REVIEW ARTICLE

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Calcium pyrophosphate dihydrate deposition disease (chondrocalcinosis): a review

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ABSTRACT

Calcium pyrophosphate dihydrate deposition disease (CPPD) is a metabolic arthropathy characterized by gross calcium pyrophosphate crystals deposition within articular cartilage, in the periarticular and articular tissues. The disease is also called by other names such as pseudogout or chondrocalcinosis. Deposition of calcium pyrophosphate dihydrate crystals provokes an inflammation within the synovial membrane followed by degenerative changes in cartilage and bone. The underlying mechanism for increased intraarticular accumulation of calcium crystals is not known. CPPD is fairly common condition affecting mostly older people. It manifests in three clinical forms: asymptomatic (the most common), acute and chronic. Diagnosis is made on the basis of X-ray or ultrasound examination, but definitive confirmation requires demonstration of calcium pyrophosphate dihydrate crystals in the synovial fluid. Treatment of acute CPPD is similar to treatment of gout attack and consists in physical measures and medication with NSAIDs, colchicine or sometimes steroids. This review summarizes recent findings about the etiopathogenesis, diagnosis and management of CPPD.

KEY WORDS: calcium pyrophosphate dihydrate deposition disease; CPPD; chondrocalcinosis; crystal-induced arthritis

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INTRODUCTION

Calcium pyrophosphate dihydrate deposition disease (CPPD) is a metabolic arthropathy characterized by gross calcium pyrophosphate crystals deposition within articular cartilage, both hyaline and fibrocartilage in the periarticular and articular tissues. The disease is also called by other names such as pseudogout or chondrocalcinosis [1-3]. It is the third most common inflammatory arthritis. Deposition of calcium pyrophosphate dihydrate crystals provokes an inflammation within the synovial membrane followed by degenerative changes in cartilage, bone and tendon sheath. Symptoms and signs, as well the course of CPPD resembles gout, hence its former name – pseudogout. Although the diseases have similar symptomatology, the cause of their occurrence is different. The CPPD prevalence in the general population is around 5-15% and increases with age, so that about 30% of population older than 80 years is affected by this condition [1, 4, 5]. The knee joint is the most commonly involved, followed by shoulder and wrist. Clinical course of CPPD is usually mild and about 70% patients is asymptomatic, while in 25% of cases the disease manifests in acute episodes, in a gout-like form. About 5% of patients with CPPD deposition develops a chronic rheumatoid arthritis-like condition [1-6].

REVIEW AND DISCUSSION

ETIOPATHOGENESIS

The underlying mechanism for increased intra-articular accumulation of calcium crystals is not known.

Basic calcium phosphate (BCP) crystals have been shown to provoke inflammatory and cartilage-damaging responses, similar to sodium urate crystals in gout. Calcium crystals are able to induce an inflammatory response resulting in the production of interleukin IL-1β after nuclear factor-Kb (NF-Kb) activation and through the NLRP3 inflammasome. Inflammatory response induced by monosodium urate, calcium pyrophosphate dihydrate and basic calcium phosphate crystals affects three distinct leukocyte populations: polymorphonuclear cells, monocytes and lymphocytes. Of these three, calcium pyrophosphate dihydrate crystals were found to be the most potent stimulators of inflammatory cytokines [2, 5]. The possible mechanisms leading to development of CPPD are shown in Table 1. **Older people** who have a genetic predisposition are more at risk for developing the condition [1, 2, 6]. An association between CPPD and osteoarthritis has been shown in some studies [3, 7]. Recent epidemiological studies have suggested that CPPD has been associated with an

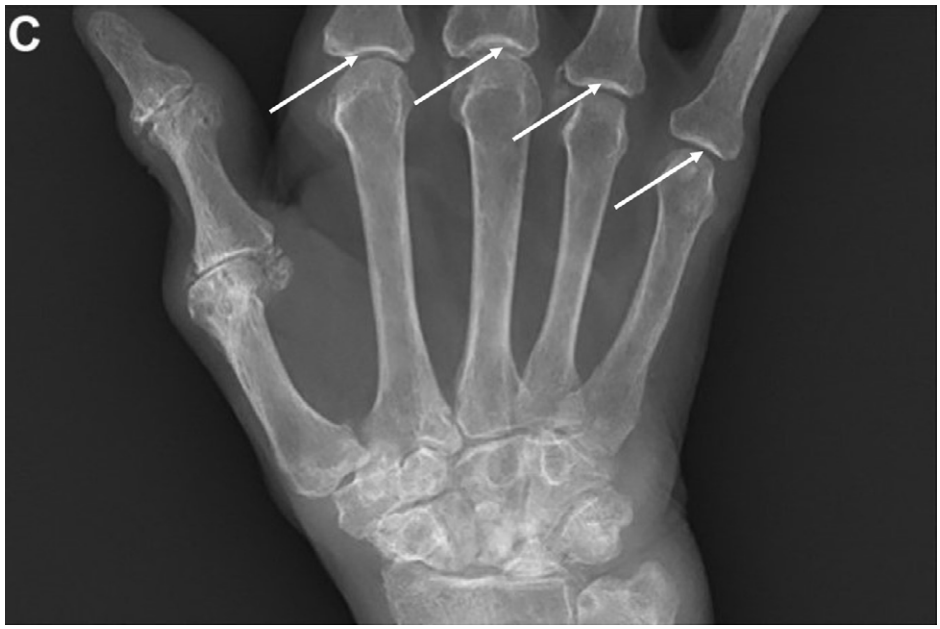

Fig. 1. X-ray of the hand demonstrating CPPD involving the metacarpo-phalangeal joints II-V (white arrows). Note also degenerative changes in the wrist and all joints of the thumb.

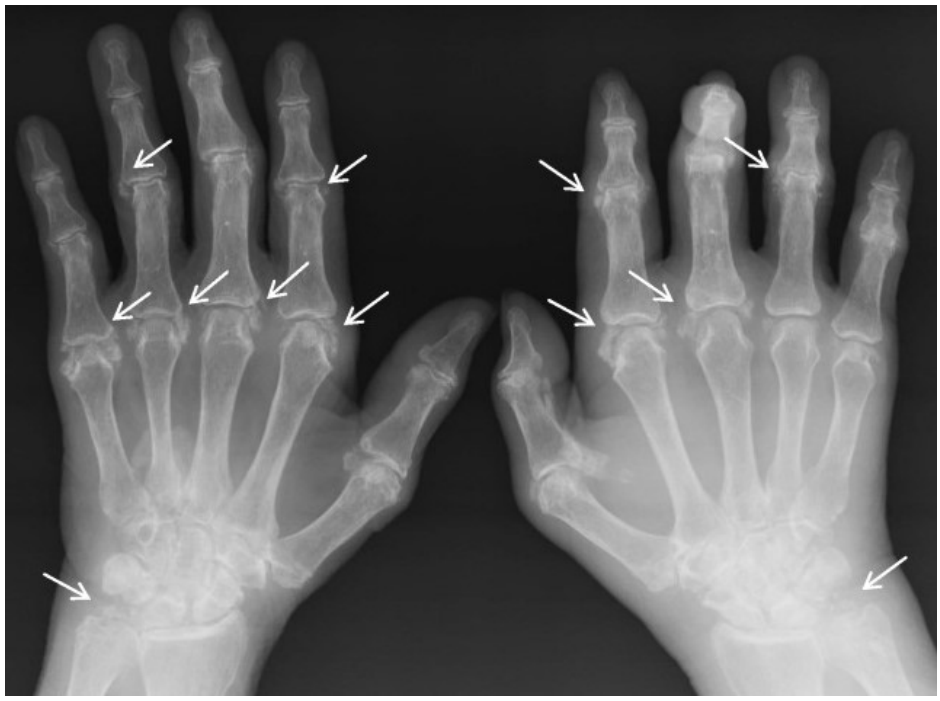

Fig. 2. X-ray of the hand demonstrating CPPD involving the multiple hand joints and ulno-carpal joint (white arrows).

elevated risk for nonfatal cardiovascular disease events, however this association is still in clinical trials [2, 5].

CLINICAL PRESENTATION AND COURSE

The disease manifests in three clinical forms, including:

- Asymptomatic CPPD (the most common, signs present only in images),
- Acute CPPD (self-limited synovitis, formerly known as pseudogout),
- Chronic CPPD

These forms differ from each other in some aspects which will be discussed in this section [1-7]:

a. The asymptomatic form is the most common, constituting about 70% of all cases. In asymptomatic disease, radiological features may be found in X-rays performed for other reasons, but they have not translation into clinical symptoms;
b. The acute form is the second common, constituting about 25% of all cases. It presents typically as an acute arthritis involving one joint, and less frequently 2-3 joints at the same time. Large joints such as knees, ankles, shoulders and wrists are more frequently involved than small joints, but the disease may affect any other joint. Presentation as migratory, polyarticular or bilateral arthritis is much

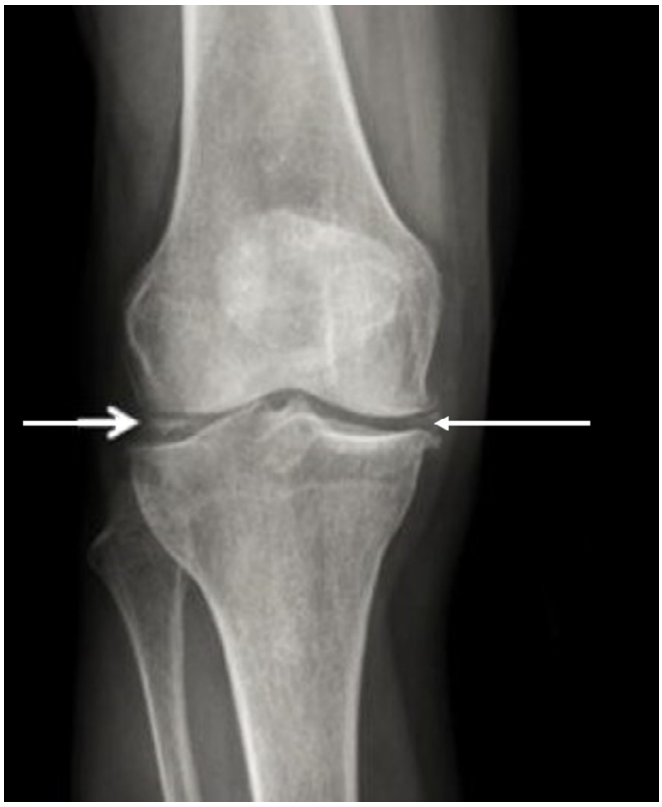

Fig. 3. X-ray of the knee demonstrating CPPD involving the menisci (white arrows).

less common. The disease typically affects older patients, over 65 years of age. The acute CPPD is characterized by rapid onset, and typical symptoms and signs include:

- Pain (local, confined to the affected joint/joints),
- Local increase of temperature,
- Swelling around the affected join(s),
- Redness over the affected joint(s),
- Reduction of movements in the affected joints.

The rapid onset in a form of attack resembles attack of a gout and can be confused with this condition. The course of an acute CPPD is usually self-limiting and symptoms and signs typically resolve slowly within one or two weeks. Attacks may be triggered by some conditions such as trauma, infection or concomitant systemic disease. Between acute episodes, most of patients remains asymptomatic. Attacks can affect the same joint or a different one in each episode. In case of involving a large joint such as hip, knee or shoulder, the patient can present systemic symptoms such as fever, chills and feeling unwell (malaise). This symptomatology may suggest septic arthritis, and if the patient has risk factors such as diabetes, history of trauma or systemic infection, septic arthritis should be considered in differential diagnosis. As it has been already mentioned, this condition can produce symptoms resembling gout, and therefore, despite differences in clinical patterns between the diseases, the definite diagnosis relies upon the microscopic examination of the synovial fluid and demonstration of the specific crystal deposits. As aspiration of the synovial fluid from small joints is not always available, other diagnostic modalities include X-ray and ultrasound examination (this will be discussed later in the article);

c. Chronic CPPD is the rarest form, constituting about 5% of all cases. It may present as bilateral, symmetrical, and deforming inflammatory arthritis. It lasts months or years, and destruction occurs over time resulting in degenerative changes of the affected joints which resembles osteoarthritis. Wrists and metacarpophalangeal (MCP) joints are commonly affected, although the disease can involve also extensor tendon sheaths. Development of wrist tenosynovitis can increase pressure in the carpal tunnel and produce symptoms of median nerve compression and may require synovectomy [8]. Similar changes around the elbow joint can produce symptoms and signs of ulnar nerve compression. When located in the wrist it can cause carpal instability (i.e. scapholunate) [9]. Radiographic findings are characterized by subchondral sclerosis, epiphyseal geodes, osteophytes, but with no marginal erosions [1-8].

Less frequently the joints of the spine may be involved in CPPD, particularly in the cervical and lumbar spine, leading to limited mobility and lower back pain (in lumbar spine involvement) [1, 2].

DIAGNOSIS

Diagnosis of the CPPD is not easy in asymptomatic patients, as it can be only recognized in an accidentally taken the X-ray. Moreover, radiologic changes are not specific and if not strongly expressed, can be easily missed (a proportion of patients with CPPD has negative X-rays). The definitive diagnosis of the condition can be made by examining of the synovial fluid. Other imaging modalities include ultrasonography, X-ray, computed tomography (CT) and magnetic resonance (MRI). Effectiveness and availability of these imaging modalities will be discussed below:

a. Examination of the synovial fluid

As it has been mentioned, the definitive diagnosis of the CPPD is made by the visualization of rhomboid-shaped crystals in the synovial fluid taken form the affected joint. This obviously requires performing aspiration of the joint, what may be demanding in small joints of the hand (it is easier in big joints such as knee or shoulder). The identification of calcium pyrophosphate dihydrate crystals in synovial fluid by light microscopy, compensated polarized light microscopy, or phase contrast microscopy is the reference standard for

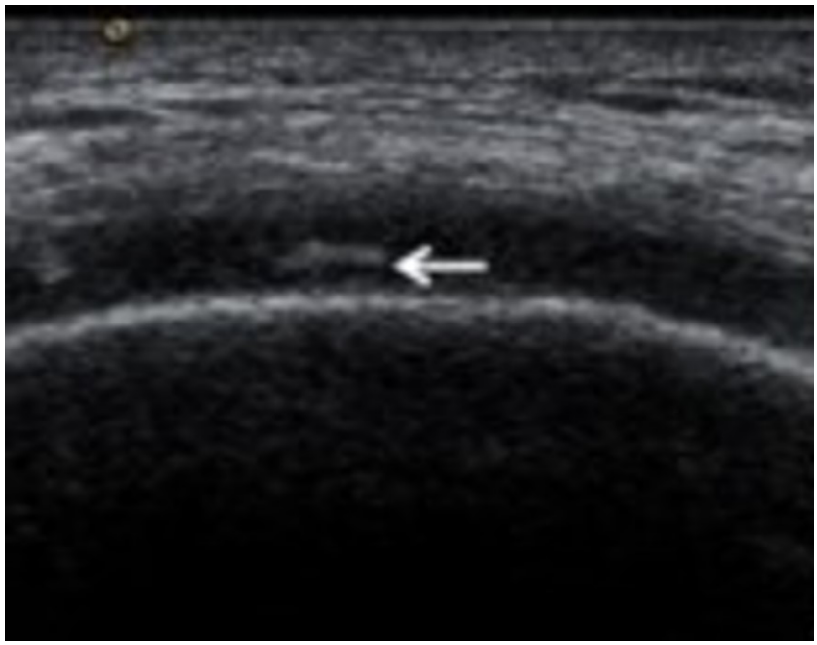

Fig. 4. US of the MCP joint affected with CPPD. Note thin, hyperechoic band within hyaline cartilage, parallel to the surface of the cartilage.

Table 1. Etiopathogenesis of calcium pyrophosphate dihydrate deposition disease (CPPD)

Pathogenetic mechanism
Calcium pyrophosphate dihydrate crystals deposition in the pericellular matrix of cartilage is considered a primary first step of the disease
Concomitant disease effect. CPPD be a manifestation of metabolic or endocrine disorders leading to abnormal Ca and P metabolism, such as hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia, hemochromatosis, gout and osteoarthritis.
Micro-trauma effect. Calcium pyrophosphate dihydrate crystals deposition may be provoked by micro-injuries that deteriorate collagen and other cartilage proteins.
Genetic predispositions. Polymorphisms in the ANKH gene which encodes a transmembrane inorganic pyrophosphate shuttle protein.
Other causes can be a lack of magnesium, excess calcium or iron

Table 2. Treatment of calcium pyrophosphate dihydrate deposition disease (CPPD)

Acute CPPD
Physical measures: cool packs, temporary rest of the affected joint (limb).
Non-steroid anti-inflammatory drugs (NSAIDs)
Colchicine (orally)
Systemic steroids
Intraarticular steroid injection.
Chronic CPPD
Generally the same as in acute form.
In refractory cases: Methotrexate or Hydroxychloroquine
Novel treatments: Anakinra and histone deacetylase inhibitors (HDACis).

CPPD diagnosis. Calcium pyrophosphate dihydrate crystals have characteristically a parallel-epipedic form, and are usually located intracellular, with absent or weak positive birefringence. In some cases more sophisticated methods are necessary such as, chemical analysis of the synovial fluid or atomic force microscopy [1, 2, 5];

b. X-ray examination

Calcium pyrophosphate dihydrate crystals may be seen on X-rays in the fibrocartilage of the joints (Fig. 1-3). Typical localization include the meniscus of the knee (Fig. 3), triangular fibrocartilage of the wrists, labra of the acetabulum, symphysis pubis and annulus fibrosus of the intervertebral discs. Synovial calcification is almost always seen in knee, metacarpophalangeal (Fig. 1), metatarsophalangeal joints, radiocarpal and distal radioulnar joints of the wrists (Fig. 2) [1, 2, 5, 10, 11]. Tendon calcifications are frequently seen in the quadriceps, triceps, and the Achilles tendon Obviously,

only a proportion of patients with symptomatic CPPD is radiologically positive. Abhishek et al., demonstrated that almost 40% of individuals with CPPC do not present with calcific radiographic findings on knees, despite being the most common site of CPPD involvement. The authors found that only 80% of patients with CPPC could be identified on the basis of radiographs of knees, pelvis, wrists or hands [7];

c. Ultrasound examination

Ultrasound evaluation has been studied extensively in the last 10 years, and has been proposed as a primary diagnostic method for CPPD by the European League against Rheumatism [1, 4, 6, 10]. This is because synovial fluid aspiration or synovial biopsy in small joints is difficult to perform. In these cases use of widely available ultrasonography to diagnose CPPD is very be useful. Ultrasonography can demonstrate calcium pyrophosphate dihydrate crystals in peripheral joints, appearing typically as thin hyperechoic bands within hyaline cartilage, parallel to the surface of the cartilage and hyperechoic sparkling spots in fibrocartilage (Fig. 4) [4, 10, 12]. Calcifications within the cartilage usually have not a posterior shadow because linear calcium pyrophosphate dihydrate crystals have not sufficient compactness to stop the ultrasound beam progression. The range of possible expression ranged from isolated hyperechoic spots to extended deposits, which might involve a great portion of the hyaline cartilage [4, 10, 12]. The sensitivity of US in diagnosing CPPD is estimated at 80% and specificity is even higher, reaching 93%-100% [2, 4, 10, 12]. Due to wide availability, US is now a first line imaging technique in diagnosing CPPD;

d. Computed tomography (CT)

CT is less frequently used in diagnosing CPPD and its use is limited to suspected disease in the spine, which is often asymptomatic. Calcium pyrophosphate dihydrate crystals may accumulate in the transverse ligaments of the atlas or alar ligaments, what results in formation of so called "crowned dens syndrome" [2, 5]. The syndrome relies on calcifications of odontoid articular structures. In the "crowned dens syndrome", CT is the first line imaging that allows identification of the different radiographic features of the disease:

- Simple band of calcification or double band of thin calcifications in the transverse ligament,
- Irregular calcifications crowning the dens apex,
- Bone erosions of the dens itself;

e. Magnetic resonance imaging (MRI)

Likewise CT, magnetic resonance imaging is rarely used in diagnosis CPPD and its usefulness is confined to the disease involving the spine. Calcium pyrophosphate dihydrate crystals uptake in ligamentous structures of the spine such as ligamentum flavum and posterior longitudinal ligament, can results in myelopathy, cord compression and spinal stenosis. Thus, MRI may be useful in diagnosing these rare complications of CPPD involving the spine [2, 5];

f. Practical tips for extended diagnostics of suspected chondrocalcinosis

Chronic chondrocalcinosis is rarely confused with rheumatoid arthritis, more often with degenerative and inflammatory changes of the joints (osteoarthritis). In such cases, extended diagnostics may not be needed, because the treatment of both diseases is basically similar. This may only be necessary if the treatment used fails. Similarly, differentiation of the acute phase of chondrocalcinosis and a gout attack is relatively easy, due to the elevated concentration of uric acid in gout. Only in doubtful cases, e.g. normal or borderline uric acid levels, or in cases of treatment failure, such diagnostics may be necessary.

DIFFERENTIAL DIAGNOSIS

The acute phase of the disease is usually differentiated from gout attack or septic arthritis. It is relatively easy to distinguish the CPPD from gout, as the patient usually presents with history of gout (diagnosed earlier). Additionally, uremic acid concentration in serum is elevated in an acute gout episode. Septic arthritis presents with more severe symptoms and, if involves big joints, is associated with systemic reaction (fever, chills, elevated inflammatory parameters – leucocyte rate, CRP). Movement of the affected joint is very painful and range of motion is limited. Ultrasonographic and radiological findings can help in making the confident diagnosis [1, 2, 5].

The chronic phase, CPPD is usually differentiated from osteoarthritis (OA) and rheumatoid arthritis (RA). Differentiating CPPD form OA can be challenging based upon clinical signs and symptoms, however, US and X-ray studies may help in making a proper diagnosis. Both of these diseases can occur simultaneously and overlap each other, so that their unambiguous distinguishing may be possible only after synovial fluid examination. Osteoarthritis combined with CPPD generally affects knees, has an atypical distribution (radiocarpal joint, glenohumeral joint, hindfoot/midfoot involvement) and may be associated with more severe signs and symptoms. In contrast, rheumatoid arthritis history and clinical presentation is usually enough different form CPPD, that confusion between these two diseases is rare.

TREATMENT

At present, there are no widely accepted, disease-modifying therapies which reduce the articular

deposition of calcium pyrophosphate dihydrate crystals. Therefore, at present the goal of treatment in CPPD is reducing the inflammatory response, the frequency and severity of clinical symptoms caused by the disease [1, 2, 5]. Patients with asymptomatic CPPD do not require any treatment. Treatment of symptomatic patients requires both non-pharmacological and pharmacological measures, according to clinical presentation and risks factors. Proper treatment should include prompt resolution of the acute episode, prevention of chronic joint damage and management of concomitant diseases. Unfortunately, most treatment approaches are based upon clinical experience, but not on scientific evidence based on results of prospective, controlled studies. The list of treatment modalities is shown in Table 2.

TREATMENT OF ACUTE CPPD

The majority of CPPD patients who require intervention are those with acute form of the disease.

In such a situation, the treatment is similar to treatment of gout attack, and includes cool packs, temporary rest of the affected joint (limb), non-steroid anti-inflammatory drugs (NSAIDs), low dose oral colchicine, and sometimes systemic steroids. Joint aspiration with intraarticular long-acting steroid injection might be necessary if primary treatment fails in relieving the symptoms [1, 2, 5]. NSAIDs and colchicine are relatively effective, but limited by toxicity and adverse effects which may be dangerous in older patients. A short course of oral or parenteral steroids is recommended in patients who failed to improve after NSAIDs or colchicine treatment, or who have contraindications to use these drugs [2, 5].

Colchicine is relatively old drug, but it has been still used in acute gout attacks. The mechanism of action is through stabilizing activity on the cytoskeleton and cell membranes, but it also inhibits the neutrophil's motility and activity, leading to an anti-inflammatory effect. Colchicine is effective in acute CPPD and in preventing recurring attacks. *Likewise in* acute gout, colchicine is most effective if treatment is started within 12-24 hours after onset of symptoms. The earlier the treatment is started, the more rapid and complete resolution occurs. Small doses of colchicine (3x0,5 mg daily, per os) are recommended at the beginning of therapy, because it reduces adverse effects of the drug on gastrointestinal tract such as diarrhoea and abdominal cramping. In most patients, the effect of this therapy is rapid and strong, and symptoms usually begin to subside in 12-24 hours [2, 5]. Intravenous administration of colchicine is not recommended, because it is associated with risk of severe pancytopenia and death. The duration of therapy for the acute episode may range from one to several weeks, depending on how early colchicine has been introduced [2, 5]. For the prophylaxis of recurrent acute CPPD, low-dose oral NSAIDs, or low-dose (0,5 mg daily) oral colchicine is recommended.

TREATMENT OF CHRONIC CPPD

Patients with chronic CPPD require a continuous treatment with low-dose NSAIDs or colchicine and sometimes with low-dose oral steroids. This therapy is usually effective, however it may be confused by acute episode of the condition. In patients who fail to improve, in whom such treatments are contraindicated or not well-tolerated, alternative therapeutic modalities can be used such as methotrexate and hydroxychloroquine [2]. Methotrexate could be considered as an for patients with severe CPPD who failed to respond to standard therapy. The drug works not only as an immunosuppressant but also as a potent anti-inflammatory agent. Hydroxychloroquine has shown some beneficial effect in chronic CPPD arthritis with no significant adverse effects [2, 4, 5].

NOVEL TREATMENTS: ANAKINRA AND HISTONE DEACETYLASE INHIBITORS (HDACIS)

Anakinra is a biologic immunosuppressant that is an antagonist of human interleukin-1 (IL-1) type I receptors. Anakinra blocks the biological activity of IL-1α and IL-1β and is approved for the treatment of rheumatoid arthritis, COVID-19 infection, periodic fever syndromes and Still's disease. Effectiveness of anakinra was compared to prednisone in the treatment of acute CPPD in a randomized controlled study. Results of this study demonstrated similar effectiveness between anakinra and prednisone, but anakinra showed faster onset of action than prednisone [13].

Histone deacetylase inhibitors (HDACis) have been shown to downregulate calcium pyrophosphate dihydrate crystal formation in human articular chondrocytes. Extracellular pyrophosphate, calcium and extracellular matrix are essential components of CPP crystal formation [5, 14]. A high concentration of extracellular pyrophosphate in synovial fluid is positively correlated with the formation of CPP crystals. Histone deacetylase inhibitors (HDACis) were able to decrease extracellular pyrophosphate and CPP formation by regulating ankylosis human (*ANKH*), ectonucleotide pyrophosphatase 1 (*ENPP1*), and tissue nonspecific alkaline phosphatase (*TNAP*) genes expressions in human

chondrocytes. The underlying molecular mechanisms of HDACis – mediated regulation of *ANKH, ENPP1*, and *TNAP* expression is probably associated with the histone acetylation status of the promoters of these three genes [5, 14]. Histone deacetylase inhibitors may have the potential to be developed into drugs to prevent calcium pyrophosphate dihydrate crystals formation or treat CPPD related diseases in the future.

CONCLUSIONS

Calcium pyrophosphate dihydrate disease (chondrocalcinosis, pseudogout) is a fairly common condition affecting mostly older people. Diagnosis is made on the basis of X-ray or ultrasound examination, but definitive confirmation requires demonstration of CPP crystals in the synovial fluid. Most of patients is asymptomatic, but when symptomatic, the disease presents in acute or chronic form. Treatment of acute CPPD is similar to treatment of gout attack and consists in physical measures and medication with NSAIDs, colchicine or steroids. Calcium crystal deposition diseases are increasing in incidence due to aging of the population. They are associated with a high burden of disability. Despite this, they remain under-studied with lack of evidence based treatment guidelines.

In conclusion, this review demonstrates several new findings with regard to CPPD, such as development of more precise classification criteria and improvements in the accuracy of diagnostics, particularly examination of the synovial fluid taken from the affected joint. New findings include identification of factors associated with acute flare of disease and an association with increased cardiovascular risk. New treatment modalities, i.e. with histone deacetylase inhibitors still remain controversial, however advances in understanding the underlying molecular mechanisms of disease suggest potential targets for future drug development.

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CONFLICT OF INTEREST

The Author declares no conflict of interest

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