Clinical presentation and diagnosis of calcium deposition diseases

Calcium pyrophosphate dihydrate and basic calcium phosphate crystals are commonly found in patients with calcium deposition diseases. Deposits of these crystals are common in the elderly and they have been implicated in the pathogenesis of osteoarthritis. The presence of crystal deposits is often asymptomatic, although it can be intermittently symptomatic and elicit acute and chronic arthritis. Acute intra- and peri-articular inflammation are clinically similar to cellulitis, gout and septic arthritis. Plain radiography of the affected joints is usually the first and most valuable diagnostic method to evaluate these conditions. Ultrasonography is highly sensitive for the detection of crystals in the synovial fluid and of crystals deposited in cartilage and soft tissue. Joint-fluid analysis is far more sensitive than radiologic study to detect calcium pyrophosphate dihydrate and basic calcium phosphate crystal deposits, and arthrocentesis is indicated in some patients to rule out septic arthritis.

KEYWORDS: ANKH ▪ **basic calcium phosphate** ▪ **calcium pyrophosphate dihydrate** ▪ **inorganic pyrophosphate** ▪ **osteoarthritis**

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Learning objectives

Upon completion of this activity, participants should be able to:

- Identify the prevalence of and risk factors for chrondocalcinosis
- Describe the clinical presentations of calcium pyrophosphate dihydrate crystals
- Describe the association between calcium crystal disease and osteoarthritis
- Characterize imaging studies useful for the diagnosis of calcium deposition diseases
- Identify metabolic causes of calcium deposition disease

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Calcium deposition diseases, the disordered calcification of cartilage and/or periarticular soft tissue, are associated with aging, degenerative joint disease, and genetic and metabolic disorders [1,2]. Calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphate (BCP), such as hydroxyapatite (HA), are the most common calcium-containing crystals. Chondrocalcinosis (CC) is a characteristic radiographic feature of calcium deposition in articular hyaline and/or fibrocartilage. Extracellular inorganic pyrophosphate (PPi) plays a key role in regulating the formation of pathologic and physiologic minerals, although the formation of calcium crystals in articular cartilage has a multifactorial background. The presence of excess extracellular PPi accompanies and possibly plays a role in CPPD crystal deposition, and it interferes with normal mineralization; a reduction in extracellular PPi, on the other hand, promotes BCP formation [3,4]. They are seen in unique clinical subsets of patients with inflammatory arthritis and progressively worsening osteoarthritis (OA) [5]. These conditions are often diagnosed by plain radiography; however, definitive diagnosis requires synovial fluid analysis. In this review, we summarize the mechanisms of CPPD and BCP crystal formation and highlight findings regarding the clinical features of accumulations of these crystals.

Calcium pyrophosphate dihydrate crystal deposition disease

Richette *et al.,* who summarized findings reported between 1998 and 2008 [1], cited aging as the main risk factor for the development of CC; its prevalence varied from 7 to 10% in persons aged approximately 60 years. The deposition of CPPD crystals in articular tissues is most common in the elderly, occurring in 10–15% of persons aged 65–75 years and in 30–50% of those aged over 85 years [6]. In large series, the gender distribution of CPPD crystal deposition disease differed; however, no marked sex predominance was obvious [1]. Attacks of pseudogout occur more frequently in men, while pseudo-OA is more common in women [101].

Pathogenesis

Extracellular inorganic pyrophosphate accumulation

Chondrocytes are the primary source of PPi in the joint [7] and compared with samples from normal controls and individuals with OA, chondrocytes from CPPD-diseased cartilage produce more extracellular PPi [8]. PPi may be produced *de novo* by chondrocyte ectoenzyme nucleoside triphosphate pyrophosphohydrolase (NTPPPH) [9], such as PC-1 [4], which hydrolyzes ATP to AMP and PPi. There is a linkage among CPPD crystal deposition, excess chondrocyte NTPPPH activity, excess PPi generation by chondrocytes and cartilage supersaturation with PPi [3,4]. The augmentation of extracellular PPi from chondrocytes is implicated in aging and in transduction pathways involving cyclic AMP and PKC signaling [3]. Transglutaminase may also be an important determinant of age-related changes in extracellular PPi production by activating the potent crystal-inducing factor latent TGF β-1 [10].

ANK for inorganic pyrophosphate transport

Alternatively, PPi is transported from the cell by mechanisms that include the multiple-pass transmembrane protein ANKH, the human homolog of the *ank* gene cloned in mice [11]. The *ank* gene codes for a protein required for the transport of PPi across the cell membrane into the extracellular environment. *ANKH* mRNA expression was higher in CPPD chondrocytes and in cartilage extracts from CPPD patients compared with OA patients and cartilage samples from normal subjects, and there was a correlation between *ANKH* expression and the extracellular PPi concentration [8]. Transfection studies demonstrated that ANKH promoted an increase in extracellular PPi in human immortalized articular chondrocytes [12]. Furthermore, *ANKH* mutations were documented in patients with familial [12–15] and sporadic CPPD [12]. Loss-of-function mutations in *ANKH* and *ank* resulting in excessive CPPD crystal deposition have been reported [11,16,17].

Other factors

Other factors playing a role in the paradigm of CPPD crystal formation are calcium, extracellular matrix, matrix vesicles and chondrocyte hypertrophy [18,19]. Calcium is necessary for CPPD crystal formation and its concentration is increased in cartilage in patients with OA [20]. However, little is known about the role of calcium in the formation of CPPD crystals. Changes in the pericellular matrix, where the smallest and earliest CPPD crystals are formed, also contribute to CPPD crystal formation [18]. *In vitro*, matrix vesicles isolated from human OA articular cartilage formed CPPD crystals in the presence of ATP [21]. Hypertrophic chondrocytes colocalize with CPPD crystal deposits in articular cartilage [22]. In this context, hypertrophic chondrocytes generate not only

more extracellular PPi [23], but also produce more mineralization-competent matrix vesicles *in vitro* [24].

Clinical presentation

Calcium pyrophosphate dihydrate crystal deposition disease is often asymptomatic, although there are various clinical manifestations, such as episodes of acute arthritis (termed pseudogout) and chronic arthritis, resulting in a variety of clinical phenotypes, including degenerative joint disease, rheumatoid arthritis and neuropathic osteoarthropathy [25]. While these are the most common types of presentation, unusual manifestations have been observed.

Asymptomatic (lanthanic) calcium pyrophosphate dihydrate

Asymptomatic CPPD is usually associated with only radiographic changes (i.e., CC) and may be the most common form of CPPD deposition disease [102]. Meniscal CPPD deposits are associated with aging and can be found in both CPPD disease and OA [26].

Pseudogout

Pseudogout refers to acute, gout-like episodes of inflammation. It tends to be monoarticular, although polyarticular acute flares are not rare. Multiple joints in the same limb are often involved. Acute monoarticular arthritis with spontaneous pain onset, edema and inflammation is a typical feature. These symptoms are due to inflammatory responses triggered by the lysis of polymorphonuclear white blood cells that have ingested CPPD crystals, as is the case after their ingestion of monosodium urate crystals [25]. As with gout, the attacks are self-limiting and last approximately 10 days, although cluster attacks may last for several weeks [6,27]. The most common sites of pseudogout arthritis are the knees, wrists and shoulders [103]. This form of CPPD deposition disease is observed in 25% of patients [102]. Among provocative factors, the most common is a stress response to intercurrent illness or to surgery. The incidence of pseudogout after arthroscopic lavage for knee OA with pre-existing CC is estimated to be 26% [28]. Bisphosphonates [29] and repeated intra-articular hyaluronan injections [30] may trigger pseudogout attacks.

Pseudo-osteoarthritis

Pseudo-OA is CPPD-associated arthropathy without acute attacks but with joint degeneration [25]. Many clinical features of pseudo-OA overlap with primary OA; however, articular cartilage bearing CPPD crystals are different from the articular cartilage disease process in OA. CPPD arthropathy tends to affect elderly women and most commonly involves the knees, wrists, metacarpophalangeal, particularly the second and third joints, the shoulders and hips [1]. Radiography reveals joint space narrowing, especially in the radiocarpal and patellofemoral joint (e.g., patella wrapped around the femur). This form of CPPD is observed in 50% of all patients and approximately half of them also present with associated pseudogout [102].

In primary OA, the presence of CPPD and BCP crystals has been reported as an adverse prognostic factor. These crystal species have been identified in more than half of the samples from OA synovial fluids [5,31]. Derfus *et al.* reported that higher mean radiographic scores correlated with the presence of calcium-containing crystals [5]. In their sequential studies, Nalbant *et al.* demonstrated that some patients with no crystal deposits at disease onset manifested deposits in the course of disease progression [31]; they found CPPD and BCP crystals, respectively, in 19 and 23% of patients at their first visit and in 34 and 58% at their last visit, spanning a term of 2–7 years. Reuge *et al.* reported that more patients with primary OA and CPPD crystal deposits required knee replacement surgery than patients with primary OA without crystal deposits [32]. However, the suggestion that CPPD may represent a marker for a poor prognosis in patients with knee OA was not validated in longitudinal studies [33,34]. A prospective analysis of CPPD deposition disease primarily involving the knee suggested that radiographic worsening of degenerative changes may be slow [33]. In a more recent MRI study of the relationship between CC and the progression of knee OA assessed cartilage loss in two cohorts of patients with knee OA, a negative association between baseline CC and risk for cartilage loss was demonstrated [34]. In fact, patients with OA and CPPD tend to undergo knee arthroplasty at an older age than patients with non-CPPD OA [35].

Pseudorheumatoid arthritis

Clinical manifestation of pseudorheumatoid arthritis closely mimics rheumatoid arthritis itself [25]. Pseudorheumatoid arthritis is found in approximately 5% of patients with CPPD crystal deposits and is associated with symmetric inflammation of the proximal interphalangeal and metacarpophalangeal joints with morning stiffness and joint swelling [102]. Radiographically, erosion can be observed, but it is usually associated with CC.

Pseudoneuropathic joints

Pseudoneuropathic joints involve a severe destructive arthropathy without a clear underlying neurological disorder. It occurs in fewer than 5% of patients with CPPD crystal deposits that tend to involve the knee [102].

Periarthritis

Calcium pyrophosphate dihydrate crystals affect periarticular structures more frequently than is generally recognized. In a cross-sectional study involving 50 subjects with CPPD-associated arthropathy, 52% presented with periarticular involvement [36]; 24% had carpal tunnel syndrome and 20% had periarthritis of the shoulder; less common were anserine bursitis and epicondylitis. Deposits of CPPD crystals may elicit symptoms that mimic rheumatic polymyalgia [37], and they have been found to be involved in spinal disorders [38,39]. Spinal involvement is frequently associated with neural impingement symptoms and spinal stenosis that require surgical decompression.

Tophaceous pseudogout

Large accumulations of calcium pyrophosphate material may produce a pseudotumor (tophaceous pseudogout) with all the consequences of other space-filling lesions. The radiologic differentiation between highly calcified masses and tumoral calcinosis can be difficult because they are similar to benign or malignant cartilaginous lesions [40–42]. The most common anatomic sites harboring tumoral CPPD crystals were the temporomandibular joint (37%), the cervical spine (22%) and the hand (18%) [42].

Familial calcium pyrophosphate dihydrate deposition disease

Familial CPPD deposition disease appears early, often as early as in the third decade of life. It tends to be aggressive and the long-term prognosis is ominous [104]. Molecular genetic studies implicated a gene with an autosomal-dominant mode of inheritance, and identified a mutation in the *ANKH* gene [16,17].

Diagnosis

Imaging studies

In patients with suspected CC, plain radiographs tend to be most useful for evaluating affected joint(s). Patients with pseudogout usually exhibit degenerative joint changes; their soft tissues, tendons or bursae may be calcified. Radiographically, a dense line in the hyaline cartilage parallels the articular surface, often resulting in a calcified hyaline cartilage surface. However, radiographs are relatively insensitive and detect only sizeable deposits of CPPD crystals [43].

Ultrasonography is an emerging highly specific, sensitive technique for the detection of CPPD deposits, particularly those too small for visualization on plain radiographs [44,45]. The most important ultrasonographic signs of CPPD deposits are a thin hyperechoic band parallel to the surface of the hyaline cartilage and a punctuated fibrocartilage pattern.

While computerized tomography has a limited role in patients with CC, it is valuable for inspecting atypical sites at which plain radiography may fail to identify calcification. On computed tomography scans, calcified masses may exhibit a lobulated configuration, typically in the ligamentum flavum or within the joint capsule [41].

For the diagnosis of calcium deposition disease, MRI has poor sensitivity, specificity and reproducibility compared with plain radiography [43], although on T1-weighted images crystal deposits are identified by a loss of signal intensity. However, MRI can be very useful for determining the extent of the disease or for identifying complications, and may be useful for obtaining a differential diagnosis [46]. Gadolinium-enhanced MRI scans are valuable for the evaluation of tendon sheath involvement and in patients with a differential diagnosis of osteomyelitis.

Laboratory studies

Joint-fluid analysis of calcium deposition diseases is far more sensitive than radiologic methods for detecting the deposition of CPPD crystals [5]. Diagnostic arthrocentesis is mandatory in patients with new-onset acute monoarthritis and is strongly recommended in patients with recurrent attacks without microscopic evidence of crystal deposits. A definitive diagnosis of CPPD deposition disease is based on the demonstration of CPPD crystals in synovial fluid. The crystals are rhomboid, long or short rods, or small squares ranging in length from 2 to 20 µm [27]. Under polarized light, they exhibit a weak birefringence and positive elongation [6].

Histologic findings

The presence of crystal deposits in soft tissue results in adjacent chondroid metaplasia. Synovial hyperplasia with inflammatory changes is often observed and may be mild to moderate, consisting of mononuclear cells [22]. In tophaceous pseudogout, giant cells are often visualized [42].

Treatment

Treatment depends on the degree of involvement. For individuals with acute episodes, NSAIDs and short courses of low-dose systemic glucocorticoids, such as prednisolone (5 mg/day), are the primary mode of treatment [47]. The intra-articular injection of steroids provides reliable prompt relief, particularly when a large, easily accessible joint is involved. Colchicine can be effective to treat recurring pseudogout, and magnesium has been used on a preventive basis [47]. Methotrexate may be a therapeutic option for chronic CPPD deposition disease [48]. The goal of pharmacotherapy is to terminate the acute attack and to prevent complications and recurrent attacks. However, at present, no prophylactic or deterrent regimen for patients with sporadic pseudogout is available. If an underlying metabolic problem is responsible for the pseudogout, the arthritis may be cured by addressing the underlying problem. Patients should also be counseled to reduce comorbidities.

Arthroscopic surgery allows debridement of superficial deposits of the calcium pyrophosphate precipitate [49]. This alone may not materially affect the course of the disease. A preferred option in patients with more advanced OA is total joint replacement. When large space-occupying tophaceous lesions are present, surgical excision is indicated. This is particularly true in patients with myelopathy or radiculopathy due to the massive focal accumulation of CPPD crystals in the ligamentum flavum [41].

Basic calcium phosphate crystal deposition disease

Pathogenesis

Inorganic pyrophosphate metabolism

The formation of BCP crystals in articular cartilage is even less well understood than the formation of CPPD crystals. In addition to fostering CPPD crystal formation, extracellular PPi also regulates the formation of BCP crystals. BCP crystal deposits in articular cartilage, synovitis and OA are associated with extracellular PPi deficiency in *ank/ank* and PC-1 knockout and PC-1-deficient *ttw/ttw* mice [11,50,51]. Excessive hydrolysis by tissue-nonspecific alkaline phosphatase of PPi to inorganic phosphate (Pi) promotes the formation of BCP crystals in cartilage by lowering the concentration of extracellular PPi [50,52]. These findings illustrate that extracellular PPi deficiency has a deleterious effect on chondrocytes and promotes calcification [3,4]. By contrast, high levels of extracellular PPi have a negative effect on BCP crystal nucleation and growth [3]. Thouverey *et al.* demonstrated the formation of CPPD when the Pi:PPi molar ratio is below 25, and HA formation when the ratio is above 70, using matrix vesicles isolated from chicken embryo growth plate cartilages [53]. The optimal Pi:PPi ratio is below 6 for CPPD formation and above 140 for HA formation, and the retardation of any mineral formation is maximal when the ratio is approximately 30.

Other factors

Matrix vesicles have been the main focus of studies on the formation of BCP crystals [54], and there is histologic evidence of matrix vesicles near BCP crystal deposits in articular cartilage [18,19]. Derfus *et al.* demonstrated the ability of human OA cartilage matrix vesicles to generate BCP in the absence of ATP *in vitro* [21]. Calcium levels may be increased in affected cartilage, and pericellular matrix changes have been documented in the course of BCP crystal formation in articular cartilage [18]. Chondrocyte hypertrophy and apoptosis are enhanced in OA cartilage; they are directly associated with BCP crystal deposition at those sites [19,55]. In this context, nitric oxide, a central mediator in OA, stimulates chondrocyte apoptosis [56]. Importantly, treatment of cultured chondrocytes with the nitric oxide donor sodium nitroprusside stimulated calcification [57].

Clinical presentation

The incidence of intra-articular BCP crystal deposits increases with age and in joints, the crystals frequently co-exist with CPPD crystals [5,31]. However, in tissues, BCP crystals are more widely distributed than CPPD crystals [18]. BCP crystal deposits in periarticular soft tissue can be asymptomatic or elicit acute calcific periarthritis, tendonitis, bursitis, enthesitis and, less often, arthritis. In acute attacks, periarticular tissues or joints can be swollen, tender and hot, and may appear clinically similar to cellulitis, gout, pseudogout and septic arthritis. BCP crystal deposits tend to produce such attacks in the shoulders, the greater trochanters of the hips, elbows, wrists and digits [27]. Acute calcific periarthritis of the first metatarsophalangeal joint (pseudopodagra) occurs predominantly in young women. Periarticular or articular BCP crystal deposits are also present in synovial fluid in an extremely destructive chronic arthropathy of the elderly that occurs most often in shoulders (Milwaukee shoulder) and in a similar process in the hips and knees, and erosive OA of fingers.

Articular BCP crystal deposition is closely correlated with the severity of articular damage in OA [5]. The BCP crystals may contribute to the pathogenesis of OA by a deleterious mechanical effect of bone chips from eroded surfaces, stimulating synovial fibroblast mitogenesis (synovial lining proliferation and increased cellularity of the synovium), upregulating IL-1β expression, and by increasing the production of matrix metalloproteinase, prostaglandins and nitric oxide [58,59]. Fuerst *et al.* recently demonstrated an extremely high rate of calcification in OA cartilage samples removed for knee replacement and correlated the extent of calcification (which was mostly BCP) with cartilage degeneration [60]. By contrast, the deposition of HA crystals was not intimately involved in the pathogenesis and progression of human OA [61]. The association between BCP deposition and the pathogenesis and progression of OA remains controversial. Further studies are needed in order to gain a better understanding of the relationship between OA and the deposition of calcium crystals.

Diagnosis

Imaging studies

Intra- and/or peri-articular calcifications with or without erosive, destructive or hypertrophic changes may be seen on radiographs. Ultrasonographic pattern of BCP-associated disease depends on the calcification phase. Ultrasonography also has a role in guiding percutaneous needle aspiration therapy in patients with BCP crystal arthropathy [62] and in the preoperative marking for arthroscopic surgery [63].

Laboratory studies

Arthritis due to BCP crystal deposition is underrecognized because individual crystals are tiny, measuring only 7–25 nm in diameter [27,64]. However, the routine analysis of joint crystals continues to rely almost exclusively on optical microscopy. Under a light microscope, clumps of apatite are not birefringent; therefore, they can be mistaken for dirt or debris [6,27]. Clumps of crystals may be phagocytized by neutrophils or monocytes. While alizarin red S staining can be used to detect BCP crystals in synovial fluid, interpretation is difficult and other calcium-containing particulates are also stained. Individual apatite crystals can only be observed under an electron microscope. Based on a review of analytical tools used for the detection of BCP crystals to date [64], some emerging technologies have been identified – that is, luminescence using modified bisphosphonates, atomic force microscopy that covers several related technologies for the imaging and measuring of surfaces on a fine scale down to the level of atoms, and Raman spectroscopy, a powerful technique for probing the molecular composition of a wide range of materials.

Treatment

Medical therapy for acute attacks is similar to those of CPPD deposition disease. Aspiration of effusions, NSAIDs, oral colchicine and/or intra- or peri-articular injection of steroids appear to shorten the duration and intensity of symptoms. Periarticular apatite deposits may be resorbed spontaneously with resolution of attacks, although deposits of apatite crystals do not dissolve in response to medication.

Pulsed ultrasonography has been demonstrated to be an effective treatment for some calcification diseases. According to Ebenbichler *et al.*, 47% of their patients with calcific tendinitis experienced a decrease of at least 50% of the calcification after 6 weeks of treatment [65]. At the 9-month follow-up, 65% presented with at least 50% reduction of calcifications, and almost half of the patients achieved complete resolution.

In patients with underlying progressive articular changes, response to medical therapy is usually less rewarding. Total joint replacement may be required for patients with severe destructive arthropathy in large joints.

Differential diagnoses

Pseudogout, gout and septic arthritis can present in very similar ways. The medical history and physical examination alone cannot reliably determine the cause of new-onset acute monoarticular arthritis. When patients present with identical recurrent episodes of crystal-induced arthritis, the diagnosis is rarely in question, although the possibility of septic arthritis must not be overlooked. Joint aspiration is the principal procedure for a diagnosis of crystal-induced arthritis and to rule out septic joint effusion.

Gout

Although pseudogout and gout cannot be reliably distinguished on clinical grounds, gout symptoms tend to develop rapidly over a few hours, whereas the symptom onset in pseudogout is usually more insidious and may occur over several days [102]. Classically, gouty arthritis is localized to the first metatarsophalangeal joint of the great toe (podagra); other commonly affected sites are the ankles, wrists and knees. Urate crystals exhibit a needle-like morphology and strong negative birefringence under polarized light [6,27].

Septic arthritis

Septic arthritis must be diagnosed and treated promptly because irreversible damage can occur within 4–6 h, and the joint can be completely destroyed within 24–48 h [105]. Unrecognized septic arthritis may result in the loss of life or a limb. Joint-fluid analysis includes cell counts, Gram staining, culture and microscopic analysis for crystals. In crystal arthritis, the white blood cell count in the joint fluid is usually 2000–50,000 cells/µl [66]; a count exceeding 50,000 cells/µl suggests a septic joint and cultures must be grown and Gram staining must be performed. Even if crystals are identified in the joint fluid, other causes of joint inflammation should not be excluded. Blood cultures are indicated in the presence of any signs of systemic toxicity. Septic arthritis can occur in patients with active crystalline arthropathy.

Chronic arthritis

The clinical manifestations of pseudogout with chronic inflammation closely mimic OA, rheumatoid arthritis and neuropathic joint disease. This renders making an accurate diagnosis challenging.

Metabolic disorders

Calcium pyrophosphate dihydrate deposition disease is clearly associated with a number of metabolic conditions, including hyperparathyroidism, hemochromatosis and hypomagnesemia [1]. Laboratory tests include serum calcium, phosphorus, magnesium and alkaline phosphatase levels, iron levels, total iron-binding capacity, and transferrin saturation and ferritin. It has been suggested that primary metabolic disorder or familial predisposition is uncommon but should be considered if CC occurs in patients younger than 55 years of age or if there is florid polyarticular CC [1]. In patients older than 55 years, hyperparathyroidism should be considered.

Conclusion

The current paradigm identifies the participation of PPi, calcium, extracellular matrix, matrix vesicles and chondrocytes in the formation of calcium crystals. As the deposition of calcium crystals produces various clinical manifestations, an accurate diagnosis based on plain radiography, ultrasonography and joint-fluid

Executive summary

Components of calcium deposition diseases

- Calcium pyrophosphate dihydrate (CPPD).
- Basic calcium phosphate (BCP), such as hydroxyapatite (HA).

Pathogenesis of crystal formation

- Extracellular inorganic pyrophosphate (PPi), calcium, extracellular matrix, matrix vesicles and chondrocyte hypertrophy are important in the formation of CPPD and BCP crystals.
- Excess extracellular PPi promotes CPPD and inhibits BCP crystal formation. By contrast, a reduction in extracellular PPi promotes BCP crystal formation.
- The metabolism of extracellular PPi is controlled by nucleoside triphosphate pyrophosphohydrolase, ANKH protein, aging, transglutaminase, TGF β-1, transduction pathways of cyclic AMP and PKC signaling, and tissue-nonspecific alkaline phosphatase.

Clinical presentation

- The clinical manifestations of CPPD crystal deposition disease vary and include asymptomatic chondrocalcinosis, pseudogout, pseudo-osteoarthritis, pseudorheumatoid arthritis and pseudoneuropathic arthropathy.
- Acute monoarthritis with swelling, tenderness and heat at the affected site is clinically similar to cellulitis, gout and septic arthritis.
- Chronic arthritis mimics other diseases, including degenerative joint disease, rheumatoid arthritis and neuropathic osteoarthropathy, rendering an accurate diagnosis challenging.
- Both CPPD and BCP crystal deposition in osteoarthritic cartilage may be strongly associated with the progression of osteoarthritis progression; however, our understanding remains incomplete.

Diagnosis

- Plain radiography is valuable for the evaluation of crystal deposits and it tends to be the first diagnostic method applied.
- Ultrasonography is a highly sensitive method to detect the presence of crystals.
- Synovial fluid analysis is the most sensitive technique for the detection of CPPD and BCP crystal deposition. Methods for the detection of BCP crystal are continuing to evolve.

Treatment

- NSAIDs and/or intra-articular steroid injections usually aid in the amelioration of acute episodes.

Conclusion

- Clinical manifestations vary and may present as asymptomatic, acute or chronic arthritis.
- Plain radiography, ultrasonography and joint-fluid analysis are valuable diagnostic methods.
- An accurate diagnosis and ruling out septic arthritis are highly important.
- The basic treatment for acute episodes consists of medications to achieve relief from the pain and inflammation.

analysis is of utmost importance, especially for a differentiation from septic arthritis. The basic treatment for acute attacks is the administration of medications to obtain relief from the pain and inflammation.

Future perspective

The pathogenesis of calcium crystal deposition disease and its participation in tissue damage remains poorly defined. Continued efforts to advance our understanding of these common crystals and their associated clinical syndromes may produce effective therapeutic strategies to inhibit the deposition of calcium-containing crystals or to enable their dissolution. Furthermore, molecular investigations on the pathologic effects of these crystals in the progression of OA will elucidate the pathologic mechanisms underlying the development of OA and may identify targets for anti-OA drugs.

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1. Which of the following is considered the most important risk factor for chondrocalcinosis (CC)?

- ☐ **A** Male gender
- ☐ **B** History of arthritis
- ☐ **C** Older age
- ☐ **D** Hypercalcemia

2. Which of the following is the most common clinical presentation of calcium pyrophosphate dihydrate (CPPD) crystal disease?

- ☐ **A** Pseudogout
- ☐ **B** Asymptomatic
- ☐ **C** Pseudo-osteoarthritis
- ☐ **D** Psuedorheumatoid arthritis

3. A 65-year-old man with primary osteoarthritis (OA) is found to have CPPD crystals. Which of the following best describes his prognosis for progression of OA?

- ☐ **A** CPPD is a marker for poor prognosis
- ☐ **B** CPPD is negatively associated with cartilage loss
- ☐ **C** No association
- ☐ **D** Unknown

4. A 70-year-old man has suspected CC of the hips and knees. Which of the following is the most useful test for evaluating his affected joints?

- ☐ **A** Plain radiographs
- ☐ **B** Magnetic resonance imaging (MRI)
- ☐ **C** Computed tomography (CT) scan
- ☐ **D** None of the above

5. A 60-year-old woman has polyarticular CC with CPPD crystals and a metabolic condition is suspected. Which of the following is most important to consider as a cause of CC?

- ☐ **A** Hemochromatosis
- ☐ **B** Hypomagnesemia
- ☐ **C** Hyperparathyroidism
- ☐ **D** Hypovitaminosis D