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Basic calcium phosphate crystal-associated musculoskeletal syndromes: an update

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Abstract

Purpose of review—Basic calcium phosphate (BCP) crystals are associated with two important musculoskeletal syndromes. Deposition of BCP crystals in tendons, bursae, and other soft tissues around joints causes calcific periarthritis, whereas intra-articular BCP crystals contribute to osteoarthritis and cause the highly destructive arthritis known as Milwaukee Shoulder Syndrome. The epidemiology and natural history of these syndromes are poorly understood, and because the pathogenesis remains unclear, few targeted therapies are available. I will review new developments in this field.

Recent findings—I will discuss a case collection of calcific periarthritis of the hip, and evidence-based management strategies for shoulder calcific periarthritis that might be applied to calcific periarthritis at other locations. I will summarize several recent articles addressing mechanisms of crystal formation and identifying pathways through which BCP crystals produce tissue damage and explore some newly identified risk factors for pathologic mineralization.

Summary—We are making slow, but steady progress in understanding the clinical presentation of calcific periarthritis in sites other than the shoulder. A growing appreciation of the mechanisms through which BCP crystals mediate tissue damage should lead to the development of novel management strategies for these common musculoskeletal syndromes.

Keywords

basic calcium phosphate crystals; calcific periarthritis; osteoarthritis

INTRODUCTION

The term ‘basic calcium phosphate’ (BCP) refers to a trio of calcium phosphate crystals consisting of carbonate substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate. BCP crystals are similar to the calcium phosphate mineral that is a normal component of bones and teeth. However, in pathologic situations, BCP crystals can produce

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There are no conflicts of interest.

vigorous inflammatory responses, disrupt normal tissue biomechanics, and directly interact with nearby cells to induce production of destructive cytokines and prostaglandins. In the musculoskeletal system, BCP crystals are most commonly associated with two clinical syndromes. These include calcific periarthritis, in which BCP crystals deposit in tendons, bursae, and other soft tissues around the joint, and BCP-associated arthritis, which produces clinical manifestations ranging from typical osteoarthritis to the aggressively destructive arthropathy known as Milwaukee Shoulder Syndrome (MSS). In this review, I will discuss some new clinical findings in calcific periarthritis at the hip and evidence-based management strategies for calcific tendinitis. I will summarize several recent advancements in understanding mechanisms through which crystals produce tissue damage, and explore some newly identified risk factors for and mechanisms of BCP crystal formation.

CALCIFIC PERIARTHRITIS

Calcific periarthritis occurs at many sites, but is most easily recognized and best studied in the shoulder. The natural history and clinical presentations of calcific periarthritis at sites other than the shoulder are still not well understood. Park *et al.* [1] recently described a large series of patients with calcific periarthritis around the hip joint. Thirty patients were identified. As is true of most series of calcific periarthritis, the majority were female (73%) and while the average age was 51 years, a wide age range (28–78) was noted. The most commonly involved tendon was the gluteus medius tendon, with the reflected head of the rectus femoris, the second most common site. Other locations included the direct head of the rectus femoris, the iliopsoas, the piriformis, and three out of 30 of the calcifications were located in the joint capsule. The latter finding supports the continued use of the more accurate term ‘calcific periarthritis’ over the commonly used term ‘calcific tendinitis’. Most patients were treated conservatively with NSAIDs and tramadol and had relatively rapid resolution of their symptoms. The mean duration of symptoms in this cohort was 4.4 months (range 0.1–18 months). As demonstrated in prior shoulder studies [2], there was a poor correlation between the size or density of the calcific deposit and the clinical course and pain severity scores. Several patients failed conservative therapy and required more aggressive interventions such as barbotage. Barbotage involves ultrasound-guided injection of corticosteroids and lidocaine with the goal of physically breaking up the crystal deposit. Those who failed this intervention were managed with arthroscopic surgery. In these patients, the insidious onset of pain and radiographically larger calcifications seemed to predict the need for more aggressive treatments. This series contributes to our knowledge of the clinical presentation and natural history of calcific periarthritis at ‘nonshoulder’ sites. Similar work in other areas may highlight similarities and differences between calcific periarthritis at the peripheral joints of the hands and feet, for example, compared with large joints such as the hip and shoulder.

In patients with recurrent or multiple sites of calcific periarthritis, metabolic abnormalities should be considered. Elevated levels of circulating calcium or phosphate, such as that associated with calcifylaxis in end-stage renal disease, may cause pathologic calcification at multiple sites. However, there are other more subtle clinical syndromes in which calcific periarthritis occurs. Mild forms of hypophosphatasia, for example, can present with calcific periarthritis. Hypophosphatasia is caused by deficiencies in alkaline phosphatase activity [3].

Guanabens *et al.* [4] recently described three middle-aged sisters in whom calcific periarthritis was the presenting clinical manifestation of this disease. These women had recurrent episodes of pain around the hips, shoulders, elbows, wrists, and Achilles tendons. They had low alkaline phosphatase activity levels, hyperphosphatemia, and increased concentrations of pyridoxal 5' phosphate. Genome sequencing revealed a unique 18 base pair duplication in the *TNSALP* gene. Hypophosphatasia should be considered in patients with recurrent or familial calcific periarthritis and findings of tooth loss, or bone abnormalities such as rickets or osteomalacia. Historically, calcium pyrophosphate (PPi) deposition has been associated with hypophosphatasia, but this interesting case description suggests that BCP crystal-related syndromes may be the presenting manifestation of this disease.

Calcific periarthritis was described recently in a family with a deficiency in ENT1 (equilibrative nucleoside transporter-1, SLC29A1) and the Augustine-null blood type [5]. The Augustine null mutation was described in 1960s as a cause of severe hemolytic transfusion reactions and mild hemolytic disease of the newborn. This ENT1 mutation presented with acute inflammatory attacks consistent with calcific periarthritis around large and small joints in three affected sisters in their early 20s. ENT-1 transports adenosine across the cell membrane and regulates levels of this highly bioactive nucleoside [6]. A loss of function in ENT-1 in mice causes ectopic spinal calcification [7]. A role for ENT-1 in pathologic calcification is plausible because adenosine metabolism is closely tied to regulation of ATP and PPi levels. ATP and PPi are critical regulators of mineral formation and abnormal adenosine levels likely directly affect levels of ATP and PPi. Further work will be necessary to confirm the chemical composition of these calcifications, but this interesting report further implicates the ENT family of enzymes in BCP mineral deposition.

Treatments for calcific periarthritis generally are not evidenced-based and few comparative effectiveness trials exist. First-line therapies include NSAIDs and intralesional corticosteroids. Large calcific densities associated with chronic symptoms are often managed with a variety of interventions designed to break up the mineral deposits. These interventions vary from barbotage to shockwave therapy. Iontophoresis with agents that dissolve mineral, such as acetic acid, has recently been shown to have little efficacy in calcific periarthritis [8]. A recent systematic review compared the effectiveness of high-energy extracorporeal shockwave (ESTW) therapy to barbotage and arthroscopic surgery [9■]. The authors identified 22 studies that satisfied their inclusion criteria, which included studies which followed patients for at least 6 months, eliminated other causes of shoulder pain such as full-thickness rotator cuff tears, and examined two relevant outcome measures based on shoulder function and size of the calcific deposit. The studies satisfying these criteria included over 1200 shoulders. Of the 22 studies, 11 were conducted as prospective randomized controlled trials. On the contrary, variations in the techniques, particularly those involving ESTW significantly affected the authors' ability to combine studies or to do head-to-head comparisons. We are left with a conclusion that all three modalities are well tolerated and effective, but little else. Carefully planned prospective studies of various management strategies will be required to determine the effectiveness of these expensive interventions.

BASIC CALCIUM PHOSPHATE-ASSOCIATED ARTHRITIS

BCP crystals are common components of osteoarthritis joints and in MSS, they cause a severe destructive arthritis. Recently, Hawellek *et al.* [10■] studied the prevalence of BCP crystal deposition in cartilage of the shoulder joint. These investigators used the highly sensitive method of digital contact radiography (DCR) to study 180 humeral head from 90 donors in this cross-sectional study of cartilage calcification in the shoulder in the general population. They excluded samples from patients with shoulder disease other than osteoarthritis, such as those with prior shoulder surgery, tumors, infection or known rheumatic disease. They correlated the presence of mineralization as seen with DCR with age and histologic grade of osteoarthritis. von Kossa and Alizarin Red S staining were used to identify the composition of the deposits. Mean donor age was 62.7 years (range 20–93). Significantly, 98.9% of the samples had DCR evidence of cartilage calcification. Significant histologic evidence of osteoarthritis was noted in 18.9% of the samples, which alone is an interesting finding, as we often think of shoulder osteoarthritis as a relatively rare condition. Using the technique of data analysis known as ‘structural equation modeling’, cartilage calcification correlated with the histologic grade and presence of osteoarthritis, but not with age. This interesting work supports older work by Scotchford and Ali [11] suggesting that calcium phosphate crystals may be common and possibly normal components of articular cartilage in large joints. Scotchford and Ali [11] found that these deposits were composed of magnesium whitlockite which may be less inflammatory than BCP crystals. Stains such as Alizarin Red S and von Kossa cannot distinguish between BCP and calcium PPi crystals. Hawellek *et al.* did not carefully identify the chemical composition of these crystals, and this is a major issue with this work.

Understanding mechanisms through which BCP crystals signal to incite inflammation or initiate catabolic responses in articular cells remains an active area of study. Initially the NLRP3 (NRL family, pyrin domain containing 3) inflammasome was implicated in the signaling mechanism based on in-vitro studies [12]. There remains some controversy in this area based on in-vivo studies which do not support a role for this pathway [13]. Recent elegant work implicated the membrane proximal kinase, spleen tyrosine kinase (Syk), and phosphatidylinositol 3 kinase (PI3K) in BCP crystal-induced inflammation. These second messengers mediate the interactions of monosodium urate (MSU) crystals with neutrophils and dendritic cells via a process known as membrane affinity-triggered signaling. This process involves the formation of lipid rafts in the membrane. Similar processes mediate macrophage phagocytosis after Fc receptor engagement [14■■]. This group demonstrated that BCP crystals activate Syk and PI3K in primary human macrophages and dendritic cells and that this drives IL-1 production and involves lipid raft formation. Significantly, the induction by synthetic BCP crystals of a variety of catabolic mediators and cytokines was augmented when macrophages were exposed to both osteoarthritis synovial fluid and BCP crystals showing that there are cofactors in synovial fluid which augment the crystals’ inflammatory effects. This important work delineates mechanisms through which BCP crystals contribute to osteoarthritis and may result in novel drug development.

This year, Cunningham *et al.* [15■■] showed that BCP crystals promote osteoclast formation by inhibiting antiosteoclastogenic factors. BCP crystals can cause extensive bone

destruction as seen in MSS, and there is increasing support for a role for subchondral bone abnormalities in osteoarthritis [16]. BCP crystals have been shown to induce prostaglandin E2, a potent inducer of osteoclast formation. The authors show that BCP and MSU crystals inhibit IL-6 and IFN-γ signaling in early and late osteoclast precursors thus promoting osteoclastogenesis. They conclude that BCP crystals contribute to osteoarthritis by opposing antiosteclastogenesis factors, resulting in increased subchondral bone dysfunction and joint destruction.

Factors involved in modulating the inflammatory potential of BCP crystals in pathologic settings remain poorly understood. Vitamin K dependent Gla-rich proteins (GRPs) have been shown to play a potential role in this process in the setting of osteoarthritis [17■■]. GRP is an understudied member of the family of vitamin K-dependent proteins. It was recently shown be upregulated in chondrocytes and synoviocytes during extracellular matrix calcification as well as after IL-1β exposure. Furthermore, when BCP crystals were coated with GRP, their inflammatory potential was decreased [17■■]. The recent work by Viegas *et al.* [18■■] further addresses the inflammation-calcification connection and GRP's role in these processes. Protein levels of GRP were increased after exposure of THP1 (a human monocytic cell line) cells or primary macrophages to BCP crystals. Coating of BCP crystals with GRP decreased their inflammatory potential, and overexpression of GRP decreased the inflammatory response to a variety of stimuli in THP1 cells and primary macrophages. This interesting work suggests that GRP and other members of this class of proteins may have both anti-inflammatory and anticalcification actions and thus may be interesting potential therapies for diseases such as osteoarthritis where both processes are involved.

There are few effective treatment strategies for BCP crystal-associated arthritis and dietary risk factors are not well defined. Joubert *et al.* [19] recently proposed that phytate (myo-inositol hexaphosphate) might contribute to pathologic vascular calcification in renal disease patients. Phytate is a polyphosphate found in nuts, whole grains, and seeds and is a natural inhibitor of calcification in a class with matrix Gla protein, PPi, and fetuin. Patients with renal disease are often on low phytate diets and levels are further reduced by dialysis. Phytate supplementation has been shown to decelerate vascular calcification in aging rats. Low levels may correlate with valvular calcification in elderly humans [20]. Sufficient levels would be difficult to achieve with diet alone, but intravenous forms of phytate are in early drug development stages. This interesting work postulates a potential role for dietary factors in pathologic BCP crystal formation and further studies may reveal a therapeutic potential for phytate in BCP crystal-associated musculoskeletal syndromes.

PPi is a key regulator of BCP crystal formation. The potential use of PPi as a therapeutic agent was recently highlighted [21■■]. For these studies, Pomozi *et al.* used a mouse model of pathologic calcification based on mutations in ATP binding cassette subfamily C member 6 (ABCC6). ABCC6 is an ATP-dependent organic anion transporter. It is critically involved in ATP efflux in some cell types and may be responsible for generating up to 60% of circulating PPi levels in plasma. Loss of function mutations in ABCC6 have been associated with diseases associated with vascular calcification such as pseudoxanthoma elasticum, generalized arterial calcification of infancy, and β thalassemia. Mice with loss of function mutations in ABCC6 have an inducible phenotype known as dystrophic cardiac calcification.

The authors of this interesting study set out to determine if intravenous PPi administration could counteract the pathologic calcification that characterizes ABCC6 deficient states. The bisphosphonate drugs, etidronate, and alendronate are PPi analogs and were used as comparisons. Although intravenously administered, PPi had a half-life of only 42 min, administration of a single dose after the initial injury that initiates calcification halted subsequent calcification. Similar results were seen with etidronate, but not with alendronate [21■■]. This fascinating work suggests that even transiently elevated levels of circulating PPi may reverse BCP crystal deposition in some settings. This work also supports a re-examination of bisphosphonates as potential therapies for some diseases involving pathologic calcification.

CONCLUSION

BCP crystal-associated musculoskeletal syndromes are common and can be challenging to treat. We are making some slow progress in understanding the clinical presentation and management of calcific periarthritis, and the role of BCP crystals in osteoarthritis. The characterization of novel modulators and mechanisms of BCP crystal formation and resultant tissue damage should ultimately lead to more effective treatment strategies for these syndromes.

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■ of special interest

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KEY POINTS

- Calcific periarthritis around the hip can cause a heterogeneous group of symptoms.
- Genetic and metabolic abnormalities including hypophosphatasia should be considered in patients with recurrent episodes of calcific periarthritis.
- BCP-induced inflammation may involve the spleen tyrosine kinase pathway and contribute to joint destruction though stimulation of osteoclastogenesis.
- Pyrophosphate and its analogs may be useful as therapeutic agents for pathologic calcification in some settings.