



CALCIUM PYROPHOSPHATE deposition disease

The arthropathy formerly
known as “Pseudogout”

A number of clinical syndromes are associated with the precipitation of calcium pyrophosphate dihydrate crystals in and around joints. These syndromes have previously been referred to by terms such as “pseudogout” or “pseudo-osteoarthritis”, but these terms are no longer favoured. Instead, the syndromes are grouped under the umbrella term calcium pyrophosphate deposition (CPPD) disease. The deposition of calcium pyrophosphate crystals results in an inflammatory reaction within the joint in a similar way that precipitation of monosodium urate monohydrate crystals does in patients with gout, and can contribute to significant chronic degenerative change in joints. Patients with CPPD disease can be asymptomatic or present with a range of symptoms and signs similar to gout or other forms of inflammatory arthritis, making an accurate clinical diagnosis difficult. In addition, unlike for gout, there is a relative lack of evidence-based research on the syndromes caused by CPPD and there is no specific medicine that can decrease the concentration of crystals. Management is therefore targeted at symptomatic relief only.

The prevalence of CPPD disease

There is little research into the prevalence of symptomatic calcium pyrophosphate deposition (CPPD) disease. Chondrocalcinosis, which is calcification of the articular cartilage, most often caused by CPPD, is estimated to affect 5% of the general population, and prevalence increases with age.^{1,2} CPPD disease may be more prevalent in females than males, but evidence is conflicting.^{1,3} There is currently no evidence available regarding ethnic differences between the prevalence of CPPD disease in Māori, Pacific peoples and New Zealand Europeans. However, there is some evidence that people of Asian descent may have a lower prevalence of CPPD disease than people of European descent.⁴

Risk factors for CPPD

Risk factors for the development of CPPD include:

- Increasing age – after age 50 years, the risk of developing CPPD approximately doubles every decade.¹ In people aged under 50 years, CPPD is rare and if diagnosed in this age group it is likely that there is a familial association or a predisposition to a metabolic disease.
- Prior joint injury or surgery
- A history of gout – it is estimated that 20% of patients with CPPD disease also have hyperuricaemia and 25% of these patients will develop gout⁵
- Hereditary/familial predisposition to CPPD – patients may present at a younger age and are more likely to have polyarticular involvement (see: “Deposition of CPP crystals, Page 23)

- A history of an endocrine or metabolic condition such as haemochromatosis, primary hyperparathyroidism, hypophosphatasia, hypomagnesaemia – metabolic changes that occur as a result of these conditions are thought to promote calcium pyrophosphate (CPP) crystal deposition by inhibiting pyrophosphatases or by a direct effect on cartilage.^{1,6}

The association between CPPD and osteoarthritis is complex. The two conditions have risk factors in common, such as increasing age and previous injury, and CPP crystal deposition is increased in the presence of damaged cartilage.¹ However, CPPD also appears to initiate and worsen existing osteoarthritic damage in joints.^{1,5} CPP crystals are found in approximately one-third of cases where samples are taken from the knees of patients with osteoarthritis who are undergoing arthroscopy.⁵

The clinical presentation of CPPD disease

Patients with CPPD disease can be asymptomatic (with the changes detected incidentally on x-ray) or may present with a range of symptoms and signs similar to those found in patients with gout or other forms of inflammatory arthritis (e.g. rheumatoid arthritis) or septic arthritis. It can be difficult to distinguish CPPD disease clinically from these other conditions affecting joints. CPPD may also co-exist with gout, osteoarthritis and joint infection, and may not always be the condition that is causing the patient’s symptoms.⁹

The deposition of CPP crystals results in an inflammatory reaction within the joint in a similar way that precipitation of monosodium urate monohydrate crystals does in patients with gout. Acute symptoms of CPPD disease therefore, include pain, swelling, stiffness, erythema, loss of function and marked tenderness of the affected joint(s).¹⁰ Patients with CPPD disease may also present with systemic features, such as neck pain, headache and fever (estimated to occur in up to 50% of people with CPPD),⁶ which may make it more difficult to differentiate between infection and inflammation.

CPPD disease often affects the large joints, most commonly the knee. Other joints likely to be involved are the wrist, ankle, elbow, toe, shoulder and hip.⁵ CPPD disease is polyarticular in approximately two-thirds of patients,⁶ and it often occurs in an asymmetric pattern. CPPD disease, however, can mimic

rheumatoid arthritis or polymyalgia rheumatica, and patients may present with symmetrical joint involvement. Rarely, there may be deposition of CPP crystals in other parts of the skeleton, e.g. in the spine, symphysis pubis or temporomandibular (TMJ) joint.³ CPPD in the neck can cause crowned dens syndrome, a rare cause of acute neck pain.¹¹ CPPD can also be associated with tendinitis, tenosynovitis and bursitis.^{1,10}

Clinical syndromes associated with CPPD

Asymptomatic CPPD – patients may have incidental x-ray findings consistent with CPPD (chondrocalcinosis) but have no apparent clinical consequence. It has been suggested, however, that if a fuller history is taken, many of these patients do have a history of joint symptoms, especially of the knee or wrist.⁵

Making the terminology crystal clear

Many terms, e.g. pseudogout, pseudo-osteoarthritis, pseudo-rheumatoid arthritis, have been used to describe the wide range of clinical syndromes associated with the deposition of calcium pyrophosphate dehydrate crystals in joints. The term “pseudogout” was adopted in 1962 following the first description of calcium phosphate crystals found in the synovial fluid of affected joints in patients with a normal serum urate level.⁷ The term was chosen to reflect a discrete type of crystal-induced synovitis that resembled an acute attack of gout. Subsequently it has been found that deposition of CPP crystals in joints is not only responsible for acute synovitis, but associated with a wide range of clinical syndromes.

Within the literature there is debate about which terms should be used and there has been a recent attempt to clarify the nomenclature. The European League against Rheumatism (EULAR) CPPD Task Force has agreed on a uniform terminology with the aim of reducing confusion and the inconsistent use of terms such as “pseudogout”. Their recommendations are that the following terminology be accepted into clinical research and practice:¹

- CPP crystals – the simplified term for calcium pyrophosphate dihydrate crystals

- Calcium pyrophosphate deposition; CPPD – the “umbrella term” for all conditions associated with the deposition of CPP crystals:
 - Asymptomatic CPPD – CPPD without any apparent clinical consequence, most often an incidental finding on x-ray
 - Acute CPP crystal arthritis (formerly pseudogout) – referring to an acute, self-limiting synovitis with CPPD
 - Osteoarthritis with CPPD (formerly pseudo-osteoarthritis) – CPPD that occurs in a joint that has pre-existing degenerative changes due to osteoarthritis
 - Chronic CPP crystal inflammatory arthritis (formerly pseudo-rheumatoid arthritis) – chronic inflammatory arthritis associated with CPPD
- Chondrocalcinosis – calcification of the articular cartilage identified on an x-ray. Chondrocalcinosis is usually caused by CPPD, however, it may be present in a joint that otherwise appears normal, or in association with structural changes consistent with osteoarthritis. The term “chondrocalcinosis” should be reserved for describing the radiologic changes of cartilage calcification rather than used to describe a clinical situation in a patient.

Acute CPP crystal arthritis – an acute onset of a painful swollen joint (or joints) reflecting a self-limiting synovitis with CPPD. An acute episode of CPPD disease may occur spontaneously or develop after trauma, surgery or a severe medical illness, in a similar way to an attack of gout. Recurrent, acute attacks of CPPD disease can cause progressive damage to the joint. The term “pseudogout” was traditionally used for this acute condition because of the similarity to an acute attack of gout, although it is estimated that only approximately 25% of patients have this classic pattern of disease.⁵

Compared to patients with acute gout, acute attacks in patients with CPPD disease are generally:⁵

- In the knee rather than the first metatarsophalangeal (MTP) joint
- Less painful
- Slower to reach their peak intensity
- Slower to resolve even with symptomatic treatment, e.g. three months

Osteoarthritis with CPPD – CPPD that occurs in a joint that has pre-existing degenerative changes due to osteoarthritis. Both osteoarthritis and CPPD disease as isolated conditions often involve the knee joint, however, patients who have osteoarthritis with CPPD tend to have:¹

- Pain that is more intense (than in osteoarthritis alone)
- Marked tenderness of the affected joints
- Systemic symptoms, e.g. fever
- An atypical distribution of affected joints – osteoarthritis alone does not usually involve joints such as the wrist, elbow, shoulder or ankle joint⁶

Chronic CPP crystal inflammatory arthritis – chronic inflammatory arthritis associated with CPPD, often with a symmetrical distribution to affected joints. This may be more frequently seen in younger patients (age < 50 years) who have a familial form of CPPD.⁶

History and examination may not always result in a definitive diagnosis

CPPD disease can mimic most other forms of inflammatory arthritis, gout and joint infection.⁵ History and clinical examination may help the clinician to distinguish CPPD disease from these other conditions, however, the clinical picture is usually not sufficiently distinct enough to allow a definite diagnosis to be made on clinical grounds alone.

Deposition of CPP crystals

The factors contributing to CPP crystal deposition and joint damage remain uncertain, however, research has contributed to the understanding of how CPP crystals are formed. Changes in cartilage as a result of ageing, trauma, genetic factors and metabolic or biochemical processes are known to contribute to the development of CPPD.^{3,6} There appears to be increased production of inorganic pyrophosphate and decreased levels of pyrophosphatases (enzymes that break down pyrophosphate).

Enhanced activity of enzymes that break down adenosine triphosphate (ATP) produces an increase in extracellular inorganic pyrophosphate. The inorganic pyrophosphate binds with calcium to form CPP crystals which are then deposited in the cartilage and synovium of joints.

A mutation in a gene that encodes a protein involved in the transport of pyrophosphate is now known to have a key causative role in the familial forms of CPPD and is also likely to be involved in the non-familial forms.⁸ The gene has been identified as ankylosis protein homolog human gene (ANKH) and is located on chromosome five.⁹ A familial form of the disease should be considered in a symptomatic person aged less than 50 years who is found to have CPPD disease.



Ask patients about:^{6,10}

- The number and site of affected joints
- The speed of onset and the severity of the pain
- The presence of systemic symptoms, e.g. fever – up to 50% of people with acute CPPD disease will have a fever, and rarely, older patients may present with delirium
- Any acute injury to the joint
- If there has been a past history of pain, trauma or surgery in the affected joint(s)
- Any history of a recent severe illness (e.g. significant infection, cardiac failure) or recent surgery (in particular parathyroidectomy). These conditions can cause a rapid decrease in serum calcium which may precipitate an attack.
- A family history of episodes of polyarticular joint pain in young relatives, particularly if the patient themselves is younger (age < 55 years)
- Co-morbidities, specifically haemochromatosis or parathyroid disease

Investigations can often confirm a clinical suspicion of CPPD disease

It is important to initially consider the possibility of septic arthritis, particularly if the patient presents with a single affected joint.

Exclude septic arthritis

If a single joint is involved, septic arthritis should be excluded, however, infection may also occur concurrently with underlying CPPD disease. If the joint is able to be aspirated, synovial fluid should be obtained and sent for microscopy and culture. There may also be a high leukocyte count (predominantly neutrophils) in the synovial fluid, however, this can occur with both infection and CPPD disease.

Whether a joint can be aspirated depends on a number of factors, including the skill of the clinician, which joint is affected (some joints are easier to aspirate than others) and any contraindications, including cellulitis overlying the affected joint, the presence of a joint prosthesis or a bleeding disorder. The use of oral anticoagulants is a relative contraindication and a decision to aspirate an affected joint should be made on an individual patient basis.¹²

Identification of CPP crystals from synovial fluid is the gold standard for diagnosis

The gold standard for a definitive diagnosis of CPPD disease is the identification of CPP crystals in synovial fluid.¹ The

characteristic crystals found in CPPD disease are generally rectangular, square, rhomboid or rod-shaped and can be seen using polarised light microscopy.^{5,6} Other types of crystals, e.g. monosodium urate, may also be visible.

Blood tests

A number of blood tests may be requested but none have as much diagnostic value as synovial fluid analysis. Consider requesting:^{5,10}

- FBC – this may show an increased white blood cell count, however, this is often not particularly useful in distinguishing between infection and inflammation
- CRP – similar limitations exist with the interpretation of a raised CRP result
- Serum urate levels – a normal result reduces the likelihood of gout, however, serum urate can be normal in some patients with acute gout and up to 20% of patients with CPPD may have an elevated serum urate. Urate levels should be taken when joint symptoms are not evident to ensure increased accuracy.
- Creatinine and electrolytes – particularly if the use of an NSAID is being considered

Patients aged less than 55 years and those who present with florid, polyarticular joint involvement should be assessed for an underlying metabolic disease, such as hypomagnesaemia, hyperparathyroidism or haemochromatosis.^{1,3} Additional investigations may include parathyroid hormone, calcium, phosphate, magnesium and iron studies.

The role of radiology

Plain x-rays can help to confirm a clinical suspicion of CPPD, particularly if synovial fluid is not able to be obtained to look for CPP crystals. X-ray may also reveal the extent of degeneration within the joint. Chondrocalcinosis (linear or punctate calcification of the hyaline and fibrocartilage) is the characteristic finding on plain x-ray that is associated with CPPD.¹³ However, the absence of chondrocalcinosis on x-ray does not exclude CPPD disease.¹ If plain x-rays are requested, the recommended joints to be imaged are the knees, wrists and an anteroposterior view of the pelvis. An x-ray of the knees alone is likely to result in a significant number of patients with CPPD being missed.¹⁴

Other forms of imaging, e.g. ultrasound, CT and MRI, have a relatively limited role in the majority of patients with CPPD disease, however, they can be useful in patients with atypical or rare presentations of the disease.¹³ Ultrasound, for example, can be useful to guide joint aspiration in some patients or may

identify calcium deposits within articular cartilage.¹³ CT and MRI scanning may be requested in secondary care to assess CPP crystal deposition at atypical sites such as in the neck (crowned dens syndrome) or in other areas of the spine where it may cause spinal cord compression.^{10,13}

Treatment of CPPD disease

Unlike in gout, there is currently no effective treatment that reduces or removes CPP crystals from a joint.^{6, 15} Treatment therefore is not indicated for patients found to have asymptomatic chondrocalcinosis on x-ray. Treatment for an acute attack provides symptomatic relief, but it does not modify the course of the disease. If untreated, an acute attack of joint pain due to CPPD disease may last from a few days or up to a month.⁶ If CPPD disease is a result of an underlying condition, e.g. haemochromatosis, primary hyperparathyroidism, this should be managed as appropriate, although there is little evidence that this improves arthropathy due to CPPD in patients with these conditions.⁵ Many patients will have associated osteoarthritis and general measures used to manage this will also be of value, including education, exercise and weight loss, joint supports and mobility aids to maintain joint mobility and reduce pain and stiffness.

There is limited evidence supporting the use of any of the medicines used in the treatment of CPPD disease, in particular, a lack of randomised controlled trials. Recommendations for the management of CPPD disease tend to be based on expert opinion or extrapolated from research on the treatment of gout.¹⁵

Treatment of an acute attack

Treatments to reduce the pain and swelling associated with an acute attack of CPPD disease include:^{3,15}

- Ice or cool packs
- Temporary rest of the affected joint
- Joint aspiration
- Oral NSAIDs
- Low dose colchicine
- Corticosteroids (intra-articular injection or oral)

Ice or cool packs and rest of the affected joint are likely to provide temporary relief from pain and can reduce swelling.

Aspiration of an affected joint not only provides fluid for confirmation of the diagnosis and exclusion of infection, it can give temporary relief from pain due to a reduction in the fluid volume within the joint. An intra-articular injection of corticosteroid can be very effective in reducing symptoms

in patients who have a single affected joint that is easily accessed.

If appropriate, an oral NSAID (with PPI cover if necessary) or low dose colchicine can be effective in reducing acute symptoms.¹⁵ Recommendations for the dose of colchicine for the management of CPPD vary. For relief of acute symptoms, EULAR recommends colchicine 0.5 mg, up to three to four times daily, with an optional loading dose of 1 mg.¹⁵ The duration of treatment depends on symptom relief and adverse effects.¹⁵ The use of both colchicine and NSAIDs will be limited by individual patient factors such as age, renal function, other co-morbidities and the risk of adverse effects or toxicity.

If NSAIDs or colchicine are unable to be used, a short tapering course of oral corticosteroids (e.g. prednisone 0.5 mg/kg, daily, with a rapid taper) may also provide relief from acute symptoms, especially in patients with severe polyarticular attacks.^{3,15}

Treatment of chronic CPPD disease

The choice of medicines used for patients with chronic CPPD is based primarily on evidence for treatments used to manage gout and osteoarthritis, and on expert opinion.¹⁵ The following treatments may be trialled as appropriate (in order of preference), in patients with chronic CPPD disease:¹⁵

- NSAIDs (with PPI protection)
- Low dose colchicine, e.g. 0.5 – 1 mg daily
- Low dose oral corticosteroids – no specific dose recommendation given; usual maintenance dose is between 2.5 mg – 15 mg daily¹⁶

Long-term use of these medicines is associated with various adverse effects; patients should be monitored appropriately. Patients taking colchicine should immediately report any gastrointestinal symptoms. Consider the need to monitor renal function, FBC (for leukopenia and thrombocytopenia) and creatinine kinase (for colchicine-induced myotoxicity). Also be aware of potential medicine interactions.

 For further information on prescribing NSAIDs, see: "NSAIDs: Making safer treatment choices", Page 8.

 For further information on prescribing long-term steroids, see: "Polymyalgia rheumatica – Practical considerations when prescribing long-term corticosteroids", BPJ 53 (Jun, 2013).

There have been some small trials of other medicines, such as methotrexate and hydroxychloroquine, in patients with chronic,

severe CPPD that has not responded to usual treatment, however, there is limited evidence of their effectiveness.^{15, 17} Referral to a Rheumatologist is recommended for patients with chronic symptomatic CPPD disease where other treatments have been unsuccessful.

Chronic disease or recurrent acute attacks of CPPD disease can cause progressive damage to the joints. Patients with CPPD in joints that have deteriorated significantly, often in combination with osteoarthritis, should be assessed for joint replacement surgery in the same way that patients with osteoarthritis alone are.

Medicines used for prophylaxis of recurrent attacks

There is some evidence that low dose colchicine (0.5 mg, once or twice daily) may be effective in reducing the number of attacks in patients with frequent recurrent episodes, but no evidence on the use of NSAIDs.¹⁵ Either of these medicines can be prescribed in an attempt to reduce the frequency of acute attacks, however, the appropriateness for an individual

patient must be considered and the patient monitored for adverse effects such as gastrointestinal disturbances (bleeding, diarrhoea), changes to renal function, myopathy and cardiovascular events.

Potential future treatments for CPPD disease

There have been suggestions that some medicines and dietary changes may theoretically work to inhibit the formation or increase the dissolution of CPP crystals, but more research is required. The treatments being studied further include: anti interleukin 1 therapy, glucosamine, magnesium, probenecid, a diet rich in vitamin C and a low cysteine diet.^{3, 5, 15}

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