Does Chondrocalcinosis Associate With a Distinct Radiographic Phenotype of Osteoarthritis in Knees and Hips? A Case–Control Study

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Objective. To examine if knee chondrocalcinosis (CC), hip CC, or CC at distant joints associates with a distinct radiographic phenotype of osteoarthritis (OA) in knees or hips.

Methods. We conducted a case–control study using data from the Genetics of Osteoarthritis and Lifestyle (GOAL) study (n = 3,170). All participants of the GOAL study had radiographs of knees, hands, and pelvis, which have been scored for CC and for individual radiographic features of OA. For this study, cases had radiographic OA and CC, and controls had radiographic OA without CC at the index joint. Data for knees and hips were analyzed separately. Binary logistic regression was used to examine the association between each radiographic phenotype and CC in joints with OA. Generalized estimating equation analysis was used to account for correlated data.

Results. Knee CC, and CC at any distant joint (without knee CC), associated with attrition in knee OA (adjusted odds ratio 2.32 [95% confidence interval 1.42–3.79] and 2.42 [1.41–4.13], respectively). There was no association between knee CC and osteophytosis or joint space narrowing (JSN) in knees with OA. Hip CC associated negatively with the summated osteophyte score and minimum JSN in hip OA. However, in hips with OA, CC did not associate with cysts or sclerosis. Additionally, distant joint CC did not associate with any structural change in hip OA.

Conclusion. This study demonstrates that knee CC and CC at distant joints associate with attrition in knee OA, and hip CC associates with a milder hip OA phenotype. There was no evidence that CC associates with a hypertrophic OA phenotype.

INTRODUCTION

Osteoarthritis (OA) associates with chondrocalcinosis (CC), which predominantly results from calcium pyrophosphate crystal deposition (CPPD), although basic calcium phosphate (BCP) crystals may coexist (1–3). The association between OA and CC has been confirmed in several independent populations (1,4,5), and CC also modifies the distribution of joints affected by OA (6,7). The association between OA and CC has been confirmed in several independent populations (1,4,5), and CC also modifies the distribution of joints affected by OA (6,7). However, it is not known if the structural changes in joints with OA and CC are different from those in joints with OA alone. Some studies suggest that joints with OA and CC have florid osteophytosis, while others report that they have minimal osteophytosis despite severe joint space narrowing (JSN), subchondral sclerosis, and attrition (5,8–13). Conversely, other studies suggest that OA with CPPD has the same radiographic phenotype as OA alone (6,14). However, with the exception of one study from Nottingham, UK, other studies are relatively small and have not examined the joint-specific radiographic phenotype associated with CPPD (5). A systematic review carried out by a European League Against Rheumatism task force also did not identify a specific phenotype of structural arthropathy associated with CPPD and recommended further research in this field (15).

Therefore, the overall aim of this study was to establish whether CC associates with a distinct radiographic phenotype of structural changes in knees and hips with OA. The specific objectives of this study were to examine whether 1) knee CC associates with a distinct set of structural changes in knees with OA, 2) hip CC associates with a distinct set of structural changes in hips with OA, and 3) in the presence of an association between CC at an index joint and structural radiographic change at that joint, if distant joint CC also associates with the same structural change when index joints with CC are excluded.
MATERIALS AND METHODS

Study design and participants. We conducted a case–control study using data from the Genetics of Osteoarthritis and Lifestyle (GOAL) study. GOAL is a case–control study of white adults, ages 45–80 years, involving 1,042 knee OA cases, 1,007 hip OA cases, and 1,121 asymptomatic controls without radiographic knee or hip OA (16). It was approved by the Nottinghamshire Research Ethics Committee, UK, and details of this study have been published previously (16). In brief, participants completed an extensive questionnaire; had a musculoskeletal examination, functional assessments, and anthropometric measurements; and gave blood and urine samples. They had posteroanterior, weight-bearing semi-flexed knee radiographs taken using the SynaFlexer positioning frame (Synarc), skyline views of patellofemoral joints, supine pelvis radiographs for hips and symphysis pubis, and anteroposterior hand views (including wrists), as well as dual x-ray absorptiometry (DXA) scans of the calcaneum (Apollo) performed.

Radiographs were scored for global OA severity (17), structural changes of OA (17–19), metacarpal index (MCI) (20), and for CC at knees, hips, symphysis pubis, wrists, and metacarpophalangeal (MCP) joints by a trained senior research metrologist (SD). CC was defined as linear or spotty calcification arranged in a linear fashion in fibro- or hyaline articular cartilage of the knees, hips, wrist, and symphysis pubis, or as cloudy synovial opacity at the MCP joints (21). As BCP crystals cause nummular calcification, it is likely that CC as defined in this study is unlikely to be due to BCP crystal deposition alone. Only joints with definite JSN and osteophytosis, defined as Kellgren/Lawrence (K/L) grade $3$ at the knee and $2a$ at the hip, were included in this study.

Case and control definition. In order to examine whether CC at an index joint associates with a structural change at that joint, cases were knees (or hips) with OA $\&$ CC, while controls were knees (or hips) with OA without radiographic CC. Each knee (or hip) was treated separately, and some patients contributed data from both knees or both hips. Similarly, in order to examine whether CC at a distant joint is associated with a structural radiographic change, cases had index joint OA and distant joint CC, and controls had index joint OA without CC at distant joints. Cases with CC at the index joint were excluded from this analysis to minimize confounding by local effects. Generalized estimating equation analysis was used to take any correlation between data from both knees or both hips from an individual into account.

Scoring of structural changes of OA. Knee. Osteophytes at 8 sites in the knee (medial and lateral: tibial, femoral, patellar, and trochlear) were scored (0–5) according to their size (18). JSN was graded for medial and lateral tibiofemoral and patellofemoral compartments using an ordinal line diagram atlas with negative scores indicating joint space widening ($-1$ to 5) (19). Knee radiographs were also scored for attrition (present, absent), which was defined as loss of bone stock with collapse of subchondral bone in addition to JSN in the affected compartment(s).

### Significance & Innovations
- Radiographic osteoarthritis (OA) phenotype should not be used to speculate whether calcium pyrophosphate crystal deposition is present or not.
- There is no evidence for a unifying radiographic phenotype of structural arthropathy in joints with OA plus chondrocalcinosis (CC).
- A previously demonstrated association between osteophytosis and CC was not confirmed in this study.

### Table 1. Association between radiographic phenotype score in knees with OA and knee CC*

| CC present (n = 255) | CC absent (n = 2,403) | OR (95%CI) | ORadj (95%CI)† |
|---------------------|----------------------|------------|---------------|
| **Osteophyte score‡** |                     |            |               |
| $\leq$9             | 71                   | 666        | 1             | 1             |
| 10–16               | 62                   | 607        | 1.08 (0.73–1.59) | 1.00 (0.67–1.50) |
| 17–38               | 71                   | 616        | 0.98 (0.66–1.45) | 0.87 (0.58–1.31) |
| **JSN score‡**      |                     |            |               |
| $\leq$4             | 73                   | 725        | 1             | 1             |
| 5                   | 68                   | 546        | 0.81 (0.56–1.15) | 0.77 (0.54–1.11) |
| 6–20                | 63                   | 619        | 1.01 (0.68–1.50) | 0.95 (0.65–1.40) |
| **Attrition**       |                     |            |               |
| Absent              | 228                  | 2,287      | 1             | 1             |
| Present             | 27                   | 115        | 2.39 (1.45–3.93) | 2.32 (1.42–3.79) |

* Values are the number unless indicated otherwise. OA = osteoarthritis; CC = chondrocalcinosis; OR = odds ratio; 95% CI = 95% confidence interval; JSN = joint space narrowing; ORadj = adjusted OR.
† Adjusted for age, sex, body mass index, metacarpal index, and calcaneal dual x-ray absorptiometry.
‡ Summated osteophyte and JSN scores were calculated for 2,093 knees, as skyline views of the patellofemoral joint were not available for the remaining knees.
Hip. Osteophytes at the femoral neck, femoral head, and acetabulum were scored (0–3) on an ordinal scale (17). Minimum joint space width was measured in millimeters correct to 2 decimal places on digitized images. Sclerosis and cysts were scored as present or absent. Summation of radiographic scores. Scores allocated to each radiographic structural change at different sites within a joint were summated to yield a global radiographic score for that joint. Osteophyte scores were added to yield a global score with range 0–40 for each knee and 0–9 for each hip. For calculating the global JSN score at the knee, negative scores were transformed to 0, and JSN for each of the 4 compartments was summated (range 0–20). Minimum joint space width at the hip was converted to tertiles.

Other covariates and inter- and intrarater agreement. Information about other covariates, age (years), sex, weight (kg), and height (cm) was collected at the study visit. Weight and height were used to calculate the body mass index (BMI) (kg/m²).

Twenty knee, hand with wrist, and pelvis radiographs of GOAL participants were randomly selected (approximately 25–35% with CC) and rescored for CC by the senior research metrologist (SD) and a rheumatologist (AA) for determining the inter- and intrarater agreement overall and at each joint. The observers were blinded to each other and to the previous readings.

Statistical analysis. Mean and SD and number (percentage) were used for descriptive purpose as the data was normally distributed. Independent sample t-tests and chi-square tests were used to compare continuous and categorical variables, respectively. Kappa statistic was used to calculate the inter- and intraobserver agreement. Summated radiographic phenotype scores and hip minimum joint space width were converted to tertiles. Other features such as attrition, sclerosis, and cysts were present or absent. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to examine the association between each structural radiographic change and CC in joints with OA. Risks were computed for increasing severity of radiographic phenotype, e.g., greater osteophyte score, and for presence of structural radiographic change, e.g., cysts. The association between CC and radiographic phenotype score was adjusted for age (tertiles), sex (female 0, male 1), BMI (tertiles), MCI (tertiles), and calcaneal DXA Z score measurements using binary logistic regression. Generalized estimating equation analysis was used to account for any correlation between data from both knees (or both hips) from an individual. MCI and calcaneal

### Table 2. Association between attrition in knees with OA and distant joint CC*

| Distant joint CC (with no radiographic knee CC) | Present (n = 288) | Absent (n = 2,112) | OR (95%CI) | ORadj (95%CI)† |
|-----------------------------------------------|------------------|-------------------|------------|----------------|
| Attrition present                             |                  |                   |            |                |
| Absent                                        | 261              | 2,024             | 1.00       | 1.00           |
| Present                                       | 27               | 88                | 2.38 (1.39–4.07) | 2.42 (1.41–4.13) |

* OA = osteoarthritis; CC = chondrocalcinosis; OR = odds ratio; 95% CI = 95% confidence interval; ORadj = adjusted OR.
† Adjusted for age, sex, body mass index, metacarpal index, and calcaneal dual x-ray absorptiometry.
DXA were included in the model, as we have previously demonstrated an association between CC and low MCI (22), and bone mineral density has been associated with OA. Statistical significance was set at $P$ less than 0.05 (2-sided analysis). All analyses were carried out using SPSS, version 21.

RESULTS

There were 3,170 participants in the GOAL study. Their detailed demographic profile has been published previously (16). Briefly, their mean $\pm$ SD age was 67 $\pm$ 7.9 years, and there were 1,536 women (48.4%). The mean $\pm$ SD MCI and calcaneal bone mineral density scores were 0.47 $\pm$ 0.10 and 0.64 $\pm$ 0.11 gm/cm$^2$, respectively. CC was present in 428 participants (13.7%). Data on the distribution of CC and the association between CC and OA have been published previously (21,23). There was excellent intra- and interrater agreement for CC at the knees, hips, and wrists with $\kappa = 1$, 1, 0.90, and 1, 0.94, and 0.94, respectively.

### Knee OA

A total of 2,658 knees with K/L grade $\geq$3 OA (from 1,606 participants, mean $\pm$ SD age 68.64 $\pm$ 7.06 years, BMI 30.70 $\pm$ 5.40 kg/m$^2$, and 782 female [48.7%]) were included in this study. Of these, 255 (9.6%) had knee CC, and 289 (10.9%) had CC at a distant joint without knee CC. Their mean $\pm$ SD summated osteophyte and JSN score was 13.33 $\pm$ 7.61 and 5.24 $\pm$ 2.25, respectively. Attrition was present in 142 knees (5.5%). There was no association between CC and increasing tertiles of summated osteophyte score and summated JSN score (Table 1 and Figure 1). Attrition at the knee associated with knee CC and with CC at distant joints, and this association was independent of age, sex, BMI, MCI, and calcaneal DXA ($OR_{adj}$ 2.32 [95% CI 1.42–3.79] and $OR_{adj}$ 2.42 [95% CI 1.41–4.13], respectively) (Tables 1 and 2, and Figure 1).

### Table 3: Association between radiographic phenotype score in hips with OA and hip CC*

|                        | CC present (n = 58) | CC absent (n = 1,667) | OR (95%CI) | OR adj (95%CI)† |
|------------------------|---------------------|-----------------------|------------|-----------------|
| **Osteophyte score**   |                     |                       |            |                 |
| $<3$                   | 28                  | 435                   | 1          | 1               |
| 4–6                    | 22                  | 804                   | 0.43 (0.23–0.77) | 0.45 (0.25–0.82) |
| 7–9                    | 8                   | 424                   | 0.29 (0.12–0.70) | 0.30 (0.12–0.71) |
| Minimum JSW, mm        |                     |                       |            |                 |
| 2.40–4.55              | 22                  | 325                   | 1          | 1               |
| 0.50–2.39              | 8                   | 342                   | 0.35 (0.15–0.80) | 0.34 (0.14–0.76) |
| $<0.50$                | 8                   | 996                   | 0.42 (0.23–0.75) | 0.42 (0.23–0.78) |
| Subchondral cyst       |                     |                       |            |                 |
| Absent                 | 32                  | 819                   | 1          | 1               |
| Present                | 26                  | 846                   | 0.79 (0.47–1.31) | 0.80 (0.49–1.32) |
| Subchondral sclerosis  |                     |                       |            |                 |
| Absent                 | 13                  | 217                   | 1          | 1               |
| Present                | 45                  | 1,449                 | 0.52 (0.27–1.01) | 0.56 (0.28–1.12) |

*$OA = osteoarthritis; CC = chondrocalcinosis; OR = odds ratio; 95% CI = 95% confidence interval; OR adj = adjusted OR; JSW = joint space width.
† Adjusted for age, sex, body mass index, metacarpal index, and calcaneal dual x-ray absorptiometry.

### Table 4: Association between radiographic phenotype score in hips with OA and distant joint CC*

|                        | Present (n = 203) | Absent (n = 1,523) | OR (95%CI) | OR adj (95%CI)† |
|------------------------|-------------------|-------------------|------------|-----------------|
| **Osteophyte score**   |                    |                   |            |                 |
| $<3$                   | 62                | 370               | 1          | 1               |
| 4–6                    | 101               | 703               | 0.85 (0.60–1.19) | 0.91 (0.64–1.29) |
| 7–9                    | 39                | 385               | 0.62 (0.38–0.99) | 0.69 (0.43–1.11) |
| Minimum JSW, mm        |                    |                   |            |                 |
| 2.40–4.55              | 45                | 280               | 1          | 1               |
| 0.50–2.39              | 43                | 297               | 0.91 (0.58–1.44) | 0.87 (0.54–1.38) |
| $<0.50$                | 115               | 880               | 0.79 (0.54–1.16) | 0.80 (0.54–1.18) |

*$OA = osteoarthritis; CC = chondrocalcinosis; OR = odds ratio; 95% CI = 95% confidence interval; OR adj = adjusted OR; JSW = joint space width.
† Adjusted for age, sex, body mass index, metacarpal index, and calcaneal dual x-ray absorptiometry.
Hip OA. A total of 1,725 hips with K/L grade ≥2 OA (from 919 participants, mean ± SD age 67.82 ± 7.04 years, BMI 29.30 ± 5.09 kg/m², and 466 female [50.7%]) were included in this study. Of these, 58 (3.4%) had hip CC, and 203 (12.2%) had CC at a distant joint without hip CC. Their mean ± SD summated osteophyte score and minimum JSN score was 4.93 ± 2.62 and 0.94 ± 1.26 mm, respectively. Cysts and sclerosis were present in 872 (50.6%) and 1,495 (86.7%) hips respectively. In hips with OA, greater summated osteophyte score and more severe JSN associated negatively with hip CC, and this association was independent of age, sex, BMI, MCI, and calcaneal DXA (Table 3 and Figure 2). There was no association between hip CC and cysts. None of the structural radiographic changes of hip OA that associated with hip CC associated with distant joint CC (Table 4).

DISCUSSION

This study examined the phenotype of structural changes associated with CC in joints with OA. It shows that both radiographic knee CC and CC at distant joints (in the absence of any knee CC) associate with attrition in knee OA. It also reports that hip CC associates with a milder, atrophic hip OA phenotype with less severe JSN and milder osteoarthrosis. It did not find any evidence to suggest that CC associates with a hypertrophic bone-forming phenotype. Therefore, the findings of this study suggest that the presence of florid osteoarthrosis should not be used to speculate on whether CPPD, the commonest cause of CC, could be present or not.

The association between knee CC and attrition in knees with OA is supported by previous reports of association between calcium pyrophosphate (CPP) crystals, high synovial fluid pyrophosphate (PPI; a precursor for CPP crystals), and attrition in knees with OA (24,25). Similarly, in a prospective study, synovial fluid CPP crystals associated with incident attrition in knees with OA (OR adj 2.41 [95% CI 1.33–4.39]) (26). The findings of the present study also concur with the earlier, anecdotal observation of destructive arthropathy characterized by loss of bone stock in those with radiographic articular CC (27).

The association between distant joint CC and attrition in knees with OA is a novel finding and has not been reported before. This may be related to the fact that high PPI level, the metabolic abnormality that predisposes to CPPD (the main constituent of CC), also inhibits hydroxyapatite crystal nucleation and growth (28–30), thereby resulting in less osteoarthrosis and failure to repair the damaged bone stock resulting in attrition. The finding of a negative association between hip CC and summated osteophyte scores in hips with OA is also consistent with this hypothesis. However, the lack of association between CC and summated osteophyte score in knees with OA is not in keeping with this explanation, and other joint-specific factors predisposing to osteoarthrosis may also operate. The association between CC at distant joints and attrition in knees with OA suggests that CC may be a marker of a predisposition to a more destructive arthropathy. It is in keeping with the findings of a previous study in which CC at distant joints associated with rapidly progressive hip OA (31) and raises the possibility that some cases with CC + OA may form a distinct subset of OA.

The lack of association between osteoarthrosis and knee CC reported in this study is in keeping with some previous reports (14,25), while the lack of association between JSN and CC in knees with OA is in keeping with most previous studies (5,14,24,25,32). Taken together, these findings suggest that radiographic knee CC does not associate either with JSN or with osteoarthrosis at the knee. On the contrary, this study reports that hip CC associates negatively with JSN in hips with OA. This is in keeping with the findings of a hospital-based case–control study (33) and suggests that hip CC identifies hips with a milder OA phenotype. It is possible that the earlier anecdotal observation of association between CC and florid osteoarthrosis, severe JSN, and multiple subchondral cysts were due to a combination of reporting bias and health care–seeking bias.

This study has several strengths. First, it used a large data set to examine the radiographic phenotype associated with CC in knees and hips with OA. It is the largest study to examine the association between CC at any distant joint and OA phenotype at an index joint. Moreover, radiographs of knees, pelvis, and hands with wrists were performed and were able to identify all instances of plain radiographic CC, providing validity to the analysis of association between distant joint CC and index joint OA (34). However, there are several caveats to this study. Firstly, this is a hospital-based study carried out by reconstituting cases and controls within a cohort assembled to examine risk factors for knee or hip OA. The study population does not resemble a community-based population and was selected for severe symptomatic large-joint OA. This limits the generalizability of these findings. It is possible that the negative association between osteoarthrosis and JSN at the hip and hip CC reported in this study is due to the fact that radiographic articular CC is difficult to visualize in hips with severe cartilage loss and osteoarthrosis. However, this is unlikely to be the case as the results were consistent across all tertiles of the radiographic phenotype score in hip OA (Table 3). Similarly, it is possible that some knees with attrition and CC at distant joints also have knee CC, which was not visualized on plain radiographs due to cartilage loss.

In conclusion, this study does not demonstrate a unifying radiographic phenotype associated with CC in large joint OA. It shows that CC associates with attrition in knees with OA, and that hip CC associates with a milder atrophic radiographic phenotype of hip OA. As this study was carried out in patients with end-stage OA, it is desirable for these findings to be confirmed in a community-based study using ultrasound examination or synovial fluid analysis, both of which have a greater sensitivity for detecting CPPD.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Abhishek had full access to all of the data in the study and takes

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responsibility for the integrity of the data and the accuracy of the data analysis.

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**ROLE OF THE STUDY SPONSOR**

AstraZeneca had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AstraZeneca.

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