EXTENDED REPORT

UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte

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Objectives: (1) To estimate the prevalence of chondrocalcinosis (CC) in the community and to characterise its compartmental distribution within the knee. (2) To investigate the associations between CC and individual radiographic features of osteoarthritis (OA) at the tibiofemoral joint (TFJ) and patellofemoral joint (PFJ).

Methods: From three community questionnaire studies investigating the prevalence of knee pain, standing anteroposterior and skyline radiographs were obtained on 1727 subjects (1084 women, 643 men; mean age 63.7; 999 (58%) with knee pain). A single observer recorded the presence and site of CC and graded osteophyte and joint space narrowing (JSN) using a line atlas. "OA" was globally defined as the presence of definite osteophyte and definite JSN. Minimum joint space width (JSW) was measured to 0.1 mm with a metred dial caliper

Results: (1) The crude prevalence of CC was 7.0% (95% confidence interval (CI) 5.8 to 8.2). This showed a strong association with age. The age adjusted odds ratio (aOR) for CC in women *v* men was 0.79 (95% CI 0.52 to 1.12). The age, sex, and knee pain standardised estimate for those aged >40 in Nottingham, UK was 4.5%. Patellofemoral CC was seen in only nine cases, all with tibiofemoral CC. (2) The age-sex aOR for the association between CC and OA was 2.08 at the PFJ (1.38 to 3.12) and 2.00 (1.11 to 3.60) at the TFJ. There was no association between measured JSW and CC at either the PFJ or TFJ. Both total osteophyte score and total number of sites with osteophyte were positively associated with CC; aOR for the upper quartile was 2.40 (1.48 to 3.90) and 1.94 (1.15 to 3.26), respectively. An association between CC and diuretic use was also demonstrated (aOR=2.07, 1.02 to 4.19).

Conclusions: In this large UK community study the age, sex, and knee pain adjusted prevalence of CC was 4.5%. There was a strong age association, but no sex predisposition. Patellofemoral CC was uncommon. An association between OA and CC was confirmed, but this appears to operate through an association with osteophyte rather than JSN. The new association between CC and diuretic use might theoretically be explained by diuretic induced hypomagnesaemia.

Chondrocalcinosis (CC), or calcification within cartilage, is usually due to deposition of calcium pyrophosphate dihydrate (CPPD) crystals. It may be sporadic, familial,[1 2] or secondary to a variety of metabolic abnormalities.[3] The sites most commonly affected are the knee, wrist, and symphysis pubis. CC is readily visualised on plain radiographs, though sensitivity varies according to film and radiographic technique.[4]

Sporadic CC is seen most commonly and is age related.[5] It has been observed in hospital based series, often in association with joint symptoms and radiographic changes of osteoarthritis (OA)—"pyrophosphate arthropathy".[6] However, studies of patients referred to hospital are prone to many biases and often exclude asymptomatic cases. Some of these biases may be overcome by sampling the general population. However, there have been few community based studies of CC. An early, American institution based survey of patients aged 59 or over found a prevalence of 7% in knee radiographs.[7] The Framingham survey, using a random sample of 1425 subjects over the age of 63, found a prevalence of 8.1% in knee radiographs.[8] A Spanish primary care based study of subjects aged 60 or over found a prevalence of 10% in radiographs of both knees and wrists.[9]

Radiographic CC and OA often coexist and CPPD crystals are often found in patients with OA.[10 11] Hospital series have suggested an association between CC and OA.[5 12] Age may be a confounding factor in some studies, though two community studies have confirmed that this association persists after adjustment for age.[8 13] The nature of the relationship between CC and OA and the mechanisms involved remain unclear, although alterations in both pyrophosphate levels and cartilage matrix factors that may influence CPPD crystal deposition have been proposed.[14]

The knee is a key target site for both CC and OA. Previous community studies of CC and OA may be considered incomplete because they have omitted the patellofemoral joint (PFJ). Furthermore, all clinical studies examining this relationship have used the global (Kellgren and Lawrence) grading system for OA that may obscure the individual factors that underpin this association. This study aimed at (*a*) determining the prevalence of CC at the knee and its compartmental distribution; (*b*) examining the associations between CC and individual radiographic features of OA; and (*c*) investigating possible associations of CC with obesity (through a biomechanical stimulus), diuretic use (through effects on pyrophosphate metabolism), and extra-articular calcification (suggestive of a generalised tendency to calcification).

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CC, chondrocalcinosis; CI, confidence interval; CPPD, calcium pyrophosphate dihydrate; JSN, joint space narrowing; JSW, joint space width; OA, osteoarthritis; PFJ, patellofemoral joint; TFJ, tibiofemoral joint

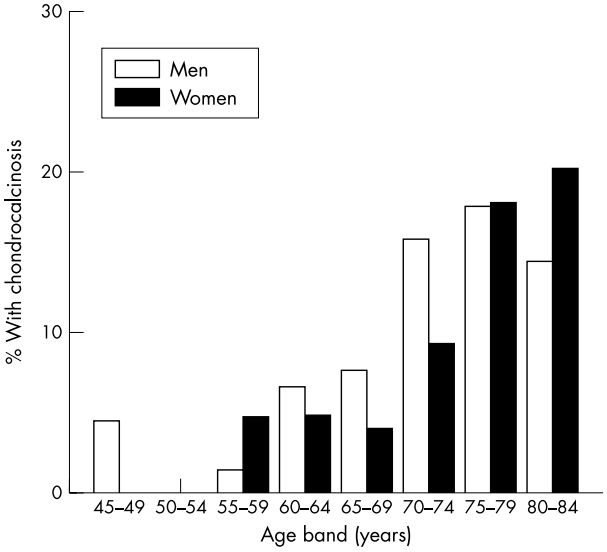

Figure 1 Prevalence of chondrocalcinosis by age and sex.

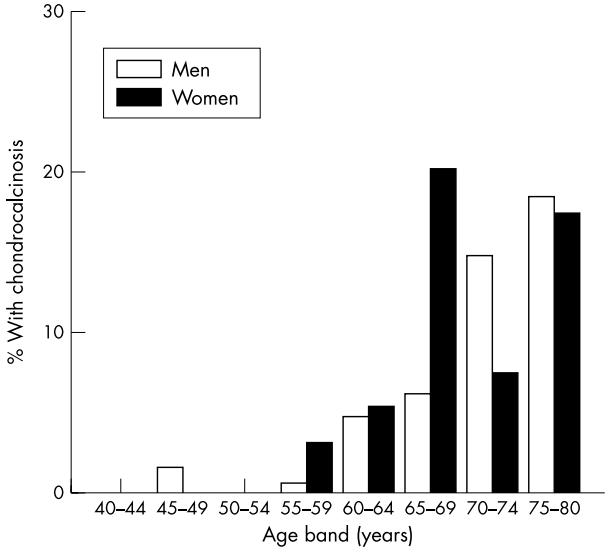

Figure 2 Pain adjusted prevalence of chondrocalcinosis by age and sex.

PATIENTS AND METHODS

Approval for the study was obtained from the local research ethics committee.

Patients

Data and radiographs from the participants in three previous Nottingham community based studies performed at our centre were used. These were concerned with the associations of knee pain in the general population. All three used postal questionnaires to survey random samples over the age of 40 from general practice lists in different areas of Nottingham. Exclusion criteria included total knee replacement, terminal illness, and inability to give informed consent. Subjects were then selected for further study on the basis of presence or absence of knee pain (defined as ever having knee pain on most days for at least a month, and having pain within the past year). Variables collected for all participants were age, sex, and body mass index (BMI). Nodal status, or presence of Heberden's or Bouchard's nodes (assessed by trained metrologists) was available for 697 subjects, and history of diuretic drug use was available for 551 subjects.

Radiographs

All radiographs were taken under the same standardised conditions using standard Fuji film, and were weightbearing, fully extended anteroposterior views (55 kV, 8 mA/s, full scale deflection 100 cm), and skyline 30° flexion views (60 kV, 10 mA/s, full scale deflection 100 cm) after the method of Laurin *et al*.[15]

Radiographic assessment

After a training period a single observer (RLN) who was unaware of the patient details read all the radiographs. Throughout the assessment period consensus about equivocal radiographs was reached by discussion with an experienced OA researcher (MD). To reduce bias, all films were randomly ordered. Films were read first for OA. Grades were concealed, and then on a separate occasion four months later films were read for CC. Halfway through reading the radiographs for OA, an independent researcher selected 40 sets of films representing a wide range of OA changes, which were then re-read (RLN) three weeks after the first assessment. Reproducibility for reading CC was assessed in the same way using a second set of 40 radiographs.

Tibiofemoral joint (TFJ) views were assigned a global Kellgren and Lawrence grade for OA.[16] An adaptation of a previously validated line drawing atlas was used to score osteophyte (0–5) at eight sites (medial and lateral femur, medial and lateral tibia, medial and lateral patella, and medial and lateral femoral trochlea).[17] We also measured minimum joint space width (JSW) by hand to 0.1 mm using a metred dial caliper (RS Components, Switzerland). Joint space narrowing (JSN) was assessed for each compartment (medial TFJ, lateral TFJ, medial PFJ, and lateral PFJ). CC was recorded as present or absent, and site of CC (TFJ or PFJ, medial or lateral, hyaline or fibrocartilage or capsular) was documented. Extra-articular vascular calcification was recorded as present or absent.

Statistical analysis

Reproducibility for CC and for the atlas scores was analysed by the κ statistic[18] using STATA for windows.[19] Reproducibility for JSW measurements was analysed using the method of Bland and Altman.[20]

The age and sex standardised prevalence estimate for Nottingham was calculated by direct standardisation using data from the 1991 census.[21] The age, sex, and knee pain adjusted prevalence estimate was calculated by direct standardisation using survey data.[22]

Subjects were categorised according to the presence or absence of CC, and associations were investigated by person rather than by knee. The relationships with each putative risk factor (age, sex, global OA, osteophyte, joint space narrowing, BMI, nodal status and diuretic use) were investigated using univariate techniques. Logistic regression was used to compute age-sex adjusted odds ratios (aORs) using SPSS.[23]

To explore the relationship between JSW and CC in each subject the minimum joint space measurements at the medial TFJs were summed, as were measurements for the lateral PFJs because narrowing was most common at these locations. These data were categorised into quartiles. The association between osteophyte and CC was investigated in two ways. Firstly, osteophyte scores were summated and, secondly, the number of sites with osteophyte was summated. These totals were obtained across all compartments and also for the TFJ and PFJ separately. Most radiographs did not have osteophytes, and so quartiles for both osteophyte score and for number of sites with osteophyte was obtained after these subjects had been selected. For analysis these subjects were categorised into the first quartiles.

Table 1 Associations of chondrocalcinosis with radiographic features of osteoarthritis

	Joint site											
	Any (tibiofemoral or patellofemoral)				Tibiofemoral				Patellofemoral			
Risk factors	Crude OR (95% CI)	Adjusted OR (95% CI)*	Overall p value	p Value for trend	Crude OR (95% CI)	Adjusted OR (95% CI)*	Overall p value	p Value for trend	Crude OR (95% CI)	Adjusted OR (95% CI)*	Overall p value	p Value for trend
Radiographic OA (global definition)	3.37 (2.29 to 4.96)	2.45 (1.65 to 3.65)			2.83 (1.60 to 5.01)	2.00 (1.11 to 3.60)			2.41 (1.62 to 3.58)	2.08 (1.38 to 3.12)		
Summated osteophyte score			0.002	0.003			0.06	0.014			0.03	0.007
1st Quartile	1.0	1.0			1.0	1.0			1.0	1.0		
2nd Quartile	2.07 (1.19 to 3.59)	1.72 (0.99 to 3.04)			1.65 (0.85 to 3.18)	1.43 (0.73 to 2.81)			1.35 (0.70 to 2.62)	1.19 (0.61 to 2.34)		
3rd Quartile	1.34 (0.69 to 2.60)	0.93 (0.47 to 1.84)			1.74 (0.90 to 3.37)	1.20 (0.61 to 2.37)			1.72 (0.93 to 3.20)	1.20 (0.64 to 2.27)		
4th Quartile	3.42 (2.14 to 5.47)	2.40 (1.48 to 3.90)			3.15 (1.81 to 5.48)	2.14 (1.21 to 3.79)			3.09 (1.90 to 5.05)	2.14 (1.29 to 3.55)		
Summated number of joint sites with osteophyte			0.02	0.02			0.27	0.05			0.06	0.008
1st Quartile	1.0	1.0			1.0	1.0			1.0	1.0		
2nd Quartile	2.54 (1.46 to 4.42)	2.05 (1.16 to 3.63)			1.85 (0.90 to 3.82)	1.40 (0.67 to 2.94)			1.23 (0.52 to 2.91)	0.99 (0.41 to 2.39)		
3rd Quartile	1.60 (0.88 to 2.93)	1.16 (0.63 to 2.15)			1.84 (0.92 to 3.68)	1.40 (0.69 to 2.84)			2.21 (1.28 to 3.81)	1.63 (0.93 to 2.85)		
4th Quartile	2.79 (1.68 to 4.63)	1.94 (1.15 to 3.26)			2.43 (1.35 to 4.36)	1.70 (0.93 to 3.10)			2.76 (1.63 to 4.67)	1.93 (1.12 to 3.33)		
Joint space width							0.39	0.12			0.08	0.49
1st Quartile					1.0	1.0			1.0	1.0		
2nd Quartile					0.91 (0.53 to 1.57)	1.02 (0.58 to 0.79)			0.47 (0.27 to 0.82)	0.57 (0.32 to 1.01)		
3rd Quartile					1.01 (0.59 to 1.74)	1.14 (0.65 to 1.98)			0.88 (0.55 to 1.42)	1.09 (0.67 to 1.80)		
4th Quartile					1.46 (0.88 to 2.43)	1.51 (0.89 to 2.57)			0.58 (0.35 to 0.99)	0.68 (0.39 to 1.21)		

OR, odds ratio; 95% CI, 95% confidence interval.
*Odds ratio adjusted for age and sex.

RESULTS

Response rate

The overall response rate to 13 349 mailed questionnaires was 69%. The age and sex of the non-responders did not differ significantly from those of the responders. The acceptance rate for eligible subjects with knee pain asked to undergo a knee *x* ray examination was 92%. The acceptance rate for pain-free subjects was 77%.

Demographic characteristics

Analyses were performed for 1727 of the 1729 subjects who had undergone radiography (radiographs for two subjects were missing). There were 1084 women and 643 men, with a mean age of 63.7 (range 40–86); 999 subjects reported knee pain.

Reproducibility

Intraobserver reproducibility for Kellgren and Lawrence grade was good (κ=0.74 for right knee, κ=0.84 for left knee). Good agreement was also seen using the line atlas. The κ value for JSN scores ranged from 0.69 (left medial PFJ) to 0.85 (left medial TFJ).The κ value for osteophyte scores ranged from 0.70 (right lateral femur) to 0.90 (left medial trochlea). Reproducibility for minimum joint space measurement (standard deviation of differences) ranged from ±0.31 mm (left medial TFJ) to ±0.51 mm (left lateral PFJ). Reproducibility for the presence of CC was very good (κ=0.9).

Prevalence estimates for CC

CC was present in 119 subjects, a crude prevalence of 7.0% (95% confidence interval (CI) 5.8 to 8.2). There was a strong association with age, the prevalence increasing from 3.7% in those aged 55–59 to 17.5% in those aged 80–84 (fig 1).

Prevalence in women was 6.1% *v* 8.2% in men. The age aOR for CC in women *v* men was 0.79 (95% CI 0.52 to 1.12). The age-sex standardised estimate for those aged >40 in Nottingham, UK was 5.6%. There was an association between knee pain and the presence of CC; 68.9% of those with CC had pain, and 57.0% of those without CC had pain (χ^2_{1df}=6.41, p=0.01). The age, sex, and knee pain standardised prevalence of CC was 4.5% (fig 2).

Cartilage distribution of CC

CC was bilateral in 86 (72%) cases. Extensive CC affecting both medial and lateral TFJ compartments of both knees occurred in 45 (38%) cases. The lateral compartment was affected in 107 knees, and the medial compartment in 98 knees. Fibrocartilage was mainly affected (113 (95%) cases). Hyaline cartilage CC was seen in 53 cases (45%) and only two of these (2% overall) were without CC of fibrocartilage. Synovial or capsular calcification was seen in 36 cases (30%). This always occurred with CC, which was extensive in 22 of these cases (61%). Patellofemoral CC was seen in only nine (8%) cases, all of whom also had tibiofemoral CC.

Prevalence estimates for OA

OA was seen in 466 subjects, a crude prevalence of 27.0% (95% CI 24.9 to 29.1). Prevalence was 15.6% at the TFJ and 19.3% at the PFJ. There was an association of OA with increasing age, prevalence rising from 24.7% in those aged 55–59, to 58.8% in those aged 80–84. At both the TFJ (Jonckheere-Terpstra test, n=1727, p<0.001) and the PFJ (Jonckheere-Terpstra test, n=1699, p<0.001) there was a negative association between JSW and degree of osteophytosis.

Association of CC with OA

The age-sex aORs for the associations of CC with global OA (table 1) confirm associations between CC and both tibiofemoral and patellofemoral OA.

There was no association between measured JSW and CC at the TFJ or PFJ (table 1). This was also seen when subjects with more severe narrowing (JSW <3 mm in either knee) were excluded from analysis. Both summated osteophyte score and total number of sites with osteophyte were positively associated with CC (table 1). The aORs for the upper quartiles of summated osteophyte score were similar for the TFJ and the PFJ, and a trend through the quartiles was present.

Other associations

The association of CC with knee pain (OR=1.67, 95% CI 1.12 to 2.49) was removed after adjusting for the presence of OA (aOR=1.3, 0.84 to 1.93). CC was not significantly associated with BMI; mean BMI in those with CC was 26.3 kg/m^2 *v* 26.8 kg/m^2 in those without CC, a difference of 0.5 kg/m^2, 95% CI –0.3 to 1.3 kg/m^2 (Student's t_{1721df}=1.20, p=0.23). There was no association with nodal status; 40.6% of those with CC had nodes and 35.1% of those without CC had nodes, (χ^2_{1df}=0.78, p=0.38). An association between CC and extra-articular vascular calcification (OR=2.27, 1.25 to 4.13) was removed after age adjustment (aOR=1.43, 0.77 to 2.64). There was an association between CC and diuretic use (ever) (OR=2.69, 1.38 to 5.27) that persisted after age-sex adjustment (aOR=2.07, 1.02 to 4.19). However, additional adjustment for diuretic use did not appreciably alter the aORs for the associations of CC with OA. The total duration of diuretic therapy in the small group of diuretic users did not differ between those with (n=14) and without CC (n=117), thus there was no dose effect (Mann-Whitney test, p=0.17). There was no association between CC and use of antihypertensive drugs other than diuretics; 4/24 (17%) subjects with CC had taken these drugs, and 88/527 (16.7%) subjects without CC had done so.

DISCUSSION

The crude prevalence of CC of 7.0% is similar to that found in previous studies. CC appears more common in our population because direct age-sex standardisation applying our estimates to the Framingham population sample[8] gives an expected prevalence of 10.4%. This may be because our sample had a high proportion of subjects with knee pain, and knee pain and CC were associated. The higher prevalence of CC in one Spanish study is to be expected as radiographs of the wrists as well as the knees were used, and the subjects were older.[9] As demonstrated previously,[5 8] we found a dramatic increase in prevalence with age. Interestingly, there was no difference in prevalence between men and women. This is contrary to previous studies, most of which have found CC to be more common in women. However, few have allowed for confounding by age and the higher prevalence of women in the elderly population. In the two population studies that did adjust for age the confidence intervals around the odds ratios for sex included unity.[8 9]

There was an association between CC and OA at both the PFJ and the TFJ. As in the Framingham Study,[8] presence of CC in those with OA was not associated with knee pain. This is perhaps not surprising as the determinants of pain in OA are complex, and include other factors not assessed in this study.[24]

Use of the line drawing atlas and JSW measurements enabled us to further define the association of CC with OA through separate analyses of the key individual features of OA—namely, osteophyte and JSN. We found an association only for osteophyte. Both the total osteophyte score and the total number of sites affected by osteophyte were positively associated with CC. These associations were seen at both the TFJ and the PFJ. As expected, and in keeping with concepts concerning the structural changes associated with OA, we observed a strong association between osteophyte and JSN, suggesting that our sample was not unusual or unrepresentative of knee OA in general. Furthermore, the lack of association remained after exclusion of subjects with severe

narrowing, suggesting that lack of cartilage available for calcification in severely narrowed knees does not account for this finding. It seems, therefore, that the strong association between CC and osteophyte alone largely accounts for the association seen between CC and OA. The Kellgren and Lawrence grading system may give undue weighting to osteophyte,[25] and this may explain the reported association between CC and OA in previous studies that defined OA by this means.[8 13]

An association between CC and a propensity to osteophyte formation has previously been suggested. Exuberant osteophyte is emphasised as one of the characteristic radiographic features that may accompany CPPD crystal deposition.[12] The presence of synovial fluid CPPD crystals is associated with higher radiographic scores for osteophyte[10]; increase in osteophyte and bone remodelling is the most common change in patients with knee OA and CC followed up prospectively[26]; and a negative association is reported between CPPD crystal deposition and rheumatoid ("atrophic") arthritis.[27 28] Such observations have prompted the hypothesis that CPPD deposition in the context of arthropathy may act as a marker for subjects with a "hypertrophic" and thus potentially reparative tissue response to joint injury.[29] That this may be a generalised skeletal response with predisposition to both osteophyte and enthesophyte formation is suggested by two small uncontrolled case series that report a higher than expected concordance of CC and vertebral hyperostosis.[30 31] The mechanisms that may link CPPD deposition and osteophyte formation remain speculative but may include shared chemical or mechanical predisposing factors, or both. For example, transforming growth factor β stimulates osteophyte formation,[32] and also enhances elaboration of extracellular pyrophosphate by hypertrophic chondrocytes, thus predisposing to pericellular CPPD crystal formation.[33] Similarly, excessive mechanical loading of joints may stimulate osteophyte formation, and also cause chondrocytes to release more ATP, a potent source of extracellular pyrophosphate.[34] Extracellular pyrophosphate is an important regulator of apatite mineralisation.[35–37] Thus, conceivably, an abnormality of pyrophosphate metabolism that causes modest increases in extracellular pyrophosphate may enhance calcification of new fibrocartilage (endochondral ossification—the mechanism of osteophyte formation) as well as predisposing to CPPD crystal deposition.

The age independent association between CC and diuretic use is also of special interest. The absence of an association with other antihypertensive drugs suggests a specific association with diuretics rather than an indirect association with comorbid disease. In theory this could be mediated through effects on magnesium. Loop diuretics and thiazides increase urinary magnesium loss and are a common cause of hypomagnesaemia and low tissue magnesium levels.[38 39] Magnesium is a cofactor for alkaline phosphatase and other pyrophosphatases that convert pyrophosphate to orthophosphate[40], and magnesium also increases the solubility of CPPD crystals.[41] Hypomagnesaemia results in increased synovial fluid pyrophosphate levels[42] and predisposes to CPPD crystal formation.[3 42] Magnesium levels were not measured in this study, but should a causative association be confirmed, this would be the first example of drug induced predisposition to CPPD crystal deposition.

There are several caveats to this study. Our study group was not a true random sample because subjects were selected on the basis of the presence or absence of knee pain. The prevalence of knee pain of 58% was higher than that of the sample from which the subjects were drawn.[22] As CC and knee pain were associated we therefore calculated the age, sex, and knee pain adjusted prevalence of CC. This was a cross sectional study and cannot deal with cause and effect for the associations determined. Observer bias could not be completely eliminated, as it is impractical to blind for OA when reading for CC and vice versa. However, to reduce bias we read these features on separate occasions. Also, the radiograph is insensitive for detection of crystals, and although CPPD is the commonest cause of radiographic CC, specific crystal identification was not attempted. Studies based on synovial fluid analysis might be more sensitive and specific for crystal detection, but such an approach is impractical for a community study. Finally, radiographs of the TFJ, performed using the same technique as in previous community studies, may show misalignment of the medial tibial plateau that influences measurement of the JSW in hospital populations.[43] However, misalignment is likely to be less of a problem in a community population whose knee pain is less severe. Further studies using semiflexed views, with or without fluoroscopic positioning, are required to confirm our finding. Importantly, we found no correlation between CC and JSN at the PFJ using the "gold standard" skyline view.

The standardised prevalence of CC in our population was 4.5%. We have confirmed that CC is age related, but having adjusted for the population characteristics our data show no difference in prevalence between men and women. Using skyline radiographs, we found that patellofemoral CC was uncommon and always coexistent with tibiofemoral CC. PFJ views are therefore not required in further studies investigating the prevalence of CC. There is an association with OA at both the TFJ and PFJ, but this is through an association with osteophytosis and not JSN. We report a new association with diuretic use that requires confirmation and further exploration.

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