



Review

Calcium Pyrophosphate and Basic Calcium Phosphate Deposition Diseases: The Year in Review 2022

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Abstract: Calcium-containing crystal deposition diseases are a common cause of pain and disability but remain relatively under-investigated. No drug has been identified that can prevent deposition or effect dissolution of either calcium pyrophosphate (CPP) or basic calcium phosphate (BCP) crystals. In comparison to the field of gout and urate biology, published research in relation to calcium crystal deposition diseases in 2022 was relatively modest in quantity. In CPP deposition (CPPD) disease, progress was made mainly in epidemiology, imaging, surgical management and Gitelman's syndrome. In relation to BCP crystals, the effect on tenocytes in vitro was explored and results indicate that BCP crystals likely reduce tendon matrix integrity via their interaction with tenocytes. The involvement of calcification in the progression of osteoarthritis (OA) was elegantly demonstrated contributing to further discovery of the process of OA progression. There was a paucity of mechanistic and genetic studies in calcium crystal deposition diseases published in 2022, nor any breakthrough in therapy, showing that there is abundant scope for investigation under these themes in the future.

Keywords: CPPD; BCP; crystal arthropathy; osteoarthritis; imaging; cartilage



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1. Introduction

Both calcium pyrophosphate (CPP) and basic calcium phosphate (BCP) crystals are the most common calcium-containing crystals associated with articular and peri-articular disorders. Both crystal types exhibit diverse clinical manifestations which are already well recognised [1]. Unfortunately, no drug is currently available to prevent deposition or lead to the dissolution of either crystal type. Consequently, much research is needed to address current deficits in diagnosis, management and pathophysiology. The aim of this review is to highlight advances published in 2022. These were presented in summary at the G-CAN conference in November 2022 in Alexandria, VA. The majority of papers related to CPP deposition (CPPD) disease and can be largely grouped into epidemiology, imaging and surgical management. Studies relevant to BCP crystals covered in vitro biological effects, a detailed examination of the stage- and location-specific pathology of cartilage calcification with an exploration of their contribution to osteoarthritis (OA) and the potential for a fetuin A-derived peptide as a therapy.

2. Calcium Pyrophosphate Deposition Disease

2.1. Epidemiology and Co-Morbidity

Calcium pyrophosphate deposition (CPPD) disease is common and the prevalence of radiographic chondrocalcinosis (CC) ranges from 4% to greater than 10% among adults of older age. However, the prevalence of symptomatic CPPD disease remains unclear [2,3]. The most widely known manifestation is acute CPP arthritis, previously known as “pseudogout”. During episodes of acute CPP arthritis, the NLRP3 inflammasome is activated, leading to interleukin-1 β release [4]. An increased risk for cardiovascular disease is well recognised in other forms of inflammatory arthritis such as rheumatoid arthritis (RA) and

gout [5,6]. It has been hypothesised that the same risk might apply in acute CPP arthritis. In a countrywide cohort of mostly male veterans, CPPD was associated with cardiovascular (CV) events following adjustment for traditional risk factors. In that cohort, CPPD was defined using billing codes for chondrocalcinosis or a calcium metabolism disorder and so was quite broad in definition [7]. This year, Tedeschi et al. published the results of a matched cohort study using electronic health record data from the Mass General Brigham Research Data Repository, 1991–2017, in which the patients were well characterised [8]. With the use of a published machine learning algorithm previously shown to have a positive predictive value of 81%, patients with acute CPP arthritis were identified. In this research, 1200 patients with acute CPP crystal arthritis were matched to 3810 controls, without evidence of having acute CPP at any time. Established risk factors for CV events such as such as hypertension and diabetes were more commonly identified in the acute CPP arthritis patients. There was a significant association between acute CPP arthritis and elevated risk, both short and long term, for non-fatal major adverse cardiovascular events (MACE), such as myocardial infarction, acute coronary syndrome, coronary revascularisation and stroke. No risk of all-cause mortality was noted in patients with acute CPP arthritis during short- or long-term follow-up periods. The authors propose that the elevated CV risk observed in this study of individuals with acute CPP arthritis supports the hypothesis that IL-1 β plays a role in the link between crystal arthritis and adverse CV events.

Since no known treatment exists to prevent the deposition of CPP crystals or to lead to their dissolution, identification and modification of risk factors is particularly important. Hypomagnesaemia is a known risk factor for CPPD. Since proton pump inhibitor (PPI) use can lead to hypomagnesaemia, Liew et al. performed a study to explore whether use of PPIs might be associated with an increased risk for incident CPPD [9]. The IQVIA Medical Research Database, based in the United Kingdom, provided data for this study. Initially, a propensity score-matched cohort study was conducted to estimate the risk of incident CPPD among PPI users in comparison to users of histamine receptor 2 (H2) blockers. Then, incident use of PPI and H2 blockers prior to incident CPPD was evaluated using a nested, case-control study, which was matched 1:4 by age and sex. No evidence was found that incident PPI use was associated with a higher risk of CPPD when compared with H2 blocker use. In the case-control study, when measured against non-users, a higher risk of incident CPPD was found in both PPI and H2 blocker users. When compared with H2 blocker use, incident PPI use was not found to be significantly associated with incident CPPD. It is conceivable that the use of H2 blockers might have a comparable effect to the use of PPIs since there was a higher risk of CPPD in users of both medications when compared with individuals who used neither medication. The precision of the results in this study is using real-world data somewhat limited by the low number of CPPD cases, however.

2.2. Clinical Observations

There was a paucity of studies related to clinical features and management of CPPD. However, a detailed analysis of Gitelman's syndrome (GS) was published in 2022. GS is a rare autosomal recessively inherited renal disease which presents clinically with hypokalaemia along with hypomagnesaemia and hypocalciuria [10]. There is a well-recognised association between GS and CC and various small studies and case series have depicted a propensity of CC to manifest at the knee, symphysis pubis and shoulder [11]. In this cross-sectional prospective study, Chotard et al. sought to determine the prevalence, clinical phenotypes, distribution patterns and risk factors for CC in individuals with GS [12]. A cohort of 57 patients with GS were identified and they underwent a systematic screening for CC. This was done by peripheral joint radiography, supplemented by US, and cervical spine CT. The presence of CPP was confirmed by polarised light microscopy (PLM) in five patients. CC was observed in 79% of patients. The mean age of patients was 46.5, with a standard deviation of 12.4 years. Women comprised 66.7% of cases and 93% of cases were carriers of SLC12A3 mutations. Serum magnesium levels were low at a mean of 0.60 mmol/L.

CC was detected in 79% of patients. The highest prevalence was at the cervical spine, where it was found in 81.8% of cases. The knee was the next most commonly affected joint, at 52.6% of cases. Next, in order of decreasing frequency, were the wrist, at 50.9%, the ankle, at 38.6%, the temporomandibular (TM) joint, at 36.4%, the shoulder, at 33.3%, the hip, at 22.8%, the elbow, at 14.0% and the sclera/choroid, at 12.1%. Both age and hypomagnesaemia were independent factors found to be associated with CC in GS [12].

This is a thorough analysis of CC in GS illustrating preferential involvement at the cervical spine and knees. These data suggest that patients with GS merit imaging of the cervical spine and peripheral joints, in particular knee joints and wrists, to quantify the extent of CC in this patient group.

2.3. Imaging

Imaging as an aid to the diagnosis of calcium crystal deposition diseases attracted substantial research effort and productivity in 2022. As a further aid to imaging studies, consensus-based definitions of imaging characteristics of CPPD as found on conventional radiography (CR), conventional computed tomography (CT) and dual-energy CT (DECT) were established. These descriptions were agreed by an international group of musculoskeletal radiologists and rheumatologists with particular expertise in CPPD. These definitions itemise key elements that are considered specific to CPPD on CR, CT and DECT, and can be applied both in research studies and clinical practice. Helpfully, a set of example images were assembled as a reference for future clinical studies as well as clinical practice [13].

Consistent with this theme, a study was performed to evaluate the accuracy and reliability of new radiographic definitions for CPPD in the knee examining patients with knee osteoarthritis (OA) scheduled for total knee replacement (TKR). These novel definitions were developed by an international multidisciplinary working group and then used for the identification of CPPD. According to these definitions, CPPD appears radiographically as “linear or punctate opacities in the region of fibro- or hyaline articular cartilage/synovial membrane or joint capsule/within tendons or entheses that are distinct from denser, nummular radio-opaque deposits due to BCP deposition”. The diagnosis of CPPD was based on the histological examination by polarised light microscopy (PLM) of tissues (meniscus and hyaline cartilage) from knees following TKR. Sixty-seven participants were enrolled in this study. The prevalence of CPPD by histology was 51% compared with 31% by radiography. Radiography was found to be specific for CPPD (92%), but sensitivity remained low at 54% at all sites and in the overall diagnosis. The conclusions of the authors were that the new imaging definitions of CPPD are highly specific and can permit a definite CPPD diagnosis. However, importantly, the absence of radiographic findings does not exclude the diagnosis [14].

Ultrasound (US) has proven to be a reliable and accurate technique for the diagnosis of CPPD and gout and validated definitions have been released by the Outcome Measures in Rheumatology (OMERACT) US working group. However, the role of US in hydroxyapatite (HA) deposition disease has not been determined. This purpose of this research was to investigate US attenuation characteristics of increasing concentrations of CPP, HA and monosodium urate (MSU) crystals *ex vivo* using radiography, CT and US. Sixteen synthetic crystal suspensions with varying and known concentrations of CPP, HA and monosodium urate (MSU) were prepared. These specific concentrations were selected to replicate the X-ray attenuation characteristics of these crystals when imaged by CR, CT and DECT *in vivo*. US scans were performed of suspensions of each crystal type and concentration placed in a plastic container filled with US gel. CR and CT confirmed X-ray attenuation of the crystal suspension types. The results of this proof-of-concept study showed that at crystal concentrations found in and around patient joints, CPP does not generate substantial acoustic shadowing, unlike HA and MSU, which attenuate US in proportion to crystal concentration. The findings highlight the potential ability of US to distinguish between the three crystal types based on their appearance and variable attenuation on grayscale images

and to improve the diagnostic accuracy of US in crystal arthritis, including HA-associated arthropathies [15].

Cipolletta et al. evaluated the spectrum of articular and peri-articular US findings at metacarpophalangeal (MCP) joints in CPPD. Sixty consecutive CPPD patients were prospectively enrolled. Thirty-three patients (55%) were diagnosed with OA and CPPD and twenty-seven patients (45%) had chronic CPP crystal inflammatory arthritis. Forty age- and sex-matched patients with RA served as controls. US findings in individuals with chronic CPP crystal inflammatory arthritis showed more evidence of synovial inflammation and more CPP deposits when compared with those with OA and CPPD. On the other hand, more US evidence of structural joint damage was seen in individuals exhibiting OA with CPPD. The study also provided pictorial evidence of the broad spectrum of US findings associated with CPP deposits at MCP joints in CPPD [16].

Also by Cipolletta et al., a study was undertaken to establish the US scanning protocol with the best performance in the diagnosis of gout or CPPD in individuals presenting with acute mono- or oligoarthritis of unspecified origin. Patients were consecutively enrolled in whom a request had been made for joint aspiration at the most clinically involved (target) joint. US was performed in each patient prior to arthrocentesis. One hundred and sixty-one patients were entered in the study: thirty-two gout patients, thirty CPPD patients and ninety-nine disease controls. Controls satisfied classification criteria for diseases other than gout or CPPD. US findings had a high specificity for gout (0.92–0.96) and CPPD (0.90–0.97), while the sensitivity ranged from 0.73 to 0.85 for gout (double contour sign and tophi, respectively) and from 0.60 to 0.90 for CPPD (hyaline and fibrocartilage deposits, respectively). US assessment of the target joint could accurately verify a diagnosis of crystal arthritis when the target joint was the knee or MTP in gout and the knee and wrist in CPPD. The authors then looked at extending the US assessment to asymptomatic joints such as knee, MTP or wrist when other joints (e.g., shoulder, elbow, hip and ankle) are involved. This targeted US scanning protocol of two joints bilaterally plus the target joint (unless the target joint was the knee or first MTP in gout or the knee and wrist in CPPD) showed great accuracy (>90%) for the diagnosis of crystal arthritis in patients presenting with acute mono/oligoarthritis [17].

2.4. Surgical Management of Patients with CPPD

It has previously been recommended that unicompartmental knee arthroplasty (UKA) should not be performed in patients with CPPD [18]. The justification was that the residual cartilage would produce additional CPP crystals, resulting in a poorer outcome. Moret et al. undertook a systematic review with the aim of assessing outcomes after unicompartmental (UKA) or total knee arthroplasty (TKA) in patients with chondrocalcinosis (CC) in comparison with patients without CC [19]. The analysis focused on clinical and functional outcomes, progression of OA and prosthesis survivorship. A total of 3718 patient knees were contained within eight publications. In relation to UKA, there was a median sample of 234 knees, with a range of 78 to 1000. For TKA, the median sample was 954, with a range of 408 to 1500.

The mean patient age was 69 years at the time that the surgery was performed and the frequency of CC ranged from 12.6 to 36%. CC was diagnosed if there were calcifications seen by radiograph in the articular or peri-articular structures prior to surgery, or if CPP crystals were found by histological examination of articular tissue samples or in synovial fluid by PLM. Data analysis indicated that the presence of CC did not substantially change clinical or functional outcome, survival of the implant nor radiographic progression after either type of joint replacement [19]. These data suggest that UKA in patients with CPPD carries less risk or clinical relevance than was previously assumed.

With continued focus on orthopaedic outcomes in CPPD, the US National Inpatient Sample database was interrogated to perform a cross-sectional study which compared patients with CPPD and patients without CPPD who underwent TKA between 2006 and 2014 to assess predictors, outcomes and resource utilisation of TKA in CPPD [20]. Patient

demographics and comorbidities were incorporated in the data collection. Outcomes of interest subsequent to TKA included mortality occurring in hospital, length of hospital stay, post-operative complications and cost of hospitalisation. A total of 5,564,005 cases were identified, of which 0.2% were identified as having CPPD. The median age was 72 and 53.7% of cases were female. When compared with patients without evidence of CPPD, patients with CPPD tended to be older, white and male. Patients who had CPPD were more likely to suffer from at least two co-morbidities and rather than being discharged home after surgery, were more likely to need further admission to a service such as a rehabilitation facility. A greater duration of hospitalisation was noted in those undergoing TKA who had CPPD when compared with those without CPPD. Furthermore, in patients with CPPD, there was a greater frequency of complications during hospitalisation, including myocardial infarction, and these patients were more likely to require repeat surgical procedures. The paper emphasises some of the post-operative problems that this multi-morbid patient group can experience [20].

3. BCP Crystals

BCP crystals are associated with numerous articular and peri-articular disorders and exert biological effects on a number of articular cell types including fibroblasts, macrophages and chondrocytes. Research continues to lead to further understanding of the *in vitro* mechanisms that underlie the clinical expression of their presence.

3.1. Biological Effects *In Vitro*

In 2022, one study presented an analysis of tenocyte responses to BCP crystals [21]. Clinical syndromes such as acute calcific tendonitis or Milwaukee shoulder syndrome (MSS) may result, at least in part, from interactions between BCP crystals and tenocytes which are stromal cells found within tendons. By regulating the expression of tendon matrix proteins, tendon matrix degrading enzymes and their inhibitors, tenocytes help maintenance and repair of tendon extracellular matrix. When the expression of these matrix enzymes and proteins is dysregulated, tendon degeneration can be the outcome. Because BCP crystals can frequently accumulate within tendon structure, it is likely that they are contiguous with resident tenocytes. Although an abundance of studies have shown how BCP crystals interact with multiple cell types including chondrocytes, fibroblasts and immune cells, with the resultant alteration of expression of metalloproteases, interleukins and prostaglandins, the effects of BCP crystals on tenocytes has not been explored previously. Accordingly, a study was performed to establish the effects of BCP crystals on tenocyte function and viability in response to direct contact. Using cultured human tenocytes, *in vitro* assays of cells incubated with BCP crystals were performed. It was found that BCP crystals can induce tenocyte gene expression of extracellular matrix-remodelling enzymes matrix metalloprotease (MMP)-1, MMP-3, ADAMTS-4 and tissue inhibitor of metalloproteases (TIMP)-1 after twenty-four hours. BCP crystals induce both cyclo-oxygenase (COX)-1 and COX-2 with the release of prostaglandin (PG)₂E₂. BCP crystals do not result in the alteration of tenocyte expression of matrix proteins, induction of pro-inflammatory cytokine expression or influence viability of tenocytes. As a result of this research, it appears that BCP crystals do not exert substantial inflammatory effects on tenocytes. However, BCP crystals likely cause a reduction in tendon matrix integrity following their interaction with tenocytes. This effect could add to the tendon damage seen in conditions such as Milwaukee shoulder syndrome, which are associated with tendinopathy [21].

Calcific tendonitis involving the rotator cuff occurs as a result of the deposition of apatite in the tendons around the shoulder. It is a cause of shoulder pain and restriction and can present acutely. An acute inflammatory response to the deposits can cause the calcification to disappear [22].

In the past, inflammation in response to HA crystals has been studied mainly with synthetic crystals, and not with calcifications extracted from patients suffering from calcific tendinopathy. Accordingly, a study was undertaken to investigate the inflammatory effects

of calcifications derived from humans and some of the mechanisms involved [23]. Human calcifications were derived from symptomatic patients undergoing image-guided needle lavage. Human monocytes and macrophages, the human myeloid cell line THP-1 and human tenocytes were utilised for these in vitro studies and were treated with human calcifications or synthetic hydroxyapatite as a comparator.

As with synthetic HA, human calcifications induced an inflammatory response with resultant IL-1 β production following NF- κ B activation and through the NLRP3 inflammasome. In some experiments, human calcifications induced smaller quantities of IL-1 β compared to that induced by synthetic apatite. The authors suggest that variation in size, shape and protein content of the calcific material might explain this observation [23].

3.2. Imaging

A clinical condition entitled the helmeted dens syndrome was published as a clinical image. This was a case of a 82-year-old female with a history of calcinosis of a finger who presented with neck pain and headaches. A cervical CT revealed a para-articular calcified mass at the cervico-occipital hinge around the C0-C1 and C1-C2 joints. It extended above the clivus muscle at the level of the lower part of the vertebral body of C2 with odontoid infiltration. There was also a homogenous intra-articular density with distension of the joint space corresponding to the presence of crystals following possible fistulation. There was benefit from treatment with colchicine [24].

3.3. Cartilage Calcification and OA

Cartilage calcification is a common finding in OA and is a hallmark of advanced OA [25]. Up until now, little has been determined concerning the progression of calcification within cartilage as OA develops. This knowledge deficit has been addressed recently in a study using multiple nano-analytical technologies. The authors investigated the characteristics of minerals in human OA cartilages focussing on both stage of calcification and location [26]. After serial sectioning, normal and OA cartilages were analysed in great detail using micro-CT, scanning electron microscopy with energy dispersive X-ray spectroscopy, micro-Raman spectroscopy, focused ion beam scanning electron microscopy, high-resolution electron energy loss spectrometry with transmission electron microscopy, nanoindentation and atomic force microscopy. Using this technology, it was observed that calcification in OA progressed beginning at the joint surface and progressing downwards ('top-down') as well as at the osteochondral interface from where it progresses upwards ('bottom-up').

The process of calcification from the top was noted to start during early-stage OA with spherical mineral particle formation at the joint surface with subsequent fibre formation and densely packed material transformation deep into the cartilage found in advanced OA. The calcification starting from the bottom in early-stage OA was manifested by an excessive layer of calcified tissue accumulating above the original calcified cartilage, displaying a calcified sandwich structure. With time, the original and upper layers of calcified cartilage joined together, which thickened the calcified cartilage area, disrupting the cartilage structure. During early OA, the calcified cartilage was hypermineralised, containing a more rigid carbonated HA. During advanced-stage OA, it was hypomineralised and encompassed softer HA. This discrepancy may be attributed to matrix vesicle nucleation during early-stage OA and carbonate cores during advanced-stage OA.

Different mineral transformation pathways are observed in mineral crystals in the joint surface cartilage compared with the osteochondral interface region. This variance is likely results from the difference in the biological environments in which they form and aided by the neighbouring transdifferentiated chondrocytes.

The predominant objective of this work was to further understand the stages of calcification as OA progresses with the aim of harnessing this information to use in the development of therapy for OA. This was a very in-depth analysis of cartilage calcifica-

tion progression and hopefully will form a basis for further research in this somewhat neglected area.

3.4. Therapeutic Considerations

Human Alpha-2-HS-Glycoprotein (AHSG/Fetuin A) is a multifunctional protein that participates in numerous essential biological activities, including the regulation of bone and calcium metabolism [27]. A potent calcium-binding peptide, a cyclic-inverso Fetuin-A-derived peptide, reduced calcification occurring in articular chondrocytes obtained from joints removed at TKR from patients with end-stage OA [28]. Furthermore, when Lewis rats with OA received intra-articular injections of the cyclic-inverso peptide, cartilage degeneration was diminished. Further studies will be necessary to establish the potential of this peptide as a therapy for OA, particularly in other models of calcification.

4. Future Directions

The newly drafted ACR/EULAR classification criteria for CPPD are undergoing ratification at the time of writing and are due to be published [29]. They perform to an excellent standard and will enable an acceleration of research in this important area. Complementing these criteria is the establishment of a framework for development of OMERACT CPPD Core Domain Sets. Separate OMERACT CPPD Core Domain Sets will be developed for “short-term” studies for an individual flare of acute CPP crystal arthritis and for “long-term” studies that may include participants with any clinical presentation of CPPD (acute CPP crystal arthritis, chronic CPP crystal inflammatory arthritis, and/or CPPD with OA) [30]. In terms of BCP crystals, a major challenge remains that crystal identification is difficult, when compared to CPP or MSU crystals [21]. It is hoped that with the further development of sensitive imaging techniques, this problem may subside laying the way for the development of therapies that might reduce their presence or interfere with their biological activities, particularly relevant in OA.

5. Conclusions

There has been substantial progress in our understanding of calcium crystal deposition diseases in the past year. Unfortunately, novel therapies are lacking so that this area is ripe for exploration. Since there have been no recent mechanistic or genetic studies in calcium crystal deposition diseases, there is abundant scope for investigation under these themes. Hopefully, in due course, there will be an exponential increase in publications in this area, especially with the establishment of the Gout, Hyperuricemia, and Crystal-associated Disease Network (G-CAN).

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