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Chondrocalcinosis and Osteoarthritis: A Literature Review

Stacey Ying Guo¹ , Cassandra A. Lee² , Barton L. Wise^{1,2} 

Abstract

Objective: The objective of this study was to review the literature on associations between chondrocalcinosis (CC) and osteoarthritis (OA) and to examine the role of colchicine, previously established as effective for calcium pyrophosphate deposition disease, in the treatment of OA.

Methods: A literature search for mechanistic and clinical studies published between 1990 and 2021 listed in PubMed was performed and studies were included if they examined the associations between OA and CC or colchicine using relevant search terms.

Results: Published evidence suggests significant radiographic and mechanistic associations between knee OA and knee CC, but there are only a limited number of studies demonstrating associations between OA and CC in the hips, hands, and ankles. We examined three studies testing the efficacy of colchicine on treatment of pain in OA and found insufficient evidence to definitively establish that colchicine is effective to ameliorate symptoms of OA, although differences in study methodologies and inclusion criteria may explain inconsistent study findings.

Conclusion: An association between CC and OA is supported at the knee joint in both radiographic and in-vitro studies, but is less definite when the relationship is evaluated at other joints, including at the hips, hands, and ankles. Further research is required to ascertain whether CC modifies symptoms in patients with osteoarthritis or is associated with OA progression. It may be worthwhile to further evaluate colchicine or other agents for potential symptom modifying roles in OA or in OA with CC.

Keywords: Osteoarthritis, Calcium pyrophosphate deposition disease, chondrocalcinosis, colchicine

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Introduction

Chondrocalcinosis (CC) is the term used for radiographic features that identify calcium crystal deposition in the articular space.^{1–3} Various imaging modalities can be used for the detection of crystal deposition including conventional radiography, computed tomography (CT) scan, ultrasound, and magnetic resonance imaging (MRI).⁴ Furthermore, though identification of calcium crystals in synovial fluid remains the standard diagnosis for CC, dual-energy CT and multi-energy photon-counting CT have become increasingly popular as noninvasive clinical tools for detecting, quantification, and mapping calcium deposition in joints.⁵ Calcium pyrophosphate dihydrate crystal deposition in joints manifests as calcium pyrophosphate deposition disease (CPPD).⁶ Symptoms are not always present, but when they are, can manifest as an acute inflammatory crystal arthritis, known as “pseudogout.” Osteoarthritis (OA) with CC was recognized by the experts as a clinical presentation of CPPD, and defined as CC in a joint that also shows changes of OA on imaging or histological examination.⁶

The relationship between CC and OA has been well established in several independent populations, but in part, because CC is a generalized multiple-joint disease, its association with OA may vary from joint to joint.^{7–11} The knee has been identified as the most common site for CC followed by the presence of CC in the wrists, hips, and symphysis pubis.³ In contrast, although OA can occur in any synovial joint in the body, it is more common in the knees, hands, and hips.¹ Findings from recent studies suggest that the association between OA and CC varies from joint to joint.¹² Given this distributional variability in the expression of OA and of CC, we will separately describe that association at each commonly involved joint. This review will summarize recent evidence regarding the associations between CC and OA by joint—knees, hips, hands, and ankles—and address the potential symptom modifying effect of colchicine for OA and OA with CC.

Table 1. Characteristics of Studies that Examined Associations Between CC and OA in the Knee, Hip, Hand, and Ankle Joints

Association of CC and OA	Reference	Mean Age (Years)	Female (%)	Sample Size (n)	Imaging or Histological Method	Study Design
Knee joint	Foreman et al. ²	66.9	56	70	MRI	Cross-sectional
	Latourte et al. ³⁰	62.2	70.3	656	X-ray	Prospective
	Chiba et al. ¹⁶	52.6	61.1	1278	X-ray	Cross-sectional
	Kleiber Balderrama et al. ²¹	68.1	95	25,157	Risk for KR	Cross-sectional
	Gersing et al. ¹⁹	67.7	55.5	90	MRI	Prospective cohort
	Pandit et al. ²⁴	62	44.8	78	X-ray	Cross-sectional
	Abhishek et al. ¹³	68.6	48.7	2658	X-ray	Case-control
	Abhishek et al. ¹⁴	66.6	48.5	3118	X-ray	Cross-sectional
	Robier et al. ²⁵	77	19	23	X-ray	Retrospective cohort
	Musacchio et al. ²³	75.2	58.1	1629	X-ray	Cross-sectional
	Neogi et al. ³¹	67/74	42/69	265/230	MRI	Prospective
	Neame et al. ⁸	63.7	62.8	1727	X-ray	Cross-sectional
	Al-Arfaj ¹⁵	67.5	34.8	92	X-ray	Cross-sectional
	Felson et al. ¹⁷	70.5	63.7	598	X-ray	Prospective cohort
	Sanmarti et al. ²⁶	68.8	53.1	130	X-ray	Cross-sectional
	Ledingham et al. ²²	73 (F), 65 (M)	63.9	252	X-ray	Cross-sectional
	Felson et al. ¹⁷	77	68	1402	X-ray	Cross-sectional
	Gordon et al. ²⁰	73	58.3	127	X-ray	Cross-sectional
	Wilkins et al. ²⁷	79.4	69	91	X-ray	Cross-sectional
	Hip joint	Hawellek et al. ³⁵	62.1	44.7	85	Histology
Hawellek et al. ³⁶		62	44.8	87	Histology	Cross-sectional
Ledingham et al. ²²		66	63	211	X-ray	Cross-sectional
Hand joint	Stucki et al. ³⁸	79	87	120	X-ray	Cross-sectional
	Sanmarti et al. ²⁶	68.8	53.1	130	X-ray	Cross-sectional
Ankle Joint	Hubert et al. ⁴⁰	62.4	42.5	80	Histology	Cross-sectional
	Muehleman et al. ³⁹	83.9% > age 50	29	4077	Histology	Cross-sectional

KR: knee arthroplasty.

*Two different study populations: The Boston OA Knee Study (BOKS)/Health, Aging and Body Composition (Health ABC) study.

Search Methodology

A search for mechanistic and clinical studies published between 1990 and 2021 was performed in PubMed. We employed the search terms “association between” “knee (or hip or hand or ankle) osteoarthritis,” “chondrocalcinosis,” “CPPD,” “pseudogout,” “calcium pyrophosphate disease,” “colchicine” and we specifically evaluated for instances where these terms were used in combination. We included relevant reports of studies, trials,

and meta-analyses, but we excluded conference abstracts, animal studies, and publications in languages other than English. We also examined the reference lists of the articles identified in the original search for further relevant papers indexed in PubMed and MEDLINE.

Association Between Knee CC and Knee OA

The relationship between knee CC and knee OA has been evaluated in several recent publications. In the most recent pooled meta-analysis study by Wang et al., out of 14 total cross-sectional studies included in the final analysis, 12 studies were included to evaluate the association between knee CC and knee OA.^{2,8,13–27} In their study, CC was defined by “radiological criteria [of] a linear or nummular calcification in the fibrocartilage or hyaline articular cartilage,”^{10,14} and OA was defined by “either radiological or clinical criteria, based on Kellgren and Lawrence grade (K–L grade)²⁸ or the American College of Rheumatology criteria (ACR criteria).”^{10,29} The authors calculated a pooled odds ratio (OR) of the prevalence of OA between the CC and the non-CC group and found a positive association between knee CC and knee OA (OR = 2.84; confidence interval [CI]: 2.12–3.81; $P < .001$).¹⁰ The caveat

to this finding was that they found substantial heterogeneity between studies ($I^2 = 58\%$; $P = .01$) which remained despite performing further sensitivity analysis, suggesting that there could be substantial differences in the methodologies and inclusion criteria of the studies examined.¹⁰ The authors further examined whether CC may be associated with progression of OA and found no relationship, based on the pooled OR of two prospective cohort studies (OR = 1.02; CI: 0.45–2.31; $P = .96$), with no substantial heterogeneity ($I^2 = 0\%$, $P = .32$).¹⁰ Since only two studies were included in this analysis, there is limited evidence here to establish whether CC may be associated with progression of OA.

Several other studies have reported relevant findings. Abhishek et al. reported a positive association between CC and OA in the knee (knee-specific adjusted OR = 2.20 [95% CI: 1.62–2.99] for right knees and OR = 2.59 [95% CI: 1.87–3.60] for left knees)¹⁴ and in a different study reported an association between CC and a more severe radiographic OA.¹³ Kleiber Balderrama et al. utilized a large US veterans database to compare those with CPPD to age-matched controls (with over 25,000 subjects in each group) and found that even after

Main Points

- An association between osteoarthritis and chondrocalcinosis is supported at the knee joint, but chondrocalcinosis is not clearly associated with progression of osteoarthritis.
- Associations between osteoarthritis and chondrocalcinosis at other joints besides the knee is less definitively established.
- Colchicine, a common treatment for calcium pyrophosphate disease, has inconsistent evidence for amelioration of OA symptoms at the knee.

controlling for the presence of OA those with CPPD were substantially and significantly more likely to have undergone knee arthroplasty (KR) (OR: 1.64 [95% CI: 1.53-1.76]),²¹ a hard outcome generally felt to be acceptable as a proxy for progression of OA.

Two different studies examined the relationship between baseline CC and risk of OA progression in the knee, using different imaging modalities and different analytic approaches. Latourte et al. evaluated 656 subjects with symptomatic knee OA, 14.2% of whom had knee CC at baseline, for the association of CC with risk of total knee replacement (TKR; occurred in 13.9% of the subjects), worsening of radiographic OA grade, or Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain or function subscores.³⁰ They reported no association with risk of TKR (hazard ratio: 1.26 [95% CI: 0.74-2.17]), worsening of radiographic grade (OR: 0.9 [95% CI: 0.4-1.7]), WOMAC pain (OR: 1.1 [95% CI: 0.7-1.4]) or WOMAC function (OR: 0.9 [95% CI: 0.4-2.0]).²⁷ Interestingly, a knee-specific model using generalized estimating equations showed a nonsignificant trend toward a protective effect of CC against TKR (OR: 0.41 [95% CI: 0.14-1.23]; $P = .11$).³⁰

Neogi et al. examined whether baseline CC was associated with cartilage loss over time as evaluated by longitudinal MRI readings in two different study populations, The Boston OA Knee Study (BOKS) and the Health, Aging and Body Composition (Health ABC) study, using the Whole-Organ Magnetic Resonance Imaging Score (WORMS).³¹ BOKS was a relatively small study population (265 knees with 23 with CC), but in that study, an inverse association was identified between CC and risk of cartilage loss over time (adjusted risk ratio [RR]: 0.4 [95% CI: 0.2-0.7]). However, in the larger Health ABC cohort (373 knees, 69 with CC) no difference in risk of cartilage loss was observed with CC (RR: 0.9 [95% CI: 0.6-1.5]).³¹ When the authors pooled the cohorts, a protective association for CC with the risk of cartilage loss was maintained (RR: 0.7 [95% CI: 0.5-0.99]).³¹ The authors overall interpreted these results as indicating no association between CC and risk of cartilage loss.

Given the relatively larger number of correlational studies delineating positive associations between knee CC and knee OA, we also reviewed studies that evaluated mechanisms for how this relationship might occur. Robier et al. found that in subjects with symptomatic OA of the knee, with a median K-L grade of 3 in initial radiographs, calcium-containing crystals were detected in all sequentially examined samples of synovial fluid, although they did not evaluate samples from subjects with

asymptomatic OA, thus may suggest verification bias is inherently present in the study.²⁵ In a more recent study by Foreman et al., the presence of calcium-containing crystals was associated with increased cartilage degeneration in the patella (correlation coefficient [r] = .33; 95% CI: 0.18-0.83), the medial femur ($r = .51$; CI: 0.18-0.83), the lateral tibia ($r = .36$; CI: 0.01-0.71), as well as the medial and lateral menisci ($r = .38$; CI: 0.00-0.75 and $r = .72$; CI: 0.12-0.32).² The authors concluded that calcium-containing crystals were associated with increased cartilage and meniscus degeneration over a study period of 4 years.² Checa and Chun hypothesized a potential explanation for this observation: Deposition of fibrocartilage in the meniscal space leads to increased stiffness.³² Aggregates of calcium within the meniscus matrix may modify the mechanical properties of that fibrocartilage rendering an increased susceptibility to failure with joint loading or minor trauma.⁷

Similarly, Gersing et al., through evaluation of gradient-echo sequences on MRI, found that compartments containing thicker cartilage, such as patella and lateral tibia, were associated with a higher crystal burden and greater cartilage damage, whereas regions with thin cartilage, such as the medial tibia, were associated with lower crystal burden and lower cartilage damage.¹⁹ This led the authors to conclude that the mineralization process of chondrocytes may be inseparable from the progression of OA.¹⁹ In *in vitro* studies, the authors found that ATP-induced calcium deposition in a monolayer culture of OA meniscal cells was much higher than that in the monolayer culture of control meniscal cells, suggesting that calcium deposition is common in OA menisci and therefore, pathological meniscal calcification may be potentially an important contributor to developing OA.³³ In contrast, Walsh et al. found in analyzing the synovium of a population of patients undergoing total knee joint replacement for OA that osteochondral and synovial angiogenesis in OA were independent processes; CC was not associated with increased angiogenesis or histological synovitis beyond that seen in OA alone.³⁴ Thus, although there appears to be a clinical/radiologic association between CC and OA in the knee, the specific mechanisms underlying this association remain unclear.

Association Between Hip CC and Hip OA

The association between CC and OA in the hip is controversial, owing to the limited number of studies published. In a systematic review and meta-analysis investigating the relationship between hip CC and hip OA based on radiographic evidence, the authors found only three studies eligible for assessing this relationship.¹⁰ Of the three observational

studies,^{14,22,23} only Ledingham et al. found that hip CC was more commonly associated with the atrophic bone response of hip OA in a case series examining 211 symptom-based subjects.^{10,22} A limitation to this study, however, was that the authors did not further define their terminology of "atrophic bone response of hip OA" and did not provide confidence intervals for classification of bone response into atrophic, hypertrophic, or indeterminate. The two other cross-sectional studies did not find a significant association.^{10,14,23} Based on our own search in PubMed, there were two other articles published in 2018, which were not captured in the original meta-analysis by Wang et al. In a cross-sectional postmortem study that analyzed 170 acetabular labrum of the hip (ALH) specimens from 85 donors, the authors found an association between the mean amount of ALH calcification, defined as "percentage of total cartilage area" and the histological degeneration grade (Krenn) of ALH ($r = .55$; $P < .001$) and histological OA grade for the hyaline cartilage (as defined by the Osteoarthritis Research Society International [OARSI] of the femoral head) ($r = .35$; $P < .001$) after adjusting for age.³⁵

The same authors published a cross-sectional postmortem study of a cohort of 87 donors that found a significant correlation between the amount of CC and histological OA ($r = .48$, $P < .001$), but not between CC and age ($r = -.09$, $P = 0.42$), suggesting that CC appears to be an early contributor of hip OA pathogenesis, independent of age.³⁶ In summary, there were a limited number of studies published thus far in our review of the recent literature examining the relationship between CC and OA at the hip joint. While the radiographic associational evidence is conflicting, there appears to be at least postmortem evidence that proposes a positive association independent of age.

Association Between Hand CC and Hand OA

The literature on the relationship between hand CC and hand OA is even more limited. In the 2019 meta-analysis authored by Wang et al., only three studies were identified that evaluated this association.^{15,26,37} One community-based cross-sectional study on a population in Spain found that while OA was more frequent in almost all areas of the hands in individuals with CC, the association was statistically significant only in metacarpophalangeal joints.²⁶ In contrast, in a case series of 253 elderly participants published by Caspi et al., the association between hand CC and hand OA was not observed.³⁷ One study by Stucki et al. performed an age and gender-matched case-control study at a university hospital outpatient clinic and found the

presence of scaphoid-trapezium (ST) joint OA is much more strongly associated with CPPD than polyarthritis of the finger joints.³⁸ This led the authors to conclude that the presence of ST osteoarthritis may be helpful for differentiating CPPD from polyarthritis in an elderly, predominantly female population.³⁸ Importantly, this study did not only include blinded readings of radiographs as the meta-analysis by Wang et al. described, but also sought to include cases diagnostic of CPPD by reviewing for evidence of pyrophosphate crystals from arthrocentesis and/or cartilage calcifications, which is considered closest to a gold standard in the diagnosis of CC.^{27,30}

Association Between Ankle CC and Ankle OA

Few studies exist that evaluate the association between ankle CC and OA. Our search identified only two articles evaluating this relationship at the ankle joint. Muehleman et al. studied this relationship by examining a sample of 7,855 human cadaveric tali for the "presence of surface and beneath-the-surface crystals."³⁹ They took a random subsample of tali and performed crystal analysis by Fourier transform infrared spectroscopy (FTIR), histologic examination, and immunohisto-chemistry.³⁹ The authors found that CC is strongly correlated with cartilage lesions in the talus.³⁹ Furthermore, the cartilage lesions appeared to be biomechanically induced, located where opposing articular surfaces might not continuously be in congruence with each other.³⁹ Similarly, Hubert et al. were able to further characterize this relationship by examining the prevalence of ankle joint cartilage calcification and determining its correlation with factors such as histological OA grade, age, and body mass index (BMI) in a general population.⁴⁰ In this study, the authors examined 160 ankle joints from 80 donors.⁴⁰ The donors were mostly male (57.5%) with a mean age of 62.4 and included only donors with bilaterally intact ankle joints with no signs of other diseases (except for OA).⁴⁰ Quantitative and qualitative analysis was conducted using high-resolution digital contact radiography and factors such as the joint's histological OA grade (OARS score), donor's age and BMI were investigated.⁴⁰ The authors discovered that the amount of ankle joint CC observed in the distal tibia and talus correlated with the histological OA-grade of the joint ($r = .70$, $P < .001$ and $r = .72$, $P < .001$, respectively), whereas no such correlation was seen in the general population with relation to age ($P = .32$ and $P = .49$) or BMI ($P = .51$ and $P = .87$).⁴⁰ Although the sample size was small, and may not be representative of the general population of OA patients (often with multiple comorbid illness and previous trauma-related injuries), the findings from the study suggest

that the relationship between the amount of ankle joint CC and OA exists independent of age and BMI, which are already well-established risk factors for OA.^{15,16,36,40} Thus, CC may serve as an important risk factor in the development of OA in ankles.

Use of Colchicine for Treatment of Knee OA

The consideration of the relation of OA with CC naturally raises the question of whether treatment previously established as effective for CPPD could serve to ameliorate the symptoms of OA itself. Although a small literature does exist examining this question, even the limited number of studies testing the effect of colchicine on pain in OA are contradictory and do not firmly demonstrate efficacy. The reason for the inconsistency in results is further obscured by differences in methodologies and definitions used for inclusion in the studies. The earliest of the studies, from 2002 by Das et al., enrolled 39 persons who met the 1986 ACR criteria for knee OA and who did not have rheumatoid arthritis (RA) by symptoms or by serum markers, and who had uncontrolled pain despite 2 weeks of piroxicam treatment.⁸ It is to be noted that on knee radiographs, 38% of participants displayed CC, and on synovial fluid aspiration, fully 74% of participants had CPPD crystals.⁸ All participants continued piroxicam throughout the trial, received an intra-articular steroid injection at the beginning of the study, and were randomized to 0.5 mg colchicine twice daily or placebo; primary endpoints were 30% reduction in visual analog pain scale and a modified version of the WOMAC pain scale at 16 weeks and 20 weeks.⁸ Both primary outcomes were found to be significantly better in the colchicine group at both 16 weeks and 20 weeks, although the effect was closer to nonsignificance at 20 weeks.⁸ Given that a large number of the participants in this trial also met the diagnostic criteria for CPPD (30% per the authors) it is unclear to what degree the colchicine was truly treating OA pain rather than CPPD; the authors did not provide subgroup analyses which might have suggested an answer to this basic issue in the study.

In 2011, Aran et al. published another blinded RCT trial to examine the question of efficacy of colchicine for treatment of moderate to severe knee OA symptoms.⁸ In this study, the authors enrolled primary knee OA patients, and specifically excluded persons with either radiographic evidence of CC or disease distribution patterns that would be atypical for OA, as well as excluding those with RA. Participants were allowed to continue "common OA treatments" (indomethacin, diclofenac, or physiotherapy) and were allowed to use acetaminophen as a rescue medication.⁴¹ Participants were randomized to either colchicine

0.5 mg twice daily or placebo, and primary endpoints were patient global assessment and physician global assessment, both recorded in the form of a visual analog scale (VAS) scale at 3 months.⁴¹ In addition, 58 participants completed the study.⁴¹ Both endpoints demonstrated profoundly better results in the colchicine group than in the placebo group that were highly significant, and acetaminophen consumption was substantially lower in the colchicine group ($P < .0001$ for all outcomes).⁴¹

Leung et al. took a similar approach in 2018.⁴² Patients meeting the ACR criteria for symptomatic and radiographic knee OA, along with a positive response to the frequent knee pain question and $\geq 40/100$ on a VAS pain scale were enrolled.⁴² The manuscript does not state whether the subjects were evaluated for the presence of radiographic CC, although it does describe excluding potential participants for gout or inflammatory arthropathy.⁴² Once enrolled, subjects were allowed to stay on their prestudy OA meds and were allowed acetaminophen as a rescue drug.⁴² They were randomized to 0.5 mg colchicine or placebo twice daily for 16 weeks, and the endpoints evaluated at that timepoint were WOMAC, Health Assessment Questionnaire (HAQ) and the Short Form 36 version 2 (SF36v2), with the primary endpoint being $\geq 30\%$ change in WOMAC. 101 subjects completed the 16 weeks follow-up.⁴² The authors found no significant differences between the colchicine and placebo groups in any of the endpoints. However, the authors note that the placebo response rate (49.1%) was higher than they had anticipated in their sample size calculations, and thus in the end they were underpowered to detect the rather robust primary endpoint of $\geq 30\%$ difference in WOMAC.⁴²

Discussion

Based on this review of recent literature evaluating the relationship between OA and CC at various joints, including the landmark meta-analysis study by Wang et al. 2019 which included several correlational studies, the evidence suggests that an association is most convincingly established at the knee joint in both radiographic and in vitro studies, but less convincingly when the relationship is evaluated at other joints, including at the hips, hands, and ankles. Furthermore, although there may be anecdotal evidence of associations between CC and OA at the elbow and shoulder, there remains a paucity of published data, based on our search in PubMed and MEDLINE. However, a significant limitation for all studies pointed out by Wang et al. is that diagnosis of CC based on radiographic findings of linear calcification in cartilage is

neither highly sensitive nor specific, such that results could be confounded due to undetected disease in complex anatomy incompletely seen on radiographs, leading to misclassification bias in studies. It is possible that studies utilizing three-dimensional imaging approaches might be more sensitive and could reduce this bias, allowing for greater approximation to the true associational relationship, but this approach has not been attempted as of current date.

In a study by Abhishek et al 2013, the authors evaluated whether there is a predisposition for articular CC to spread to other joints, and found that not only is this true, but that the association between OA and CC is joint-specific.¹⁴ Based on radiographic scoring for the severity of disease, the authors found that knee, wrist, and metacarpophalangeal (MCP) joint OA but not hip OA was associated with CC at the same joint.¹⁴ When evaluating plain radiographic imaging—knees, wrists, hips, pubic symphysis, and MCP joints are affected by CC in a descending order of frequency.¹² The reason for this distributional ordering of CC remains obscure. While CPPD may result from a systemic predisposition involving multiple joints, osteoarthritis is most often felt to be caused by aberrant local mechanical factors acting within a context of systemic susceptibility, which may tend to affect “loading” or “weight-bearing” joints such as the knees or ankles as opposed to the shoulders or hands.⁴³ Furthermore, the distribution of joint involvement in crystal-induced tissue damage does not seem to parallel the distribution of primary OA, with crystal deposition disease frequently associated with degeneration involving the shoulders, wrists, and elbows, sites not as commonly affected by primary OA.⁴⁴ Primary OA may affect specific joints affected due to local shearing forces and traumatic mechanisms while crystal-induced deposition of CC that results in a radiographic osteoarthritic phenotype may affect an alternate distribution of joints because of a different underlying mechanism. It is possible that the degree of CC in the joint space, particularly in meniscal space, and the damage it induces to the local environment, may predispose to OA or lead to progression of OA: There is enough data to support a key role of calcium-containing crystals in OA pathogenesis.⁴⁴ The presence of these crystals, “far higher in OA than in any other form of arthritis,” correlates with the degree of radiographic degeneration.⁴⁴ However, whether this correlates with symptom progression in OA remains an area for future study.

There is evidence to suggest CC is associated with certain phenotypes of radiographic OA,

but many specific elements of difference in symptoms, joint distribution, and clinical outcomes between OA with and without CC remain insufficiently characterized. Furthermore, whether and how chondrocalcinosis modifies the progression of the clinical and radiographic outcomes of OA is not yet known.¹² Other than Neogi et al.³⁰ and Latourte et al.,³¹ neither of which supported a longitudinal relationship between knee CC and knee OA, and Kleiber Balderrama et al. which supported an association between CC and progression to arthroplasty,²¹ to our knowledge there are no studies that have allowed for observation of temporal relationships between OA and CC in humans,⁶ making an understanding of the mechanistic relationship between the two limited and incomplete.

Further complicating the understanding of the relationship between CC and OA is the existence of the clinical pathologic entity of CPPD. Although CPPD is comprised of acute calcium pyrophosphate (CPP) crystal arthritis and chronic CPP crystal inflammatory arthritis and has been described in numerous studies through decades, a full picture of the phenotype of chondrocalcinosis with OA has yet to be clearly described in the literature. This also has resulted in only rudimentary approaches to the treatment of chondrocalcinosis-related OA. Acute CPP crystal arthritis is typically “treated with rest, local application of ice packs, joint aspiration, colchicine and/or intra-articular corticosteroid injection (once infection is excluded)”, while “colchicine, low-dose corticosteroids, hydroxychloroquine, and radiosynovectomy are recommended for the treatment of chronic or recurrent acute CPP crystal arthritis.”⁴⁵ The current limited evidence evaluating the use of colchicine for knee OA is not definitive but is suggestive, with two studies suggesting efficacy for reducing knee OA pain and one (the largest) which failed to demonstrate the difference from placebo; studies evaluating colchicine for symptomatic treatment of OA in other joints is lacking. Further research may be required to more definitively ascertain if CC modifies the symptoms in patients with OA, whether this manifests as a distinct clinical phenotype or additive synergy that causes worsening of presentation or progression of osteoarthritis.¹ If future studies demonstrate that CC is associated with or causes OA progression, it may even be worthwhile to consider colchicine or other agents for potential disease or symptom modifying roles.

In summary, an association between CC and OA is supported at the knee joint in both radiographic and in vitro studies, but is less definitive when the relationship is evaluated at

other joints, including at the hips, hands, and ankles. Further research is required to ascertain whether CC modifies symptoms in patients with osteoarthritis or is associated with OA progression. Based on these disease associations and inconsistent findings in treatment trials, it may be worthwhile to further evaluate colchicine or other agents for potential symptom modifying roles in OA or in OA with CC.

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References

1. Ea HK, Liote F. Advances in understanding calcium-containing crystal disease. *Curr Opin Rheumatol*. 2009;21(2):150-157. [\[CrossRef\]](#)
2. Foreman SC, Gersing AS, von Schacky CE, et al. Chondrocalcinosis is associated with increased knee joint degeneration over 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage*. 2020;28(2):201-207. [\[CrossRef\]](#)
3. Steinbach LS. Calcium pyrophosphate dihydrate and calcium hydroxyapatite crystal deposition diseases: imaging perspectives. *Radiol Clin North Am*. 2004;42(1):185-205, vii. [\[Cross-Ref\]](#)
4. Barskova VG, Kudaeva FM, Bozhieva LA, Smirnov AV, Volkov AV, Nasonov EL. Comparison of three imaging techniques in diagnosis of chondrocalcinosis of the knees in calcium pyrophosphate deposition disease. *Rheumatology (Oxford)*. 2013;52(6):1090-1094. [\[CrossRef\]](#)
5. Hajri R, Hajdu SD, Hugle T, Zufferey P, Guiral L, Becce F. Dual-Energy Computed Tomography for the Noninvasive Diagnosis of Coexisting Gout and Calcium Pyrophosphate Deposition Disease. *Arthritis Rheumatol*. 2019;71(8):1392. [\[CrossRef\]](#)
6. Zhang W, Doherty M, Bardin T, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Ann Rheum Dis*. 2011;70(4):563-570. [\[CrossRef\]](#)
7. Felson DT, Anderson JJ, Naimark A, Kannel W, Meenan RF. The prevalence of chondrocalcinosis in the elderly and its association with knee osteoarthritis: the Framingham Study. *J Rheumatol*. 1989;16(9):1241-1245. [\[CrossRef\]](#)

8. Neame RL, Carr AJ, Muir K, Doherty M. UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte. *Ann Rheum Dis.* 2003;62(6):513-518. [\[Cross-Ref\]](#)
9. Ramonda R, Musacchio E, Perissinotto E, et al. Prevalence of chondrocalcinosis in Italian subjects from northeastern Italy. The Pro.V.A. (PROgetto Veneto Anziani) study. *Clin Exp Rheumatol.* 2009;27(6):981-984.
10. Wang Y, Wei J, Zeng C, et al. Association between chondrocalcinosis and osteoarthritis: A systematic review and meta-analysis. *Int J Rheum Dis.* 2019;22(7):1175-1182. [\[Cross-Ref\]](#)
11. Zhang W, Neame R, Doherty S, Doherty M. Relative risk of knee chondrocalcinosis in siblings of index cases with pyrophosphate arthropathy. *Ann Rheum Dis.* 2004;63(8):969-973. [\[CrossRef\]](#)
12. Abhishek A. Calcium pyrophosphate deposition disease: a review of epidemiologic findings. *Curr Opin Rheumatol.* 2016;28(2):133-139. [\[CrossRef\]](#)
13. Abhishek A, Doherty S, Maciewicz RA, Muir K, Zhang W, Doherty M. Does Chondrocalcinosis Associate With a Distinct Radiographic Phenotype of Osteoarthritis in Knees and Hips? A Case-Control Study. *Arthritis Care Res (Hoboken).* 2016;68(2):211-216. [\[CrossRef\]](#)
14. Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M. Evidence of a systemic predisposition to chondrocalcinosis and association between chondrocalcinosis and osteoarthritis at distant joints: a cross-sectional study. *Arthritis Care Res (Hoboken).* 2013;65(7):1052-1058. [\[CrossRef\]](#)
15. Al-Arfaj AS. The relationship between chondrocalcinosis and osteoarthritis in Saudi Arabia. *Clin Rheumatol.* 2002;21(6):493-496. [\[Cross-Ref\]](#)
16. Chiba D, Tsuda E, Sasaki E, Takahashi I, Nakaji S, Ishibashi Y. Low prevalence of knee chondrocalcinosis and its catabolic association with serum matrix metalloproteinase 3: A rural Japanese population study. *Int J Rheum Dis.* 2018;21(11):2011-2018. [\[CrossRef\]](#)
17. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. *Semin Arthritis Rheum.* 1990;20(3 Suppl 1):42-50. [\[CrossRef\]](#)
18. Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum.* 1997;40(4):728-733. [\[Cross-Ref\]](#)
19. Gersing AS, Schwaiger BJ, Heilmeyer U, et al. Evaluation of Chondrocalcinosis and Associated Knee Joint Degeneration Using MR Imaging: Data from the Osteoarthritis Initiative. *Eur Radiol.* 2017;27(6):2497-2506. [\[CrossRef\]](#)
20. Gordon TP, Smith M, Ebert B, McCredie M, Brooks PM. Articular chondrocalcinosis in a hospital population: an Australian experience. *Aust N Z J Med.* 1984;14(5):655-659. [\[CrossRef\]](#)
21. Kleiber Balderrama C, Rosenthal AK, Lans D, Singh JA, Bartels CM. Calcium Pyrophosphate Deposition Disease and Associated Medical Comorbidities: A National Cross-Sectional Study of US Veterans. *Arthritis Care Res (Hoboken).* 2017;69(9):1400-1406. [\[CrossRef\]](#)
22. Ledingham J, Dawson S, Preston B, Milligan G, Doherty M. Radiographic patterns and associations of osteoarthritis of the hip. *Ann Rheum Dis.* 1992;51(10):1111-1116. [\[CrossRef\]](#)
23. Musacchio E, Ramonda R, Perissinotto E, et al. The impact of knee and hip chondrocalcinosis on disability in older people: the ProVA Study from northeastern Italy. *Ann Rheum Dis.* 2011;70(11):1937-1943. [\[CrossRef\]](#)
24. Pandit H, Spiegelberg B, Clave A, McGrath C, Liddle AD, Murray DW. Aetiology of lateral progression of arthritis following Oxford medial unicompartmental knee replacement: a case-control study. *Musculoskelet Surg.* 2016;100(2):97-102. [\[CrossRef\]](#)
25. Robier C, Neubauer M, Fritz K, Lippitz P, Stettin M, Rainer F. The detection of calcium pyrophosphate crystals in sequential synovial fluid examinations of patients with osteoarthritis: once positive, always positive. *Clin Rheumatol.* 2013;32(5):671-672. [\[CrossRef\]](#)
26. Sanmarti R, Kanterewicz E, Pladevall M, Panella D, Tarradellas JB, Gomez JM. Analysis of the association between chondrocalcinosis and osteoarthritis: a community based study. *Ann Rheum Dis.* 1996;55(1):30-33. [\[CrossRef\]](#)
27. Wilkins E, Dieppe P, Maddison P, Evison G. Osteoarthritis and articular chondrocalcinosis in the elderly. *Ann Rheum Dis.* 1983;42(3):280-284. [\[CrossRef\]](#)
28. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis.* 1957;16(4):494-502. [\[CrossRef\]](#)
29. Altman RD. Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl.* 1991;27:10-12. [\[CrossRef\]](#)
30. Latourte A, Rat AC, Nguenon Sime W, et al. Chondrocalcinosis of the Knee and the Risk of Osteoarthritis Progression: Data From the Knee and Hip Osteoarthritis Long-term Assessment Cohort. *Arthritis Rheumatol.* 2020;72(5):726-732. [\[CrossRef\]](#)
31. Neogi T, Nevitt M, Niu J, et al. Lack of association between chondrocalcinosis and increased risk of cartilage loss in knees with osteoarthritis: results of two prospective longitudinal magnetic resonance imaging studies. *Arthritis Rheum.* 2006;54(6):1822-1828. [\[Cross-Ref\]](#)
32. Checa A, Chun W. Rates of meniscal tearing in patients with chondrocalcinosis. *Clin Rheumatol.* 2015;34(3):573-577. [\[CrossRef\]](#)
33. Sun Y, Mauerhan DR, Honeycutt PR, et al. Calcium deposition in osteoarthritic meniscus and meniscal cell culture. *Arthritis Res Ther.* 2010;12(2):R56. [\[CrossRef\]](#)
34. Walsh DA, Bonnet CS, Turner EL, Wilson D, Situ M, McWilliams DF. Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthritis Cartilage.* 2007;15(7):743-751. [\[CrossRef\]](#)
35. Hawellek T, Hubert J, Hischke S, et al. Calcification of the acetabular labrum of the hip: prevalence in the general population and relation to hip articular cartilage and fibrocartilage degeneration. *Arthritis Res Ther.* 2018;20(1):104. [\[CrossRef\]](#)
36. Hawellek T, Hubert J, Hischke S, et al. Articular cartilage calcification of the hip and knee is highly prevalent, independent of age but associated with histological osteoarthritis: evidence for a systemic disorder. *Osteoarthritis Cartilage.* 2016;24(12):2092-2099. [\[Cross-Ref\]](#)
37. Caspi D, Flusser G, Farber I, et al. Clinical, radiologic, demographic, and occupational aspects of hand osteoarthritis in the elderly. *Semin Arthritis Rheum.* 2001;30(5):321-331. [\[Cross-Ref\]](#)
38. Stucki G, Hardegger D, Bohni U, Michel BA. Degeneration of the scaphoid-trapezium joint: a useful finding to differentiate calcium pyrophosphate deposition disease from osteoarthritis. *Clin Rheumatol.* 1999;18(3):232-237. [\[CrossRef\]](#)
39. Muehleman C, Li J, Aigner T, et al. Association between crystals and cartilage degeneration in the ankle. *J Rheumatol.* 2008;35(6):1108-1117.
40. Hubert J, Weiser L, Hischke S, et al. Cartilage calcification of the ankle joint is associated with osteoarthritis in the general population. *BMC Musculoskelet Disord.* 2018;19(1):169. [\[CrossRef\]](#)
41. Aran S, Malekzadeh S, Seifrad S. A double-blind randomized controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. *Clin Exp Rheumatol.* 2011;29(3):513-518.
42. Leung YY, Haaland B, Huebner JL, et al. Colchicine lack of effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA): a randomized controlled trial. *Osteoarthritis Cartilage.* 2018;26(5):631-640. [\[CrossRef\]](#)
43. Hunter DJ, Felson DT. Osteoarthritis. *BMJ.* 2006;332(7542):639-642. [\[CrossRef\]](#)
44. Morgan MP, McCarthy GM. Signaling mechanisms involved in crystal-induced tissue damage. *Curr Opin Rheumatol.* 2002;14(3):292-297. [\[CrossRef\]](#)
45. Abhishek A, Doherty M. Update on calcium pyrophosphate deposition. *Clin Exp Rheumatol.* 2016;34(4 Suppl 98):32-38.