Skeletal Radiology (2023) 52:2037–2043
https://doi.org/10.1007/s00256-022-04246-8

REVIEW ARTICLE

Crystal arthropathies and osteoarthritis—where is the link?

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Received: 18 September 2022 / Revised: 28 November 2022 / Accepted: 28 November 2022 / Published online: 20 December 2022

Abstract
Osteoarthritis (OA) is one of the leading causes of disability worldwide. As our understanding of OA progressively has moved from a purely mechanical "wear and tear" concept toward a complex multi-tissue condition in which inflammation plays a central role, the possible role of crystal-induced inflammation in OA incidence and progression may be relevant. In addition to gout, which affects 4% of the US population, basic calcium phosphate and calcium pyrophosphate deposition both may induce joint inflammation and may play a role in pain in OA. This narrative review article discusses the possible mechanisms underlying the associations between crystal-induced arthropathies and OA, and the important implications of these for clinical practice and future research.

Keywords Osteoarthritis · Gout · Monosodium urate · Calcium pyrophosphate

Introduction

Osteoarthritis (OA) is one of the leading causes of disability worldwide, affecting 10–15% of adults, with a lifetime risk as high as 50% [1]. Currently, OA affects 30 million individuals in the U.S.A. [2] and 302 million worldwide [3]. Despite the advances in understanding the roles of biomechanical stress and cellular responses in OA pathophysiology [4], there are no disease modifying OA drugs to prevent or halt the progression of the disease.

Although OA has not been considered an inflammatory joint disorder, inflammation is an important feature in disease incidence and progression that is commonly assessed using either ultrasound or magnetic resonance imaging (MRI) [5–7]. Synovitis in OA is associated with inflammatory cytokines [8], structural OA severity [9], and fluctuation of pain in the same direction [7]. The etiopathogenesis of synovitis in knee OA is controversial. One hypothesis is that synovitis is a secondary reaction to cartilage fragments and other debris that promote synovial production of inflammatory mediators [10]. As our understanding of OA moves away from a purely mechanical "wear and tear" condition towards a complex multifaceted disease of the whole joint in which inflammation plays a central role, the question of a possible relationship between OA and calcium- and monosodium urate (MSU) crystal-induced inflammation in the context of OA has gained increasing attention [11, 12]. Both gout and OA are associated with calcium pyrophosphate (CPP) crystal deposition.

From a clinical perspective, there are several indicators suggesting an association between OA and crystal-induced arthropathies. For instance, OA and radiographically detected intra-articular mineralization (i.e., chondrocalcinosis, are often seen concurrently). In addition, gout and OA have many overlapping joint distributions, including the first metatarsophalangeal (MTP), knee, midfoot, and interphalangeal joints [11]. This clinically observed co-occurrence may be not merely coincidental.

In this review, we will discuss in narrative fashion the current knowledge of crystal-induced arthropathies and their role in structural OA incidence and progression, including the role of imaging in helping to understand such associations.

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Calcium crystal arthropathy and OA

Calcium crystal arthropathies can be secondary to CPP and/or basic calcium phosphate (BCP). CPP crystals are rod- or rhomboid-shaped, 1–22 μm in size, and birefringent in polarized light [13]. BCP crystals, however, are much smaller (20–100 nm) and cannot be readily visualized on light or polarized microscopy [14]. There are three types of BCP crystals: partially carbonate-substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate [15]. Of note, BCP is often termed "hydroxyapatite" in the radiological literature, although the "BCP" terminology is more accurate, since hydroxyapatite is only one subtype of BCP, and any of the BCP elements can be associated with calcific periarthritis. BCP crystals are similar to the mineral calcium phosphate that is a normal component of bone, but in pathologic situations, BCP crystals can produce a strong inflammatory response with large amounts of destructive cytokines and prostaglandins [16], such as have been associated with the highly destructive Milwaukee shoulder syndrome [17].

A major hurdle to understanding the contribution of CPP and BCP crystals to OA incidence and progression is that they have an identical presentation on imaging, which is chondrocalcinosis. When chondrocalcinosis is present on radiographs, computed tomography (CT), or ultrasound imaging, it may reflect either CPP or BCP crystal deposition. Outside of relatively rare metabolic diseases, such as hereditary hemochromatosis, hyperparathyroidism, and hypomagnesemia [18], the mechanism of occurrence of chondrocalcinosis is not well understood. It is known that the prevalence of chondrocalcinosis increases with a history of prior joint damage, such as prior meniscectomy [19]. The association between chondrocalcinosis and OA is also well established and supported by evidence from large epidemiological cohorts [20, 21] (Fig. 1), but the causal relationship between the two remains largely unclear. The Boston University Calcium Knee Score (BUCKS) is a new CT-based scoring system for the evaluation of knee chondrocalcinosis [22]. The BUCKS has been used in a large epidemiological cohort, to describe the prevalence of chondrocalcinosis and study its association with knee pain and other features of OA [23]. The use of the BUCKS system will help studying correlations between intra-articular mineralization deposition and MRI-based semi-quantitative features of knee OA, which in turn will lay the groundwork for a better understanding of knee OA pathophysiology and more specifically the role of crystal deposition in knee OA. Additional research is needed on the relationship between chondrocalcinosis and OA. Both CPP and BCP are commonly detected in cartilage and synovial fluid of the joints affected by OA [24]. Both crystals are also associated with the severity of OA and may become easier to detect as OA progresses [25, 26].

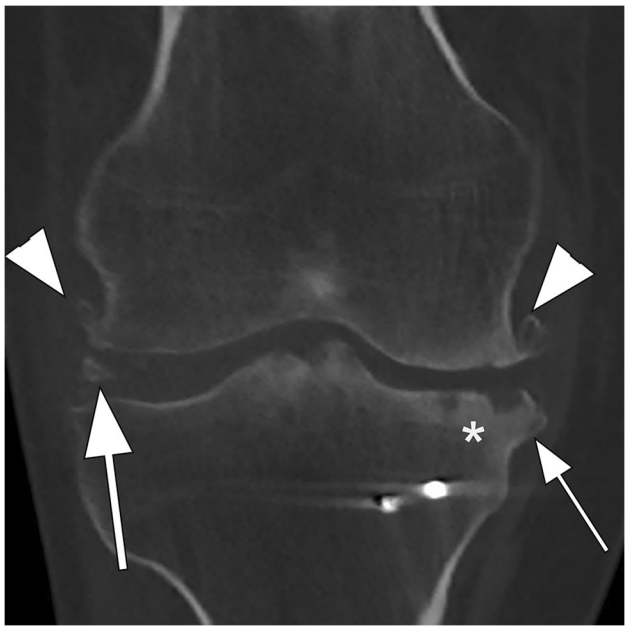

Fig. 1 Example of co-occurrence of chondrocalcinosis and knee OA. Coronal CT reformation shows definite medial and lateral tibiofemoral OA. There are large osteophytes at the femoral joint margins (arrowheads). In addition, there is severe meniscal calcification at the lateral meniscus (large arrow). There is a large osteophyte at the medial tibia (small arrow) and signs of severe sclerosis at the subchondral medial tibia (asterisk)

The studies that examined what types and proportion of calcium crystals are involved in chondrocalcinosis are rather limited, and to further complicate the matter, some published research has been based on the assumption that chondrocalcinosis is related to CPP deposition without consideration for the role of BCP [27]. Partly because of the difficulty in identifying BCP, these crystals are often ignored [28]; as a result, the clinical research on this matter is limited, and the clinical significance of BCP crystals is poorly understood.

A cadaveric study that included 106 knee specimens from cadaveric donors showed that every knee contained some measurable cartilage mineralization, and that cartilage mineralization was more strongly associated with age rather than the grade of OA. These findings seem to suggest that intra-articular mineralization is an "innocent bystander" rather than the cause of damage and senescence [29]. However, several other studies have emphasized the oxidative stress induced by intra-articular mineralization through the release of inflammatory cytokines and other inflammatory mediators [30]. For instance, CPP crystals were shown to activate nucleotide-binding domain-like receptor protein-3 (NLRP3) inflammasome (in human and mice cells), which cleaves and expresses interleukin-1β (IL-1β), in a similar way

to gout [14, 31]. BCP on the other hand can operate via dependent and independent NLRP3 pathways [32]. For instance, BCP increases the production of prostaglandin E2 production [33], matrix metalloproteinases-13 from human *fibroblasts* [34], and the release of tumor necrosis factor-α [35].

A recent study showed that BCP, but not CPP, is associated with hypertrophy of chondrocytes [27], a feature that is thought to be associated with the initiation and progression of OA [36]. CPP on the other hand was found to be associated with cellular senescence [27]. In other ex vivo studies, BCP crystals were shown to increase chondrocyte apoptosis [37] and cartilage degradation [32]. In an animal study, intra-articular injection of CPP resulted in accelerated OA [38]. Finally, a large community-based case–control study in the UK showed CPP deposits were associated with osteophyte formation [39].

Of note, therapeutic strategies targeting various inflammatory pathways, including IL-1β blockade, have been trialed in OA with varying success [40, 41]. The role of calcium-containing crystals in the pathogenesis of OA remains to be determined. Although developments in clinical and translational research suggest an important role, particularly for BCP crystals, the importance of calcium crystals in overall OA initiation and propagation requires further investigation.

Gout and osteoarthritis

Gout is an increasingly prevalent disorder, with a reported U.S. prevalence of nearly 4% in 2008 [42]. Hyperuricemia, which had a U.S. prevalence of 21.4% in 2008 [42], is defined as a serum urate level of > 6.8 mg/dL. This concentration is the threshold above which the risk of MSU crystallization increases [43]. The progression from asymptomatic hyperuricemia to symptomatic gout implies a state of increased MSU crystal deposition in the tissues around the joint, including the formation of tophi, complex biologically—active structures that reflect chronic inflammatory granulomatous and fibrotic tissue responses to MSU crystals [11, 44]. Gouty arthropathy is clinically characterized by episodes of intense inflammatory arthritis and sometimes a chronic inflammatory arthritis. Gouty flares are usually mono-articular or less commonly polyarticular, whereas painful flares in OA are usually less intense, more variable in its manifestations and less inflammatory (e.g., effusions may be cool to touch). Pain in OA has been associated with the presence of synovitis and bone marrow lesions on MRI [45, 46].

The similar distribution of affected joints in OA and gout and, in particular, the striking predilection of gout for the first MTP joint [47] has long been considered a clue of a relationship between the two conditions (Fig. 2). In addition, the common occurrence of acute gouty attacks in nodal OA has long been recognized [48]. Moreover, the two entities

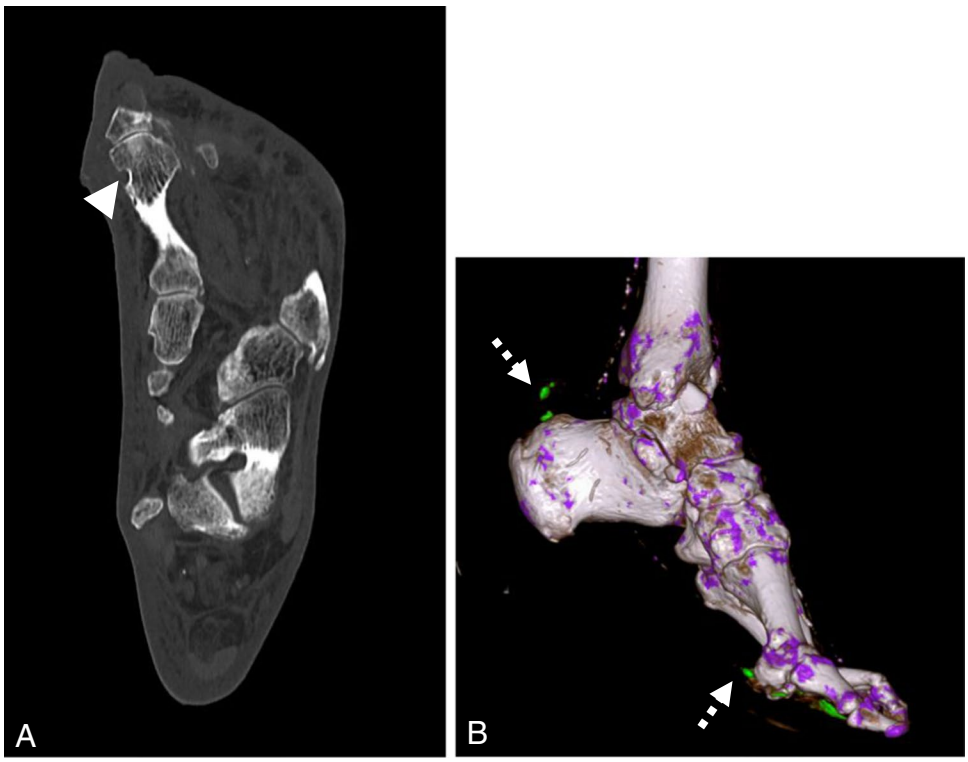

Fig. 2 Example of gout in a 65-year-old man. **A** Axial CT of the foot shows an erosion of the medial aspect of the first metatarsal head (arrowhead). **B** Three-dimensional volume rendering technique (VRT) image post gout processing shows green-color coded deposits in the hallux and along the Achilles tendon (dashed arrows). The first MTP joint is also a common location for osteoarthritis

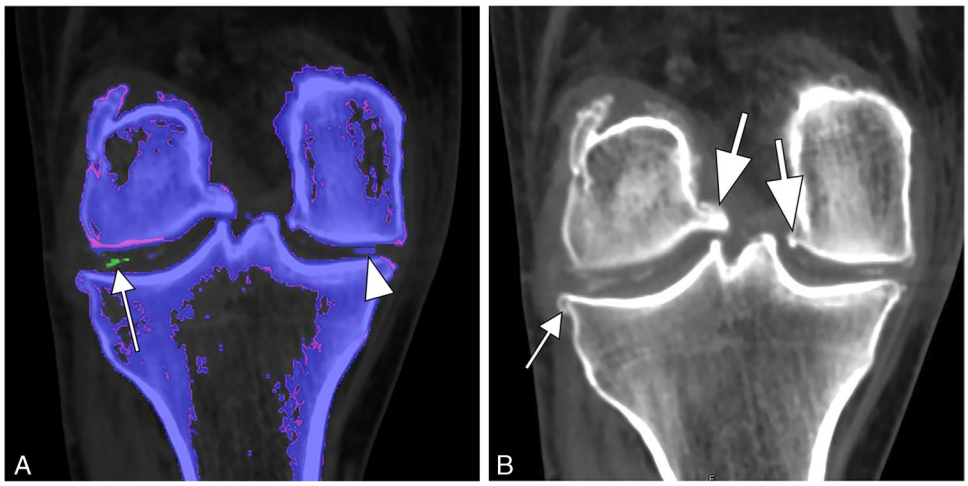

Fig. 3 Gout, CPPD, and OA may be present concomitantly in a painful knee. **A** Color-coded coronal dual-energy CT reformation shows definitive mono-sodium urate crystal deposition in the lateral joint space (arrow). In the medial joint space, meniscal calcification is observed consistent with CPPD (arrowhead). **B** Plain CT reformation shows a definite osteophyte at the lateral joint margin (small arrow) and large notch osteophytes (large arrows)

share similar risk factors, including age, obesity, and prior joint injury [49, 50]. A cadaveric study including 7855 adult human tali found a strong correlation between MSU deposition and sites of cartilage lesions in zones of biomechanical stresses (typical of OA) [51]. In addition, OA has been associated with interleukin (IL)-1β response genes [52]. This is similar to gouty arthropathy since IL-1β is also an important mediator in the inflammatory response of gout [53] and is released in response to the presence of MSU crystals [54].

There are also non-overlapping features between gout and OA, however, including differences in risk factors and joint distributions. For instance, men are more likely to develop gout whereas women are more likely to develop OA [11]. Renal insufficiency is a risk factor for gout but not for OA [11]. The genetic associations of both diseases are also different, with OA genetics relating to BMI and cartilage biology [55], whereas gout genetics largely relate to renal urate excretion [56]. In terms of distribution, the hip joint is commonly affected in OA but not in gout [11].

A prior in vitro study demonstrated a deleterious effect of microcrystalline urate leading to the generation of chondrocyte death, which in turn leads to the generation of additional urate in a feed-forward amplification loop [57]. These responses only occurred at high concentrations of MSU, consistent with a higher likelihood MSU crystal deposition. In contrast, at lower (physiological) concentration, soluble uric acid may have an antioxidant chondroprotective and anti-inflammatory effect, thereby acting as a protective against OA [58]. In a recent animal study, the repeated injection of MSU into the knee joint was found to cause distinctive pathological changes reflecting OA as investigated by translational imaging [59].

In a large community-based study of 4249 participants, a highly significant association between the site of acute attacks of gout and the presence of OA was demonstrated, including in the first MTP, the midfoot joint, knee, and DIP joints [60].

High levels of uric acid have been associated with generalized OA among those undergoing hip replacement, but not among those undergoing knee replacement [61]. Although another case–control study found generalized OA to be no more common among people with gout than those without gout after matching for age and gender and adjusting for BMI and diuretic use [62], chronic knee and hallux pain, and hallux valgus were more frequent among those with gout. This suggests that the association between OA and gout lies at the individual-affected joint level. In addition, a study using patient databases from Taiwan and the UK showed an association between gout and both hip and knee replacement [63]; the risk of joint replacement was not reduced with urate-lowering therapy, however.

In a large case–control study of 39,111 patients with incident gout [64], a review of medical records over a 10-year period prior to and after the index date showed that the risk of incident OA was significantly higher in subjects with gout than in controls (hazard ratio 1.45 (95% C.I., 1.35–1.54)). However, the subjects with gout were also more likely to have had a preceding diagnosis of OA (OR 1.27) versus controls.

From an imaging perspective, a cross-sectional study of 92 patients with tophaceous gout of the feet reported that joints with MSU crystal deposition detected on dual-energy CT (DECT) were up to 10 times more likely to display features such as osteophytes, subchondral sclerosis, and joint space narrowing, which are typical of OA but not of gout [65]. DECT is commonly used in clinical practice to differentiate between gout and CPP arthropathy (Fig. 3) though a recent study showed that ultrasound has higher sensitivity than DECT for the detection of MSU and CPP crystals [66].

Advanced MRI sequences that included T2 mapping and T1rho, which are biomarkers for early-stage OA [67, 68], showed abnormal cartilage and meniscal changes in patients with hyperuricemia [69, 70].

Summary

The links between OA, uric acid, CPP, and BCP are complex and require further investigation. Both gout and OA are associated with CPP crystal deposition. Gout and OA appear to be risk factors for each other, with some overlap in terms of the joint distribution. The associations among OA, CPP, and BCP are complex and less understood, partly because of the challenges for the detection of BCP. As for CPP deposition, the lack of longitudinal studies limits our understanding of the causality direction between CPP and OA.

Declarations

Conflict of interest AG: received consultancy fees from Pfizer, Novartis, MerckSerono, TissueGene, AstraZeneca, and Regeneron. He is a shareholder of Boston Imaging Core Lab., LLC. FWR: Consultant to Calibr and Grünenthal. He is a shareholder of Boston Imaging Core Lab., LLC. CKK has received consultancy fees from Thuasne, Regeneron, Novartis, Kolon Tissue Gene, Taiwan Liposome, Amzell AZ, LG Chem, Express Scripts, and has received grants from Lilly, Pfizer GSK, Cumberland.

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