CT may be utilized in conjunction with conventional radiography for enhanced diagnostic accuracy [4].

Imaging

Conventional radiography is the first-line imaging method for the diagnosis of CPPD due to its ease, accessibility, and low cost. Detection of calcification in the joint cartilage on radiological imaging is important for chondrocalcinosis, but it is not specific. Detection of calcification in the knee joint cartilage has been reported to have high specificity (92%) but low sensitivity (54%) for CPPD [36].

Even if detected in synovial fluid, CPP crystals may not always be detected on imaging if they are not of sufficient density. BCP crystals are found in the typical structure of bones and refer to a trio of calcium phosphate crystals consisting of carbonate-substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate. In pathological conditions, BCP crystals cause inflammation and clinical and radiological appearances as calcific tendonitis and soft tissue accumulation around the joint. It can cause destructive joint damage, such as Milwaukee syndrome [37]. The knee joint, wrist triangular cartilage and lunotriquatral ligament, acetabulum of the hip joint, symphysis pubis, and intervertebral disc and dens involvement may be seen. CPP crystals are mostly located within the joint, but BCP deposits are seen around the joint, as in Milwaukee syndrome [38]. CPP crystals are linear and punctate in the joint. In BCP, a larger and more homogeneous accumulation is observed [39].

US

US is a non-invasive method that is more sensitive than radiography in detecting crystal structures in the joint area. It can be used as a guide in synovial fluid aspiration [29].

The OMERACT initiative documented the US methodology utilized for the diagnosis of CPPD in the knee joint, revealing a sensitivity of 91% and a specificity of 54%. Nonetheless, it was elucidated that both sensitivity and specificity exhibited variability contingent upon the specific anatomical region under examination. The article indicated that sensitivity reached as high as 87% in the medial meniscus, whereas specificity attained a maximum of 92% in the hyaline cartilage of the medial condyle. Consequently, it was posited that a comprehensive assessment of both the medial meniscus and the hyaline cartilage of the medial epicondyle should be conducted in conjunction. Furthermore, the study reported the absence of a statistically significant difference in synovial inflammation between patients with OA and those with concurrent CPPD and OA when utilizing the US technique [40]. In a study examining the prevalence of CPPD in patients with knee pain, they reported that CPPD deposition was detected in fibrocartilage at a younger age than in hyaline cartilage. In the same study, they found fibrocartilage involvement at a rate of 46.7% and hyaline cartilage involvement at a rate of 23.3% in those over the age of 80 [14]. In the literature,

studies comparing the US technique with conventional radiography have reported that US is more sensitive [41, 42]. CPP deposits located within the articular cartilage may be subject to displacement due to joint mobility, and US represents a beneficial modality for evaluating such displacement. The efficacy of the ultrasonographic technique is contingent upon the proficiency of the operator and is unable to differentiate between CPP dihydrate crystals and BCP crystals [38].

CT

CT represents a superior modality for the assessment of deep joints and yields more precise outcomes compared to traditional radiographic techniques. CT serves as an efficacious tool for the differential diagnosis of crowned dens syndrome, particularly in cases characterized by an acute onset of cervical and shoulder discomfort. The detection of linear calcific deposits within the transverse ligament of the atlas, which exhibit a radiographic density less than that of cortical bone, constitutes a hallmark involvement pattern associated with crowned dens syndrome. The manifestation of linear or punctate opacities is observed with diminished density (< 300 Hounsfield Units) utilizing this imaging methodology. It is noteworthy that CPP and BCD crystals remain indistinguishable via CT [4]. DECT represents an advanced imaging modality that facilitates the distinction between CPPD and BCP crystals through the application of a specific color coding system associated with the crystals. DECT effectively identifies both linear and punctate calcifications present within fibrocartilage or hyaline cartilage matrices. Such calcifications exhibit enhanced detectability when utilizing imaging techniques characterized by reduced thickness and lower density (< 300 Hounsfield Units) in contrast to cortical bone structures [43]. In one study, it was reported that the distinction between CPP and BCP could be made with 90% sensitivity using the DECT technique [44].

Synovial fluid analysis

The analysis of synovial fluid ought to be conducted from the appropriate anatomical region utilizing US guidance. The identification of calcium CPP crystals through polarized light microscopy (PLM) is regarded as the gold standard approach for the diagnosis of CPPD, exhibiting a sensitivity and specificity of 95%. The crystalline morphology serves as the primary criterion for diagnosis, with no established threshold pertaining to their quantity. CPP crystals exhibit a morphology akin to a rectangle characterized by slender parallel extensions, and demonstrate birefringence in PLM. Research has indicated that CPP crystals may remain intact for an extended duration of 24 to 48 hours at ambient temperature [45]. Pastor et al. [46] reported that CPP crystals in the synovial fluid could be detected at 100% in heparin and 89% in EDTA at room temperature in 24 hours and at 89% in heparin and 83% in EDTA at refrigerated temperatures. Crystals can sometimes be found inside vacuoles in a phagocytosed form and may not show birefringence, which may lead to false positive results. Therefore, synovial fluid analysis should be performed by experienced clinicians [47].

Conclusions

Although CPPD has been recognized for many years, its clinical diagnosis remains challenging. CPPD presents as a disease spectrum encompassing numerous clinical forms. To better understand the clinical forms, the EULAR has classified the disease under four main headings, and in 2023, the ACR/EULAR developed comprehensive classification criteria for CPPD. Careful consideration of genetic, inflammatory, and infectious causes is crucial for differential diagnosis. The pathophysiology of the disease is associated with CPP crystals stimulating the innate immune system, triggering an inflammatory response; however, this topic remains an open area for medical research. CPPD generally affects the elderly population and will become more prominent in society with increasing life expectancy. Genetic and metabolic diseases should be kept in mind, especially in young patients. Imaging methods such as US, DECT, and CT can be used in the diagnostic process in addition to conventional radiography. However, the demonstration of CPP crystals in joint fluid using PLM is considered the gold standard for disease diagnosis. This article was prepared in light of current literature and clinical research and aims to be helpful to clinicians in understanding the disease and in the diagnosis process.

Abbreviations

ACVs: articular cartilage vesicles

AMP: adenosine monophosphate

ANKH: progressive ankylosis protein

ATP: adenosine triphosphate

BCP: basic calcium phosphate

CHA: calcium hydroxyapatite

CPPD: calcium pyrophosphate deposition

CT: computed tomography

DECT: dual-energy computed tomography

ENPP1: ectonucleotide pyrophosphatase/phosphodiesterase 1

ePPi: extracellular inorganic pyrophosphate

IL: interleukin

MAPK: mitogen-activated protein kinase

MCP: metacarpophalangeal

NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells

NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3

OA: osteoarthritis

OMERACT: Outcome Measures in Rheumatology

Pi: inorganic phosphate

PLM: polarized light microscopy

PMR: polymyalgia rheumatica

PPi: inorganic pyrophosphate

RA: rheumatoid arthritis

TGF-β: transforming growth factor-beta

TLRs: Toll-like receptors

TNAP: tissue nonspecific alkaline phosphatase

US: ultrasonography

Declarations

Author contributions

GD: Writing—original draft, Writing—review & editing. MKU: Investigation, Formal analysis. KN: Conceptualization. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

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