Calcium pyrophosphate deposition

Introduction

Radiographic articular cartilage calcification (chondrocalcinosis) was first described in the 1920s. Chondrocalcinosis most often results from calcium pyrophosphate dihydrate crystal deposition. Calcium pyrophosphate crystals were first identified in synovial fluids from joints with apparently acute 'gouty' arthritis (McCarty et al, 1962). Subsequently, calcium pyrophosphate crystal deposition was recognized as a common cause of arthritis in the elderly. However, calcium pyrophosphate crystal deposition also occurs in the younger age group. This review describes the pathogenesis, epidemiology, clinical features, diagnosis and management of calcium pyrophosphate crystal deposition.

Nomenclature

A large number of confusing and overlapping pseudo-syndromes, e.g. pseudogout, pseudo-osteoarthritis, pseudo-rheumatoid arthritis or pseudo-neuropathic arthritis, were used to describe the diverse and often rare manifestations of calcium pyrophosphate crystal deposition. This system of nomenclature is not ideal as joints may evolve from one pseudo-syndrome to another, and different joints in an individual may have distinct phenotypes at the same time. Standardized nomenclature of calcium pyrophosphate crystal deposition has been developed by a European task force and is used in this review (*Table 1*) (Zhang et al, 2011a).

Pathogenesis

Calcium pyrophosphate crystals form extracellularly. Their formation requires adequate extracellular calcium, excess extracellular pyrophosphate and extracellular matrix changes that allow crystal nucleation and growth (Abhishek and Doherty, 2011). Pyrophosphate is a by-product of many intracellular reactions. However, intracellular pyrophosphate is too large to diffuse passively across the cell membrane and is rapidly hydrolysed to phosphate. Thus, extracellular pyrophosphate is either synthesized by plasma membrane-bound plasma cell glycoprotein 1, or transported across cell membranes by ankylosis human protein (ANKH) (*Figure 1*).

As would be expected, the synovial fluid pyrophosphate level is high in joints with calcium pyrophosphate crystal deposition (Russell et al, 1970). However, unlike gout which associates with elevated serum urate, serum pyrophosphate levels are normal in calcium pyrophosphate crystal deposition (Russell et al, 1970). This suggests that the metabolic abnormality resulting in calcium pyrophosphate crystal deposition occurs at the joint level.

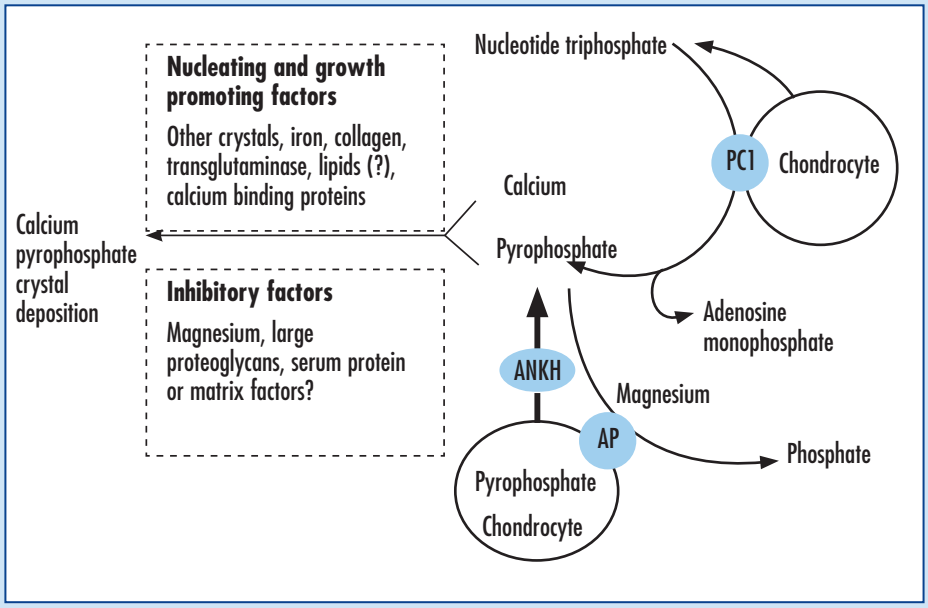
Calcium pyrophosphate crystals deposit in cartilage matrix, and induce inflammation when shed. Protein coating of calcium pyrophosphate crystals further increases their inflammatory potential. Calcium pyrophosphate crystals induce inflammation by activating the NALP-3 inflammasome resulting in cytokine synthesis (Martinon and Glimcher, 2006); failed phagocytosis of calcium pyrophosphate crystals resulting in release of cytokines and lysozymes, and by other mechanisms

Table 1. European League against Rheumatology nomenclature of calcium pyrophosphate deposition and associated diseases

Calcium pyrophosphate (CPP) crystals	Simplified term for calcium pyrophosphate dihydrate crystals
Calcium pyrophosphate deposition (CPPD)	Umbrella term for all instances of occurrence of CPP crystals
Chondrocalcinosis	Cartilage calcification, identified by imaging or histology
Clinical presentations associated with CPPD	
Asymptomatic CPPD	With no clinical consequence
Acute CPP crystal arthritis	Previously 'pseudogout'
Osteoarthritis with CPPD	CPPD in a joint showing evidence of osteoarthritis
Chronic CPP crystal inflammatory arthritis	CPPD in a joint with inflammatory arthritis

From Zhang et al (2011a)

Figure 1. Extracellular pyrophosphate metabolism and calcium pyrophosphate crystal deposition. ANKH = ankylosis human protein; AP = tissue non-specific alkaline phosphatase; PC1 = plasma cell glycoprotein 1.



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that are beyond the scope of this review. The factors resulting in resolution of acute calcium pyrophosphate crystal arthritis are not well understood.

Epidemiology

The prevalence of radiographic chondrocalcinosis is 7.0% at the knees, and 10% at the knees or pelvis in those over 60 years of age (Felson et al, 1989; Ramonda et al, 2009). Calcium pyrophosphate crystal deposition occurs in all races but is more common in caucasians. Calcium pyrophosphate crystal deposition is associated with increasing age and osteoarthritis, but not with gender or obesity (Felson et al, 1989; Ramonda et al, 2009). Hyperparathyroidism, haemochromatosis, hypomagnesaemia (as a result of renal or gastrointestinal losses; Richette et al, 2007), hypophosphatasia and diuretic use are associated with calcium pyrophosphate crystal deposition (Richette et al, 2009; Rho et al, 2012). The association with diuretic use is believed to be mediated by hypomagnesaemia. Previous joint surgery, e.g. knee meniscectomy, is associated with chondrocalcinosis (Doherty et al, 1982). Chronic kidney disease stage 5 has been identified as a risk factor for acute calcium pyrophosphate crystal arthritis (Rho et al, 2012).

Calcium pyrophosphate crystal deposition can be hereditary. Autosomal dominant, monogenic calcium pyrophosphate crystal deposition as a result of mutations in the ANKH gene (CCAL2) has been reported from all over the world (Abhishek and Doherty, 2011). Hereditary calcium pyrophosphate crystal deposition also occurs as a result of mutations in chromosome 8 (CCAL1). However, calcium pyrophosphate crystal deposition in this family may be secondary to dysplastic osteoarthritis, and CCAL1 is not believed to be a common cause of hereditary calcium pyrophosphate crystal deposition. Single nucleotide polymorphisms in ANKH play a role in pathogenesis of apparently sporadic calcium pyrophosphate crystal deposition as well (Zhang et al, 2006). Calcium pyrophosphate crystal deposition rarely associates with ochronosis, Wilson's disease, acromegaly and familial hypocalciuric hypercalcaemia (Jones et al, 1992). These associations are based on a few reports of florid calcium pyrophosphate crystal deposition in young adults, and routine screening for these conditions is not warranted.

Clinical features

Calcium pyrophosphate crystal deposition most commonly occurs at the knees. Wrists, symphysis pubis and hips are other commonly affected joints (*Figures 2–4*) (Abhishek et al, 2012). Shoulders, ankle, elbow and metacarpophalangeal joints can also be affected. The clinical features of calcium pyrophosphate crystal deposition outlined below have been summarized by Zhang et al (2011a).

Asymptomatic calcium pyrophosphate crystal deposition is often asymptomatic, manifesting as chondrocalcinosis on plain radiographs.

Acute calcium pyrophosphate crystal arthritis (formerly pseudogout) develops rapidly with pain, stiffness and swelling often maximal within 6–24 hours. The joint is swollen, erythematous, warm, tender, and has restricted movement. Pitting peri-articular oedema is common at the wrist, ankle and in the mid-foot. Fever may be present, and older patients may become confused. Acute attacks usually resolve within a few days to 1–3 weeks. Knees, wrists, shoulders, ankles and elbows are commonly affected. Most episodes develop spontaneously while some attacks are preceded by injury, intercurrent illness and surgery (especially parathyroidectomy).

Osteoarthritis with calcium pyrophosphate crystal deposition associates with greater stiffness, effusion and frequently targets the knees. There may be atypical distribution of joint involvement, i.e. involvement of wrist, gleno-humeral, ankle and mid-foot joints, compared to osteoarthritis alone. Clinical features of osteoarthritis may be present at other joints.

Chronic calcium pyrophosphate crystal inflammatory arthritis presents as chronic

Figure 2. Knee radiograph showing calcification of lateral and medial meniscus.

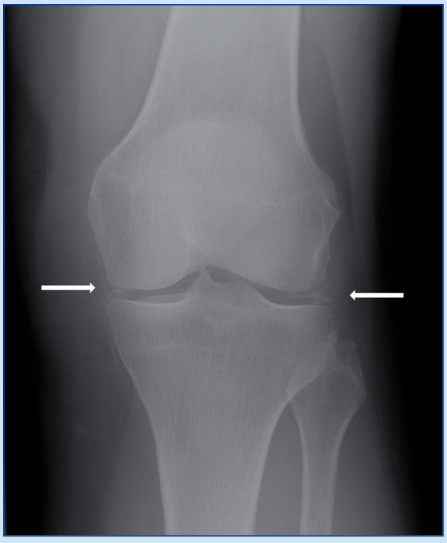


Figure 4. Wrist radiograph showing chondrocalcinosis.

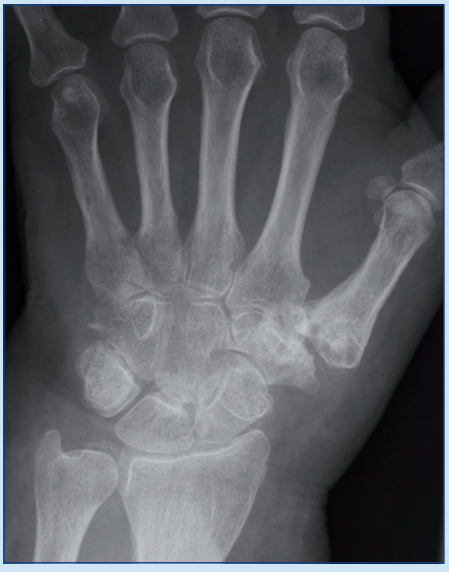
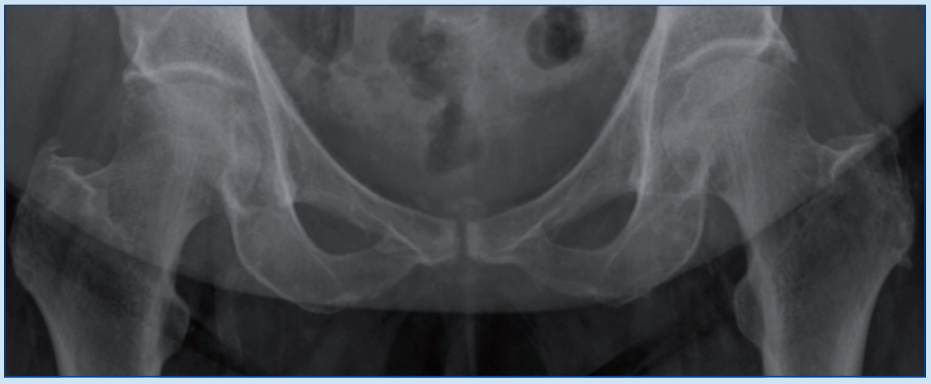


Figure 3. Pelvis radiograph showing faint calcification of fibro- and hyaline cartilage (right hip), and fibro-cartilaginous labrum (left hip).



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oligoarthritis or polyarthritis. Signs of osteoarthritis and synovitis, e.g. warmth, joint line and/or capsular tenderness, stress pain, effusion and soft tissue thickening, may be present. Superimposed episodes of acute synovitis can be present as well. Knees, wrists, shoulders, elbows, hips, mid-tarsal and metacarpophalangeal joints (particularly the second and third) are affected. Osteoarthritis with calcium pyrophosphate crystal deposition and chronic calcium pyrophosphate crystal inflammatory arthritis may co-exist in the same patient.

Rare manifestations

Acute tendinitis or tenosynovitis (elbows, wrists and ankles) and bursitis (olecranon, infra-patellar and retrocalcaneal) are not uncommon. Marked proximal stiffness accompanying glenohumeral and polyarticular involvement may suggest polymyalgia rheumatica; and severe spinal stiffness may present as 'pseudo-ankylosing spondylitis'. Tophaceous calcium pyrophosphate crystal deposition (similar to tophaceous gout) most commonly occurs at the temporo-mandibular joint.

Metabolic disease-associated calcium pyrophosphate crystal deposition presents with asymptomatic chondrocalcinosis or with recurrent acute calcium pyrophosphate crystal synovitis with the notable exception of haemochromatosis which is associated with structural arthropathy at metacarpophalangeal joints, hips, ankles and knees (Jones et al, 1992). Hereditary calcium pyrophosphate crystal deposition generally presents with young onset acute calcium pyrophosphate crystal synovitis. However, some families develop deforming arthropathy with ankylosis of sacro-iliac joints and the spine.

Differential diagnosis

The differential diagnosis of acute calcium pyrophosphate crystal arthritis includes septic arthritis and gout. Chronic arthropathy can be confused with rheumatoid arthritis in elderly. However, absence of auto-antibodies, peri-articular osteopenia, and presence of chondrocalcinosis helps. Differentiation from uncomplicated osteoarthritis is by a more florid inflammatory component including superimposed acute attacks. Although rare, differential diagnosis of tophaceous calcium pyrophosphate crystal deposition includes malignancy and tophaceous gout.

Diagnostic workup

Key investigations for diagnosis are synovial fluid analysis and radiographic assessment. Once the diagnosis is confirmed, further investigation for predisposing metabolic diseases may be carried out if indicated.

Synovial fluid

In acute calcium pyrophosphate crystal arthritis, aspirated fluid is often turbid, blood-stained, less viscous, and has a high white cell count (>90% neutrophil). Macroscopic appearance, viscosity and cell count in chronic arthropathy ranges from inflammatory to normal. Calcium pyrophosphate crystals are 2–10 μm long, and rhomboid or rod shaped. Classic weak positive birefringence under compensated polarized microscopy is not always present. Gram stain and culture should be performed as septic arthritis is the principal differential, and septic arthritis and acute calcium pyrophosphate crystal arthritis can rarely co-exist (Zhang et al, 2011a).

Imaging

Plain radiograph

Chondrocalcinosis is more common in fibrocartilage (knee menisci, wrist triangular cartilage, symphysis pubis, hip labrum) than in hyaline articular cartilage (knee, shoulder, hip). It appears as an irregular shaggy linear deposit in fibrocartilage and as fine linear deposits parallel to but separate from subchondral bone in hyaline cartilage (*Figures 2–4*). It is unlikely to be present in radiographs of other joints if absent from the knee, wrist, hip and symphysis pubis (Resnick et al, 1977).

Chondrocalcinosis may increase or decrease with time, becoming less evident if there is cartilage loss (severe osteo-arthritis) or if crystals are 'shed' during an inflammatory episodes. Several radiographic phenotypes like exuberant osteophytosis, prominent cysts, severe sclerosis and marked attrition have been associated with calcium pyrophosphate crystal deposition with osteoarthritis. However, a meta-analysis suggests that the radiographic phenotype of calcium pyrophosphate crystal deposition with osteoarthritis is similar to that of osteoarthritis alone (Zhang et al, 2011a). The distribution of joints affected by structural arthropathy in calcium pyrophosphate crystal deposition and osteoarthritis is different from that of osteoarthritis, with a greater likelihood of structural arthropathy at the wrist, glenohumeral, metacarpophalangeal, ankle or elbow joint in those with calcium pyrophosphate crystal deposition and osteoarthritis.

Other imaging modalities

Ultrasound is more sensitive for detecting calcium pyrophosphate crystal deposition than plain radiographs (Zhang et al, 2011a). Calcium pyrophosphate crystal deposition appears as linear hyperechoic bands within hyaline articular cartilage and as rounded or amorphous hyperechoic spots in fibrocartilage. Computed tomography is useful in the evaluation of calcium pyrophosphate crystal deposition in the spine. Computed tomography of the cervico-occipital junction may show peri-odontoid calcification, subchondral cysts and erosion in crowned dens syndrome. Magnetic resonance imaging may be used for further evaluation of suspected spinal cord compression, but is insensitive for detecting calcium pyrophosphate crystal deposition itself.

Blood tests

Acute calcium pyrophosphate crystal arthritis commonly triggers an acute phase response, with elevated erythrocyte sedimentation rate, C-reactive protein and white blood cell count (predominantly neutrophilia). Mild anaemia with modestly elevated acute phase reactants may be present in chronic calcium pyrophosphate crystal inflammatory arthritis.

Metabolic predisposition to calcium pyrophosphate crystal deposition is uncommon, and routine screening of all patients with calcium pyrophosphate crystal deposition for the presence of a metabolic predisposition is unrewarding. Screening tests are warranted in those with early onset arthritis (<55 years) and florid polyarticular chondrocalcinosis (Zhang et al, 2011a). The screening tests include calcium, alkaline phosphatase, liver function tests, magnesium, ferritin and transferrin saturation. Parathyroid hormone should also be checked as patients with hyperparathyroidism may have normal serum calcium levels.

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Management

Evidence-based consensus driven guidelines have been produced for the management of calcium pyrophosphate crystal deposition (Zhang et al, 2011b). However, most recommendations are based on expert opinion as there is a paucity of good quality studies on the treatment of clinical syndromes associated with calcium pyrophosphate crystal deposition. No current treatment modifies calcium pyrophosphate crystal formation or dissolution, and asymptomatic chondrocalcinosis does not require treatment. Associated metabolic conditions should be treated if present. However, other than possibly for correction of hypomagnesaemia, such treatment does not influence the outcome of calcium pyrophosphate crystal-associated diseases. Iron chelation therapy does not reverse the structural arthropathy in haemochromatosis.

Acute calcium pyrophosphate crystal arthritis

Rest, ice and simple analgesics may be used. Joint aspiration and intra-articular injection of long-acting corticosteroids (e.g. 40–80 mg methylprednisolone or triamcinolone acetonid) is often sufficient. Data extrapolated from gout trials, and recommendations from expert groups suggest that oral colchicine (e.g. 0.5 mg twice or thrice a day with or without an initial dose of 1 mg) is effective for acute calcium pyrophosphate crystal arthritis, and can be given for a week to 10 days. The dose should be reduced in renal impairment and in the elderly.

Expert group recommendations and clinical experience support the use of short courses of corticosteroids, e.g. prednisolone 15–20 mg/day for 7–10 days in the elderly and for polyarticular attacks. A few case reports suggest that anakinra (an IL-1 antagonist) can be effective in the treatment of polyarticular acute calcium pyrophosphate crystal arthritis unresponsive to oral corticosteroids. A small study suggests that prophylaxis against recurrent acute calcium pyrophosphate crystal arthritis can be achieved with oral colchicine (0.5–1 mg/day) (Alvarellos and Spilberg, 1986). Non-steroidal anti-inflammatory drugs are effective in controlling acute calcium pyrophosphate crystal arthritis. However, their use should be avoided in the elderly.

Osteoarthritis with calcium pyrophosphate crystal deposition

The choice of interventions is the same as for osteoarthritis alone, i.e. patient education, analgesia, exercises, and aids and appliances as required. Despite the presence of significant structural abnormality, intra-articular corticosteroid injection improves symptoms temporarily.

Chronic calcium pyrophosphate crystal inflammatory arthritis

Pharmacological options based on small studies include colchicine (0.5–1.0 mg daily), hydroxychloroquine (200–400 mg daily) and methotrexate (10–20 mg/week). The use of low dose prednisolone (<7.5 mg/day) for chronic calcium pyrophosphate inflammatory arthritis is supported by expert opinion alone (Zhang et al, 2011b). Patients with severe large-joint arthropathy may require joint replacement, and do as well as those with osteoarthritis alone.

Conclusions

Calcium pyrophosphate crystal deposition frequently affects the elderly. It is commonly asymptomatic. Common presentations include acute synovitis and chronic arthritis. Most cases of calcium pyrophosphate crystal deposition are the result of ageing or osteoarthritis. Rarely, calcium pyrophosphate crystal deposition can be a result of metabolic diseases, or can be hereditary. Treatment of calcium pyrophosphate crystal deposition-associated arthropathy is mainly symptomatic, and there is no treatment to reduce the calcium pyrophosphate crystal load. Treatment of any underlying metabolic disease is appropriate. BJHM

Conflict of interest: none.

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KEY POINTS

- Calcium pyrophosphate deposition is a common cause of arthritis in the elderly.
- Calcium pyrophosphate deposition can be asymptomatic, or cause both acute and chronic arthritis.
- Risk factors for calcium pyrophosphate deposition include age, osteoarthritis, meniscectomy, haemochromatosis, hyperparathyroidism, hypomagnesaemia and hypophosphatasia.
- Screening for metabolic diseases should only be carried out in the correct clinical context.

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