Update on calcium pyrophosphate deposition

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Received and accepted on June 29, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 98): S00-S00.

Key words: calcium pyrophosphate crystal deposition (CPPD), ankylosis human gene (ANKH), ageing, osteoarthritis

Competing interests: none declared.

ABSTRACT

Calcium pyrophosphate crystal deposition (CPPD) associates with ageing, osteoarthritis (OA), uncommon metabolic diseases, mutations and polymorphisms in the ankylosis human gene (ANKH). CPPD is frequently polyarticular, occurs due to a generalised articular predisposition, and the association between CPPD and OA is joint specific, for example CPPD associates with knee OA, but not with hip OA. Other recently identified associations include knee malalignment (knee CC), low cortical BMD and soft-tissue calcification. CPPD is generally asymptomatic. A recent study reported that knees with OA plus CC at the index joint, or at distant joints (in absence of index joint CC), were more likely to have attrition.

CPPD can cause acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and is frequently present in joints with OA. Joint aspiration remains the gold standard for diagnosing CPPD, although other promising techniques are emerging. Patients with polyarticular or young onset CPPD should be screened for underlying metabolic abnormalities, however, such testing can be unrewarding.

The treatment of CPPD is symptomatic. Acute CPP crystal arthritis is treated with rest, local application of ice-packs, joint aspiration, colchicine and/or intra-articular corticosteroid injection (once infection is excluded). Colchicine, low-dose corticosteroids, hydroxychloroquine and radiosynovectomy are recommended for the treatment of chronic or recurrent acute CPP crystal arthritis. Recent RCTs did not confirm any benefit from methotrexate, and although there is increasing interest in the use of anti-IL1 agents for acute or chronic CPP crystal arthritis, their efficacy has not been formally examined. Unlike gout, currently there are no treatments to eliminate CPP crystal deposits.

Introduction

Calcium pyrophosphate (CPP) crystal deposition (CPPD) occurs mainly in the elderly, can present with acute CPP crystal arthritis or chronic arthropathy with structural changes of osteoarthritis (OA), or may be asymptomatic, presenting as an incidental finding of chondrocalcinosis (CC) on imaging studies (1, 2). Several diverse presentations *e.g.* pseudo-rheumatoid, pseudo-polymyalgia rheumatica, pseudo-ankylosing spondylitis etc. were attributed to CPPD in the 1960s and 1970s (3). These presentations were supported by hospital based case series, with no clear evidence for causality, resulting in a potentially confusing and complex phenotypic classification. A European League Against Rheumatism (EULAR) task force has recommended simpler terminology in order to standardise the terminology and classification of CPPD (Table I) (4).

CPPD is common, and the prevalence depends on the joints surveyed. In plain radiographic surveys, CC, a surrogate for CPPD in epidemiologic studies, affects 7.0-8.1% knees, 10.0-10.4% knees plus either hand/wrist or hip/symphysis pubis respectively (5-7). It was the 4th most prevalent musculoskeletal condition in an Italian population survey with a prevalence of 0.42% (8). CPPD predominantly affects the knees, but wrists, hips, and symphysis pubis CC may occur in the absence of knee CC (9).

Risk factors

Both ageing and OA independently associate with CPPD (6, 7). The association between OA and CC may be joint specific as knee, wrist, scapho-trapezoid joint, and metacarpophalangeal joint (MCPJ) OA associates with CC (10-13), but hip OA does not associate with hip CC or with CC at distant joints (5, 14). CPPD can rarely be inherited as a monogenic autosomal dominant disease, generally due to mutations in the

ANKH (ankylosis human) gene, or other genes such as the procollagen type 2, CCAL1 and osteoprotegerin genes (15). Even apparently sporadic CPPD has a genetic component, and associates with the -4bp G to A polymorphism in the 5'-UTR of ANKH, and this association is independent of age, sex, body mass index and OA (16, 17).

Metabolic disease associations of CPPD include haemochromatosis (18), hyperparathyroidism (19, 20), hypomagnesemia (21) and hypophosphatasia (22). Other diseases such as diabetes mellitus and hypothyroidism do not associate with CPPD once adjusted for age (22, 23). Haemochromatosis is the only metabolic disease associated with CPPD that results in structural arthropathy, and this commonly affects the knees, wrists, hips, MCPJs, and ankles (18, 24).

CC associates with local joint insult *e.g.* meniscectomy (25), self-reported varus knee malalignment in young adult life (26), low cortical bone mineral density (27), gout (28) but not hyperuricemia (29), and associates negatively with rheumatoid arthritis (RA) (pooled OR (95%CI) 0.18 (0.08-0.41)) (4). The latter observation is supported mechanistically by the subnormal levels of inorganic pyrophosphate (PPi) in the synovial fluid of patients with RA (30). OA, hyperparathyroidism, chronic kidney disease (CKD) 5, and loop diuretic use associate with acute CPP crystal arthritis independent of age and sex (31).

Table I. Classification of calcium pyrophosphate crystal deposition (CPPD) (4).

Asymptomatic CPPD: CPPD with no apparent clinical consequence
OA with CPPD: CPPD in a joint that also shows structural changes of OA, on imaging or histological examination (previously "pseudo-OA"). As with OA without CPPD, this can be symptomatic or asymptomatic.
Acute CPP crystal arthritis: acute onset, self-limiting painful synovitis with CPPD (previously "pseudogout")
Chronic CPP crystal inflammatory arthritis: chronic inflammatory arthritis associated with CPPD (previously "pseudo-rheumatoid arthritis")

(OA: osteoarthritis).

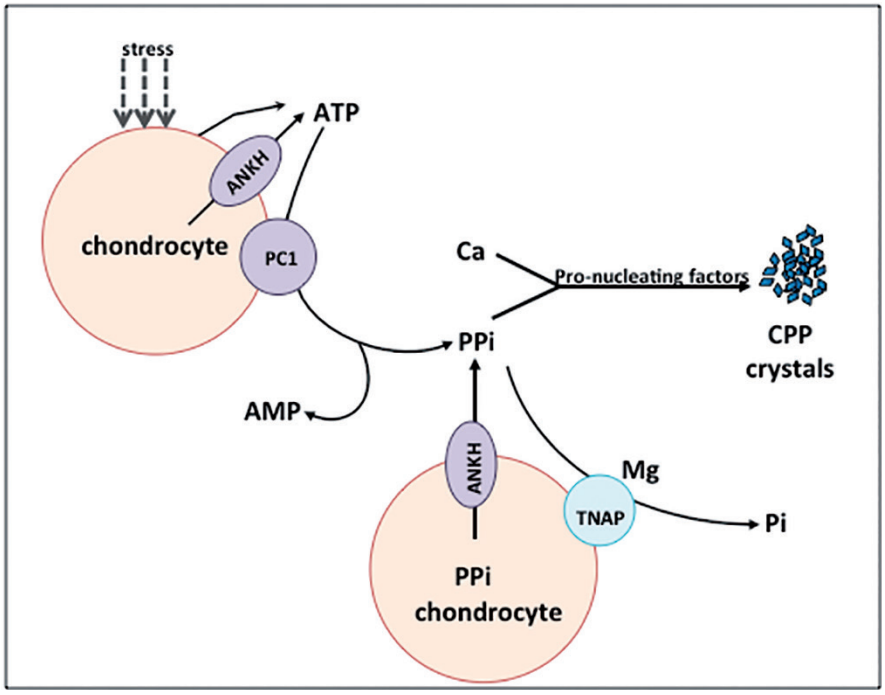

Fig. 1. Extracellular pyrophosphate (PPi) metabolism. AMP: adenosine monophosphate, ATP: adenosine triphosphate, ANKH: ankylosis human, TNAP: alkaline phosphatase, Ca: calcium, CPP: calcium pyrophosphate, Mg: magnesium, Pi: phosphate, PC1: plasma cell glycoprotein 1 (belongs to the ENPP/PDNP family). Similar processes take place on the enzyme rich articular cartilage vesicles, and matrix vesicles.

Pathogenesis

CPP crystals form extracellularly *in vivo* (32), and their formation requires sufficient extracellular PPi (ePPi), calcium, and a cartilage matrix that facilitates crystal nucleation and growth. Of these, PPi concentration is best studied, and promotes CPP crystal formation over other types of calcium crystals *e.g.* BCP crystals (33). PPi inhibits abnormal BCP related calcification in the vasculature, saliva, and the urinary tract, and is used as an industrial water softener.

PPi and CPPD PPi is not absorbed directly from the gastrointestinal tract, but is derived entirely endogenously from the breakdown of nucleoside triphosphates (NTPs). Despite a turnover of several kilograms/day, PPi concentrations are maintained at low levels by ubiquitous pyrophosphatase enzymes. Patients with CPPD have high synovial fluid PPi levels, and the plasma and urinary concentrations are normal, which strongly supports local production as the main contributor to a high ePPi (34, 35). Compared to normal knees, elevated synovial fluid PPi concentrations are reported in OA ± CPPD, hyperparathyroidism, hypomagnesaemia, and haemochromatosis (30, 34, 36, 37). Extracellular PPi (ePPi) is derived either from local production by the breakdown of ATP to AMP and PPi by plasma cell membrane bound phosphodiesterase nucleotide pyrophosphatase (PDNP) enzyme plasma cell membrane glycoprotein 1 (PC-1) or by the export of intracellular PPi by the multi-pass transmembrane ankylosis human protein (ANKH) (15, 16, 38) (Fig. 1).

PC-1 has a greater contribution to ePPi than ANKH (39, 40). Gain in function mutations and polymorphisms in ANKH result in elevated ePPi (frequently quantified as low iPPi) and CPPD (15, 16). Apart from PPi, ANKH also exports ATP which may be broken down to ePPi (41). The amount of extracellular ATP, which determines the concentration of ePPi, and whether

CPP or BCP crystals are formed, depends on mechanical loading, metabolic cell activity, cell division and injury (34, 42, 43).

Regulation of ePPi

The concentration of ePPi is regulated by several growth factors and cytokines such as TGF-β, IL-1β and IGF-I. TGF-β promotes PC-1, ANKH, cartilage intermediate layer protein (CILP) and transglutaminase activity and down regulates TNAP activity, thus increasing ePPi levels (15). IGF-1 and inflammatory cytokines such as IL-1β have the opposite effect to TGF-β resulting in lower ePPi levels.

Pi and PPi levels are inter-related via complex biofeedback mechanism. For example, the TGF-β induced increase in ANKH expression increases the expression of PiT-1 resulting in high intracellular Pi levels which then stimulates TNAP activity, thereby lowering ePPi concentration (44). Type 2 transglutaminase, factor XIIIa, and osteopontin also promote CPP crystal formation (45-49).

CPP crystal formation

The formation of CPP crystal *in vivo* appears restricted to higher primates, and occurs principally in fibro- and hyaline articular cartilage, or in areas of chondroid metaplasia in the synovium (50). Of the twelve known crystallographic forms of CPP crystals only the rod-like monoclinic (M-) or squat triclinic (T-) forms are deposited *in vivo* (51). Histologic studies suggest that CPP crystals form initially in pericellular locations, usually in the collagenous matrix in the midzone of fibro- and hyaline articular cartilage that is depleted of proteoglycan and rich in Sudan-positive lipid granules (32). They form close to metabolically active hypertrophic chondrocytes that are rich in iPPi and readily release ATP (52).

CPP crystal induced inflammation

Crystal shedding is the preferred mech anism to explain the occurrence of CPP crystals within synovial fluid (53, 54). CPP crystals induce inflammation by their effects on the NALP-3 inflammasome which results in IL-1β production (55). IL-1β then orchestrates the release of other cytokines such as TNF-α (55). They also activate the toll like receptors (56). CPP crystals induce a neutrophilic inflammatory response predominantly due to their preferential induction of IL-8 (and not macrophage inflammatory protein-1α), and inhibition of neutrophil apoptosis (57, 58). Cells that phagocytose CPP crystals respond with increased metabolic activity, and the release of myelo-peroxidase, IL-1β, IL-8, IL-6 and neutrophil extracellular traps which can damage bystander cells (59, 60). The inflammatory potential of CPP crystals depends on their size, type, surface charge, protein coating, with negatively charged small M-CPP crystals with protein and immunoglobulin coating being more inflammatory (51). Chronic CPP-crystal induced tissue damage is less well understood, though postulated mechanisms include increased matrix metalloproteinase expression, NO release, persistent synovial inflammation, altered cell metabolism, prostaglandin E2 release, altered osteoblast activity (56) and mechanical shear (61, 62).

Clinical features

Acute CPP crystal arthritis develops over a few hours, with pain, stiffness, erythema and swelling, and is usually maximal within a day of onset. Fever and confusion may be present. Acute attacks are self-limiting and usually resolve within 1 to 3 weeks. Although any joint can be affected, acute attacks occur most commonly in knees and then wrists. Most episodes of acute CPP crystal arthritis develop spontaneously, but several provoking factors such as intercurrent illness are implicated.

Chronic arthropathy

Chronic arthropathy most commonly presents as OA with CPPD. Some patients present with chronic oligoarthritis or polyarthritis with more overt inflammatory symptoms and signs and occasional systemic upset (with elevated inflammatory markers) and additional episodes of superimposed acute crystal synovitis.

Uncommon presentations include familial CPPD which may either present as part of a premature dysplastic OA phenotype, or be the only manifestation presenting with recurrent episodes of acute CPP crystal arthritis (15, 63). Most instances are inherited in an autosomal dominant manner (15). Other rare manifestations include spinal CPPD presenting as crowned-dens syndrome or with acute localized meningism and/or myelo-radiculopathy, and tophaceous CPPD ("tumoral") CPPD which usually presents as slow growing painless lumps, and most commonly occurs at the temporo-mandibular joint (64).

The differential diagnosis of acute CPP crystal arthritis includes gout, joint infection (which may rarely co-exist), and rarer crystal deposition dieases. In older patients, however, a marked inflammatory component, polyarthritis with metacarpophalangeal joint involvement and modest elevation of ESR may lead to consideration of RA or polymyalgia rheumatica.

Investigations

The definite diagnosis of CPPD requires synovial fluid examination and identification of CPP crystals. The aspirated synovial fluid in acute CPP crystal arthritis is often turbid, can be blood stained, and has reduced viscosity. The white cell (WBC) count is elevated, averages >19,000/mm^3 with over 76% polymorphonuclear cells (65). The synovial fluid WBC count is also elevated in the intercritical period (mean: 301 cells/μl (95% CI: 217 - 386)), with >80% WBCs being mononuclear (66). The WBC count and % polymorphonuclear cells are significantly higher in OA synovial fluid positive for CPP crystals than those without CPP crystals (65). Examination of fresh synovial fluid is ideal, but if not possible, the synovial fluid may be stored at 4°C or at a stable room temperature of 20°C for up to 3 days without any significant reduction in crystal count (67). Low speed centrifugation and examination of the aspirate from base of the tube can increase the diagnostic yield (65). CPP crystals can be present intracellularly in both actively inflamed and intercritical joints (66). CPP crystals are

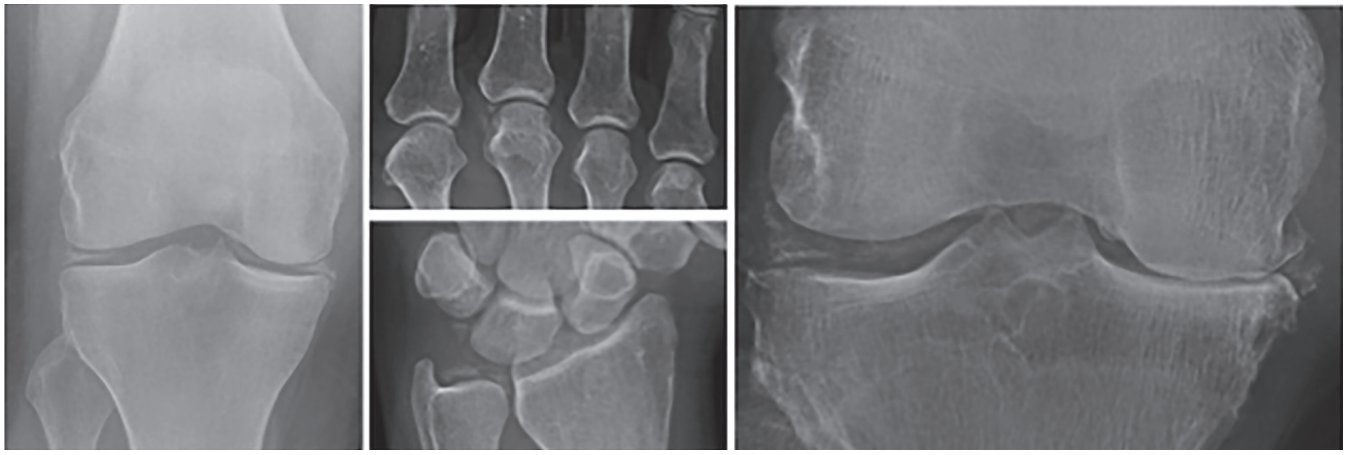

Fig. 2. Chondrocalcinosis affecting both the medial and lateral knee menisci (left panel), triangular and distal radioulnar joint (middle panel, bottom image), and intracapsular calcification and chondrocalcinosis affecting the middle metacarpophalangeal joint (middle panel, top image). Structural radiographic change in knees with chondrocalcinosis (right panel) - note osteophytes, joint space narrowing and subchondral sclerosis in the medial tibio-femoral joint.

less readily identified than monosodium urate crystals (68), and lack of consistency between different observers in identifying CPP crystals is a potential problem, though training improves the levels of inter-observer agreement (69). A recent study has demonstrated that a small inexpensive point of care Raman spectroscope device can detect CPP crystals with a greater sensitivity than polarized light microscopy (70).

Once CPPD is confirmed, consideration should be given to the need for further investigations to determine if an underlying metabolic predisposition is present. Metabolic disease predisposition to CPPD is uncomomon, and routine screening of all patients with CPPD is unrewarding. Nevertheless, screening tests are warranted in those with early-onset CPPD (younger than 55 years), florid polyarticular CC, clinical presentation with recurrent acute attacks, or additional clinical clues that suggest an underlying metabolic abnormality (71). After the age of 55 years the presence of hyperparathyroidism should be looked for in all patients with CPPD because both conditions are more common in this age group (22, 71). Testing for iron overload is especially relevant in those with chondrocalcinosis and an atypical distribution of early onset OA. Tests for rarer diseases *e.g.* acromegaly or Wilson's disease associated with CPPD are only warranted if there are clinical features suggestive of these conditions or in those with polyarticular CPPD at a very young age. Genotyping for mutations and polymorphisms, especially in the ANKH gene may be carried out in those with a family history of premature CPPD if there is no evidence of an associated metabolic predisposing condition.

Imaging

Plain radiography, ultrasonography, and computerised tomography (CT) can be used to identify CPPD (Fig. 2). Magnetic resonance imaging has low sensitivity for detecting CPPD (72). Ultrasonography has excellent specificity (96.4%), good sensitivity (86.7%), a positive predictive value of 92% and a negative predictive value of 93% for detecting CPPD compared to synovial fluid examination (73) and is reported to perform better than CT (74). However, ultrasonography may not be able to detect CPPD in joints with acute CPP crystal arthritis, and further research is needed to compare the diagnostic performance of ultrasonography and joint aspiration in detecting CPPD (75). CPPD appears as single or multiple hyperechoic deposits or as thin hyperechoic bands parallel to the surface of hyaline cartilage on ultrasonography (76).

CPPD associates with OA, and modifies the distribution of OA with greater involvement of lateral tibio-femoral joints, MCPJs, and trapezio-scaphoid joints (10, 77). Some studies reporting an association with osteophytosis while other studies suggest that CPPD does not modify the phenotype of OA (7, 77, 78), while another study reported an association with knee attrition (79). Thus, further research is required to identify the structural changes that can be attributed to CPPD plus OA.

Treatment

Asymptomatic CPPD (chondrocalcinosis) does not require any treatment, although screening for underlying metabolic predispositions may be warranted. Other manifestations of CPPD should be managed to provide optimum symptom control.

Acute CPP crystal arthritis

The treatment of acute CPP crystal arthritis includes joint aspiration and intra-articular injection of slow-release intermediate-acting corticosteroids once infection is excluded, or colchicine 0.5 or 0.6 mg bd or tds (this may also prevent recurrent acute attacks (80)). An NSAID plus a proton pump inhibitor are another option if there are no contraindications. However, in a predominantly elderly population a short course of systemic corticosteroids are preferable to an NSAID or colchicine (once infection has been excluded as a trigger) and produce a more rapid relief (81). Adrenocorticotrophic hormone (ACTH) may be an effective alternative, and a recent retrospective case series reported a dramatic response, with attenuation of signs of inflammation within 24 hours in 13 of 14 patients with mono-articular acute CPP crystal

arthritis who were given a single intramuscular injection of 1 mg (100 units) of synthetic depot ACTH as sole therapy, with one patient requiring a second injection the following day (82).

Anakinra (IL-1 receptor antagonist) has been used in the treatment (100 mg/day for 3 days) and prophylaxis of polyarticular acute CPP crystal arthritis unresponsive to oral corticosteroids (83). In a case-series of patients with predominantly refractory polyarticular acute CPP crystal arthritis 14/16 patients reported a good or partial improvement on day four after receiving anakinra injections (100 mg/day for 3 days) (84). Some patients continued Anakinra for longer duration, up to six months, and more than a third of patients had a relapse when Anakinra was stopped.

OA with CPPD should be managed as OA without CPPD. Some patients with persistent or recurrent inflammatory symptoms may benefit from intra-articular radiocolloid (yttrium-90) injection (number needed to treat (NNT) 2, for >33.3% improvement in knee pain and 50% improvement in global knee symptom) (85).

Chronic CPP crystal inflammatory arthritis

Reccommended pharmacotherapy for chronic CPP crystal arthritis includes oral NSAIDs or low dose corticosteroids (both based on expert opinion and clinical experience), colchicine, hydroxychloroquine, and methotrexate (86). Colchicine (0.5 mg bd for 8 weeks and then as required), resulted in >30% improvement in pain (NNT 2 at 4 months, 4 at 5 months) in knee OA and persistent inflammation due to CPP crystals (87). A small (n=36), double-blind, placebo-controlled study reported rapid improvement from oral hydroxychloroquine over six months (NNT 2 for 30% reduction in swollen and tender joint counts) (88). However, the findings of this study have not been replicated in a larger trial. Two retrospective case series reported beneficial effects of methotrexate (89, 90), however, another case series did not find any benefit (91), and a prospective double blind randomised placebo controlled cross-over trial (n=26) did not report any statistically significant improvement with methotrexate (maximum dose 15 mg/week) in chronic CPP inflammatory arthritis who had an unsatisfactory response or were contraindicated to oral NSAID or low-dose glucocorticoids (92). Therefore, overall there is no convincing evidence to recommend methotrexate in the treatment of recurrent acute or chronic CPP crystal inflammatory arthritis. Other treatment options like anakinra, and radiosynovectomy, may be used.

Crystal dissolution

Once deposited, CPP crystals cannot be safely dissolved *in vivo* (93). Phosphocitrate inhibits the deposition and growth of CPP crystals in vitro (94) and polyphosphates dissolve synthetic CPP crystals and CPP crystals from human menisci without cell damage (95), but these have not been tested *in vivo*.

Surgery

Patients with severe large joint arthropathy who require total or unicompartmental joint replacement appear to derive equal benefits to those with uncomplicated OA, without an increase in the risk of prosthetic failure (96, 97). Treatment of underlying metabolic diseases that predispose to CPPD is appropriate, however, other than possibly for correction of hypomagnesaemia, such treatment does not appear to influence the outcome of CPP crystal-associated arthropathy.

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