

Calcium-Containing Crystal-Associated Arthropathies in the Elderly

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Challenges still remain in the diagnosis, crystal identification, and treatment of pseudogout due to coexisting comorbid conditions and polypharmacy commonly found in veterans.

Calcium pyrophosphate (CPP) crystals may deposit in both articular tissues (predominantly hyaline cartilage and fibrocartilage) and periarticular soft tissues.^{1,2} Calcium pyrophosphate deposition disease (CPPD) may be asymptomatic or be associated with a spectrum of clinical syndromes, including both acute and chronic inflammatory arthritis.²

The European League Against Rheumatism (EULAR) recently suggested changes in CPPD terminology.² According to the new EULAR classification, pseudogout, or CPPD, has been reclassified based on new key terms that include several of the previously described disease phenotypes: asymptomatic CPPD; acute CPP crystal arthritis (previously known as pseudogout); osteoarthritis (OA) with CPPD (previously, pseudo-OA); and the chronic CCP crystal inflammatory arthritis (previously, pseudorheumatoid arthritis). In similar fashion, chondrocalcinosis (CC) refers to calcification of the fibrocartilage and/or hyaline cartilage identified by imaging or histologic analysis. Although CC is most commonly seen in CPPD, it is not exclu-

sive to this disease, as it can be seen in other crystal diseases (oxalosis, basic calcium phosphate [BCP]) and can appear as casual finding or coexist with OA.²

CLINICAL MANIFESTATIONS

In clinical practice, CPPD may present with several phenotypic forms. In asymptomatic CPPD, CC is a common radiographic finding without clinical symptoms. Acute CPP arthritis always should be suspected in any patient aged > 65 years presenting with acute monoarticular or oligoarticular, migratory or additive, symmetrical, or polyarticular arthritis.³ Acute CCP arthritis is characterized by self-limited acute or subacute attacks of arthritis involving 1 or several extremity joints (knees, wrists, ankles; rarely affects large toe). Typically, the acute attacks last 7 to 10 days. Several unusual sites (eg, the hip joints, trochanteric bursa, and deep spinal joints) also may be affected. However, differences in pattern of joint involvement are insufficient to permit definitive diagnosis without demonstration of the specific crystal type in the inflammatory joint fluid.

Pseudogout attacks closely resemble gouty arthritis; CPPD presents

as intermittent flares and often is asymptomatic between flares. Trauma, surgery, or severe medical illness frequently provokes attacks of monosodium urate (MSU) as well as acute CPP arthritis. Systemic findings, such as fever; leukocytosis with a left shift in the differential count; inflammatory markers, such as elevated sedimentation rate (ESR); or C-reactive protein, also can occur, resembling pyogenic arthritis, osteomyelitis, and/or systemic sepsis in the elderly patient.

Diagnosis must be confirmed with aspiration, Gram stain and cultures of the synovial fluid, and evaluation for the presence of CPP crystals under polarized light microscopy.² The diagnosis can be difficult to confirm secondary to the weakly birefringent nature of CPP crystals.⁴ Coexistence of MSU and CPP crystals in a single inflammatory effusion is neither uncommon nor unexplained given increased frequencies of both hyperuricemia/gout and CC among elderly patients.⁵

Chronic CPP crystal inflammatory arthritis may present as a chronic, symmetrical, bilateral, and deforming polyarthritis. It frequently affects the wrists and metacarpophalangeal joints and tendon sheaths. Chronic CPP may resemble rheumatoid arthritis (RA) and produce wrist

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tenosynovitis, which may manifest as carpal tunnel syndrome and/or cubital tunnel syndrome. Calcium pyrophosphate deposition disease should be on the differential diagnosis in the elderly patient presenting with a clinical picture that resembles “seronegative” RA, with morning stiffness, synovial thickening, localized edema, and restricted motion due to active inflammation or flexion contracture of the hands/wrist. It may present with prominent systemic features, such as leukocytosis, fevers, mental confusion, and inflammatory oligoarthritis or polyarthritis. The diagnosis of CPPD still may be possible even though the rheumatoid factor (RF) is positive, given the increasing likelihood of elevated RF in the older population. In this setting, aspiration of joint fluid and radiography will assist in clarification of the diagnosis. Furthermore, CPPD typically does not cause the type of erosive disease that is often seen in RA.

Calcium pyrophosphate deposition disease also can mimic polymyalgia rheumatica (PMR). A direct comparison of a cohort of patients with pseudo-PMR (PMR/CPPD) with actual PMR patients found that increased age at diagnosis, presence of knee osteoarthritis, tendinous calcifications, and ankle arthritis carried the highest predictive value in patients with CPPD presenting with PMR-like symptoms.⁶ However, the PMR/CPPD variant can be difficult to distinguish, because both conditions can have elevated systemic inflammatory markers, and both are steroid responsive.

Calcium pyrophosphate deposition disease involving a single joint can rarely lead to extensive destruction—as with neuropathic joints in the absence of any neurologic deficits—and is extremely debilitating. This presentation is not well under-

stood and does not have good treatment alternatives. Calcium pyrophosphate crystals often are associated with manifestations of OA.^{1,2} Indeed, up to 20% of OA joints have been found to be positive for CPP crystals in various studies. Given the extensive evidence supporting treatment of OA, usually they are treated in a similar fashion with good results. Occasionally, these will have unusual manifestations for typical OA, such as involvement of wrists and metacarpophalangeal joints; however, the presentation is often indolent like OA.

Calcium pyrophosphate crystal deposition involving the spine has been associated with a number of clinical manifestations. Spine stiffness, sometimes associated with bony ankylosis, can resemble ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis. Such symptoms are seen more commonly in familial CPPD rather than in the elderly. However, crystal deposition in the ligamentum flavum at the cervical spine levels has been associated with a condition called crowned dens syndrome.⁷ Although mostly asymptomatic, it may be present with acute neck pain, fever, and an increased ESR, sometimes mimicking PMR or giant cell arteritis or neurologic symptoms. Similarly, CPP crystal deposition in the posterior longitudinal ligament at the lower levels of the spine may lead to spinal cord com-



pression syndromes or symptoms of either acute nerve compression or chronic spinal stenosis.^{8,9} Calcium pyrophosphate crystal deposition also can occur in other soft tissues, such as bursae, ligaments, and tendons and may be sufficient to cause local nerve compression, such as carpal or cubital tunnel syndrome.

Epidemiology

Radiographic surveys of the knees, hands, wrists, and pelvis and epidemiologic studies have demonstrated an age-related increase in the prevalence of CPPD: 15% prevalence in patients aged 65 to 74 years, 36% prevalence in patients aged 75 to 84 years, and 50% prevalence in patients aged > 84 years.¹⁰ In a recent radiographic study, 40% of patients with CPPD did not present with CC of the knee, and the study's authors recommended additional radiographs of pelvis, wrists, or hands for accurate diagnosis of radiographic CC.¹¹

Table. Comparative Treatment Options^a

	Gout ^{1,2}	CPPD ³	Basic Calcium Phosphate
Local/intra-articular treatment	Intra-articular corticosteroid injection	Intra-articular corticosteroid injection	Periarticular corticosteroid injection Calcification aspiration/needling Shockwave therapy
Treatment of acute flare Colchicine Nonsteroidal anti-inflammatory drugs Corticosteroids (systemic) Others	Effective Effective Effective ACTH, IL-1 inhibitors	Effective (no loading dose) Effective Effective (polyarticular)	Limited data Effective Limited data
Preventive treatments Treating associated metabolic conditions Inhibit crystal formation	Hyperuricemia Xanthine oxidase inhibitors, uricosuric, recombinant uricase	Magnesium, iron chelators Probenecid, ^b phosphocitrate ^c	None None
Prevent inflammasome activation Other	Colchicine	Colchicine (emerging role) Methotrexate, hydroxychloroquine ^d	Colchicine (emerging role) None
Anti IL-1 treatment (anakinra, canakinumab, IL-1 trap)	Available	Possible	Possible

Abbreviations: ACTH, adrenocorticotropic hormone; CPPD, calcium pyrophosphate deposition disease.

^aBased on guidelines from the American College of Radiology 2012,¹ European League Against Rheumatism (2006 and 2011),^{2,3} No guidelines available for basic calcium phosphate at time of publication.

^bProbenecid is a transmembrane-transport inhibitor that reduces the production of extracellular pyrophosphate in vitro but to date has never been demonstrated to decrease CPPD crystal deposition in humans.³¹

^cNo evidence based on human trials for phosphocitrate (mouse model of murine progressive ankylosis).

^dVery limited data on methotrexate and hydroxychloroquine used for the prevention of CPPD flares.

Diagnosis

Accurate diagnosis should be achieved on the basis of the clinical picture and demonstration of CPP crystals in synovial fluid or tissue by compensated polarized light microscopy (Figures 1A and 1B).² The sensitivity and specificity for CPP crystal detection has been shown to be 95.9% and 86.5%, respectively.¹² However, the CPP crystal is more readily identified by a rheumatologist rather than in a standard hospital laboratory, which misses 30% of CPP crystals.¹³

Findings of CC on radiograph strengthens a CPPD diagnosis, but its absence does not rule it out (Figure 2A).² More recently, the use of new imaging modalities, such as musculoskeletal ul-

trasound, provides the capacity to visualize crystal deposits within the joint structures, the hyaline cartilage, and/or fibrocartilage (Figure 2B and 2C).¹⁴ The presence of hyperechoic bands within the intermediate layer hyaline cartilage and hyperechoic spots in fibrocartilage are consistent with CPP crystal deposits.^{2,14} The use of computed tomography is the gold standard imaging modality for the identification of CPPD of the spine.¹⁵ There is not enough evidence to support the use of magnetic resonance imaging in CPPD, but it may play a role in rare complications.²

Treatment

The EULAR recently defined new guidelines for the management of

CPPD.¹⁶ Asymptomatic CPPD needs no treatment. In other CPPD phenotypes, the goals are to attempt prompt resolution of the acute synovitis, reduction in chronic damage, and management of associated conditions. In acute attacks, treatment modalities used in gout are often required; however, data for CPPD treatment are limited (Table). Treatment relies on the use of colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs), but toxicity and comorbidities in the elderly limit the usage of these drugs.

Given increased renal impairment, the loading dose of colchicine is not recommended.¹⁶ Colchicine has recently been shown to completely block crystal-induced maturation of IL-1 β in vitro, indicating that the

drug acts upstream of inflammasome activation.¹⁷ This is in addition to the well-known role of colchicine in inhibition of micro-tubule formation, which likely leads to prevention of cell migration, phagocytosis, and activation of inflammasome.¹⁸⁻²⁰

Intra-articular injection of corticosteroid is an efficient and well-tolerated treatment alternative for monoarticular CPP flares. Oral or parenteral corticosteroids are frequently used for polyarticular flares in particular for those patients in which NSAIDs and colchicine are contraindicated.¹⁶ Parenteral adrenocorticotropic hormone has been used in patients with congestive heart failure, renal insufficiency, gastrointestinal bleeding, or resistance to NSAIDs.²¹ For prophylaxis of acute CPP crystal arthritis, a low dose of oral NSAIDs, oral colchicine, or prednisone may be used with good results.¹⁶ In chronic CPP arthritis, continuous use of colchicine, NSAIDs, or low-dose prednisone is often appropriate. If these interventions are ineffective or contraindicated, using hydroxychloroquine (HCQ) and methotrexate (MTX) have been successfully used to control chronic CPP crystal inflammation.^{22,23} Recent trials have raised questions about MTX, and further trials on HCQ usage are underway.²⁴ Biologic agents targeting IL-1 are not currently approved for the treatment of CPPD, but there are suggestions that it may be effective in refractory cases and induce rapid stable remissions after 3 days of therapy.²⁵

In contrast to gout, there is no specific target therapy for lowering CPP crystal load in the elderly. Crucial in the management of CPPD in the elderly is the search for as-

sociated diseases, such as hyperparathyroidism, hemochromatosis, hypomagnesemia, and hypophosphatemia, as well as avoidance of tacrolimus, which facilitates or causes CC.¹⁶ Correction of the underlying metabolic disorder, especially when undertaken early, may reduce the severity of CPPD. However, there is little evidence to suggest that treatment of associated disease results in resolution of CPPD—most famously, although therapeutic phlebotomy does not help in hemochromatosis for prevention of crystal disease, chelating agents do seem to be moderately effective.²⁶ Only oral administration of magnesium has shown a reduction in meniscal CC in a patient with CPPD arthropathy.²⁷ In addition, this was in the setting of familial hypomagnesemia associated CPPD. However, unlike uricosuric agents for gout, no pharmacologic treatments can prevent CPPD crystal formation and deposition in tissues.

THERAPEUTIC AGENTS Magnesium

Magnesium is a cofactor for the activity of pyrophosphatases that converts inorganic pyrophosphates (PPi) into orthophosphates. In addition, magnesium can increase the solubility of CPP crystals. Early de-

tection and management of hypomagnesemia are recommended, because it occurs in patients who have well-defined conditions and situations: Gitelman syndrome, thiazide and loop diuretics use, tacrolimus use, familial forms of renal magnesium wasting or use of proton pump inhibitors, short bowel syndrome, and intestinal failure in patients receiving home parenteral nutrition. Long-term administration of magnesium in some patients with chronic hypomagnesemia decreased meniscal calcification.²⁷⁻²⁹

Dietary Calcium

Epidemiologic studies showed a lower incidence of CC in Chinese subjects. The authors of the study speculate that this lower prevalence of CPPD could result from high levels of calcium found in the drinking water in Beijing, which may affect parathyroid hormone secretion.³⁰ Further studies are needed to confirm this hypothesis, as it could be a cheaper approach to pseudogout prevention.

Probenecid

Probenecid is an in vitro inhibitor of the transmembrane PPi transporter thought to possibly prevent extracellular PPi elaboration. However, this observation has not been

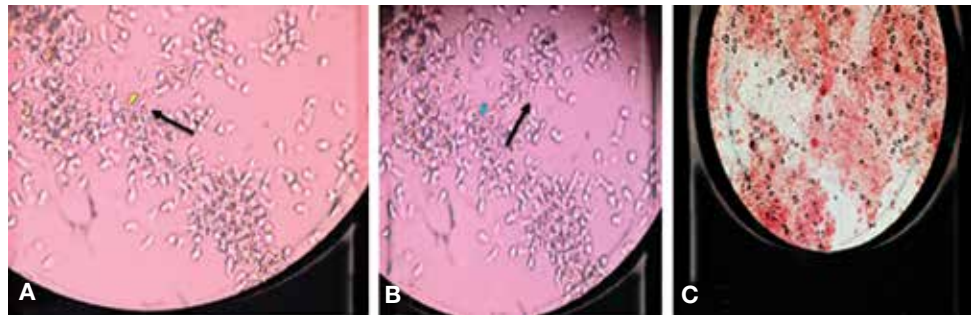


Figure 1. Compensated polarized light microscopy demonstrating calcium pyrophosphate crystal (A and B) and alizarin red S stain of basic calcium phosphate crystals (C). Arrow shows the direction of polarizer. Perpendicular-yellow crystal (A) and parallel-blue crystal (B).

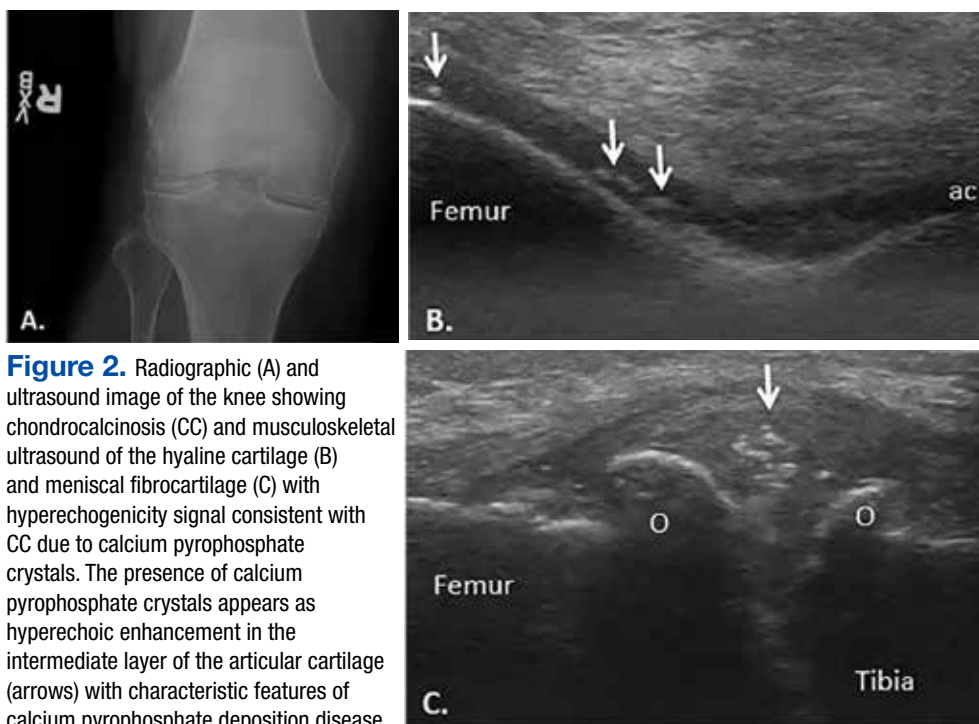


Figure 2. Radiographic (A) and ultrasound image of the knee showing chondrocalcinosis (CC) and musculoskeletal ultrasound of the hyaline cartilage (B) and meniscal fibrocartilage (C) with hyperechogenicity signal consistent with CC due to calcium pyrophosphate crystals. The presence of calcium pyrophosphate crystals appears as hyperechoic enhancement in the intermediate layer of the articular cartilage (arrows) with characteristic features of calcium pyrophosphate deposition disease.

confirmed by either case reports or clinical trials.³¹

Phosphocitrate

Phosphocitrate acts directly on preventing crystal deposition in tissues in CPPD as well as BCP based on *in vitro* evidence and mouse models.^{32,33}

Hyaluronan

An amelioration of pain and increased range of motion were observed in radiographic CC with OA.³⁴ However, it is associated with increased acute CPP arthritis.³⁵

Radiosynovectomy

In a double-blind study of 15 patients with symmetrical CPPD arthropathy, the knee that underwent intra-articular injection of yttrium-90 (5 mCi) plus steroid had less pain, stiffness, joint line tenderness, and effusion compared with the contralateral control knee injected with saline and steroids.³⁶

PRECIPITATORS OF ACUTE PSEUDOGOUT

Diuretics are known to exacerbate gout, but they also can exacerbate pseudogout. A recent case-control study nested within a United Kingdom general practice database found that loop diuretics rather than hydrochlorothiazide was associated with increased risk of CPPD mediated primarily by magnesium reabsorption in the loop of Henle.²⁸ Chronic kidney disease associated with secondary and tertiary hyperparathyroidism increases calcium or PPI concentration, which leads to CPP-crystal deposition.

In addition, multiple case reports have described acute pseudogout caused by bisphosphonate administration for osteoporosis or Paget disease—more likely in the elderly population. Intravenous pamidronate, oral etidronate, and alendronate therapy have all been described in the elderly.³⁷ The overall mechanism

behind this link is not completely understood, but bisphosphonates are structurally similar to PPI. Pseudogout attacks also have been described in neutropenic patients undergoing treatment with granulocyte-colony stimulating factor.³⁸

In addition to pharmaceutical exacerbation of pseudogout, surgical procedures and trauma can precipitate attacks. Joint lavage has been described to increase the incidence of pseudogout.³⁹ It was hypothesized that joint lavage with fluid induced “crystal shedding” from CPPD crystals imbedded in the joint tissue. Patients who underwent meniscectomy of the knee

20 years ago had a 20% incidence of CC in the knee that was operated compared with 4% CC in the contralateral nonoperated knee.⁴⁰ Overall, the surgery most linked with a pseudogout attack, however, is parathyroidectomy.⁴¹

BASIC CALCIUM PHOSPHATE CRYSTALS

Basic calcium phosphate crystals are common but rarely diagnosed due to the cumbersome and expensive methods required to identify these crystals.⁴² Basic calcium phosphate crystals are difficult to identify by light microscopy, as they congregate into clumps that can appear as a stack of “shiny coins.” Multiple techniques, including X-ray diffraction and electron microscopy with energy dispersive analysis, have been shown to be specific for BCP crystal identification; however, the expense and technical knowledge required to

conduct these techniques is prohibitive. Similarly, BCP crystals can be identified with alizarin red S stain, performed in specialized centers, but has high degree of false positive (Figure 1C).⁴³

Basic calcium phosphate and CPPD crystals may coexist in synovial fluid. Similar to CPPD, BCP crystal disease is often concurrent with OA and can cause calcification of articular cartilage. Basic calcium phosphate is more common than CPP crystals with occurrence of 30% to 50% in OA synovial fluid.⁴² Additionally, BCP crystal disease has been linked to increased severity of OA. Basic calcium phosphate crystals in knee joints were found to have radiographically more severe arthritis with larger effusions.^{44,45} Similarly, BCP crystals in OA synovial fluid correlated with higher Kellgren-Lawrence grade scores by radiography.^{42,46}

It is currently believed that BCP crystals are continuously formed in the extracellular matrix, and their deposition is actively prevented by PPI present in the matrix.⁴⁷ Elevated PPI levels, on the other hand, favor the formation of CPP crystals.⁴⁸ The clinical upshot seems to be that although CPP crystals are almost universally intra-articular and released by chondrocytes, BCD crystals and deposits are more frequently present in soft tissues.

Acute Calcific Tendinitis

Typically, this type of tendinitis involves the shoulder joint and is extra-articular. Common treatments help, including NSAIDs, intra-articular steroids, ice, and rest. In addition, high-energy extracorporeal shock wave therapy has been shown to be effective when used with conscious sedation.^{49,50} Needling or barbotage in association with lavage and steroid injections

also is effective and has occasionally been shown to reduce the size of the calcium deposit as well, often in combination with IV drugs like ethylenediaminetetraacetic acid.⁵¹⁻⁵³

Acute calcific periarthritis of the hand presents similar to gout or pseudogout, affecting the wrist, usually in postmenopausal women.⁵⁴ Basic calcium phosphate crystals are aspirated from the joint, and periarticular crystals may be subtle. Local steroid injections are beneficial.

Milwaukee shoulder syndrome is an arthropathy associated with BCP crystals in the joint fluid and results in extensive destruction of shoulder articular cartilage and surrounding tissues. It is commonly bilateral and occurs in elderly women more often than it does in men.⁵⁵ Aspiration of the shoulder joint typically reveals a serosanguinous fluid. Fluid samples can be assessed for hydroxyapatite crystals by staining with alizarin red dye, which produces a characteristic “halo” or orange-red stain by light microscopy.⁴³ Surgical treatment of Milwaukee shoulder syndrome is difficult due to increased age of the population affected and the severity of the shoulder destruction. Usually a conservative approach of analgesics, recurrent shoulder aspirations, and steroid injections is the best treatment option.

CONCLUSIONS

Calcium-containing crystal-associated arthropathies are a complex array of entities that target the veteran elderly population with increasing frequency. Challenges still remain in the diagnosis, crystal identification, and treatment due to coexisting comorbid conditions and polypharmacy commonly seen in veterans. Overall morbidity associated with calcium-containing

crystal-associated arthropathies and the coexisting osteoarthritis is great, and focused identification of the disease process with tailored treatment can achieve the goal of decreasing symptoms and improving quality of life. ●

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