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Chondrocalcinosis in Knee joints is associated with Pain but not with Synovitis: Data from the Osteoarthritis Initiative

Bobby Kwanghoon Han, MD,
Division of Rheumatology, University of Washington School of Medicine. Seattle, WA. hank4@uw.edu

Woojin Kim, MD,
Division of Musculoskeletal Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania. Philadelphia, PA. woojin.kim@uphs.upenn.edu

Jingbo Niu, MD,
Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA. niujp@bu.edu

Shristi Basnyat, MD,
Division of Rheumatology, Cooper Medical School of Rowan University. Voorhees, NJ. basnyat-shristi@cooperhealth.edu

Veniamin Barshay, MD,
Department of Radiology, Cooper Medical School of Rowan University. Camden, NJ. barshay-veniamin@cooperhealth.edu

John P Gaughan, PhD,
Cooper Research Institute, Cooper Medical School of Rowan University, Camden, NJ. gaughan-john@cooperhealth.edu

Charlene Williams, PhD,
Department of Biomedical Sciences, Cooper Medical School of Rowan University. Camden, NJ. williamsch@rowan.edu

Sharon L Kolasinski, MD, and
Division of Rheumatology, Perelman School of Medicine, University of Pennsylvania. Philadelphia, PA. sharon.kolasinski@uphs.upenn.edu

David T Felson, MD, MPH
Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA. dfelson@bu.edu

Corresponding author: Bobby Kwanghoon Han. University of Washington School of Medicine. Division of Rheumatology. 1959 NE Pacific Street, Box 356428. Seattle, WA 98195. T: 206-685-9950. F: 206-685-9397. hank4@uw.edu.

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Abstract

Objective—To evaluate the relationship between chondrocalcinosis and pain or synovitis in knee joints by examining data from the Osteoarthritis Initiative (OAI).

Methods—Data were obtained from the OAI public use data sets. The relationship between chondrocalcinosis on baseline knee radiograph and pain at baseline and at 4 years was examined. Analyses were adjusted for age, gender, body mass index, and Kellgren-Lawrence (KL) grade and the correlation between two knees in a subject was controlled using generalized estimating equations. The relationship between chondrocalcinosis and synovitis on MRI was examined by comparing knees with chondrocalcinosis at baseline and age, gender, KL grade-matched knees with no chondrocalcinosis. We read MRIs of a subset of knees for synovitis using MRI Osteoarthritis Knee Score (MOAKS) on baseline and 4-year MRI.

Results—Knees with chondrocalcinosis (n=162) more often had pain compared to knees without chondrocalcinosis (n=2030) at baseline and had higher Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores both at baseline (2.4 (95% CI 1.9,2.9) vs 1.8 (1.7,1.9)) and at 4 years (2.5 (1.9,3.1) vs 1.6 (1.5,1.8)) as well as higher Intermittent and Constant Osteoarthritis Pain (ICOAP) intermittent pain scores at 4 years. There was no difference in MOAKS synovitis scores at baseline and at 4 years between the chondrocalcinosis group (n=102) and the control group (n=99).

Conclusion—Knees with chondrocalcinosis had increased pain and did not have higher synovitis scores on MRI compared to knees without chondrocalcinosis. The mechanisms by which chondrocalcinosis is associated with increased pain remain to be determined.

Calcium-containing crystals, including calcium pyrophosphate dihydrate (CPP) crystals and basic calcium phosphate (BCP) crystals, are commonly deposited in hyaline cartilage and meniscal fibrocartilage in joints and are detected radiographically as linear calcifications, termed chondrocalcinosis. Chondrocalcinosis is associated with osteoarthritis (OA) (1) and several studies have found an association between the presence of CPP crystals in synovial fluid and radiographic severity of OA (2, 3). However, others have suggested that chondrocalcinosis is not associated with joint space width on knee radiographs (4). Furthermore, chondrocalcinosis was not associated with increased cartilage loss or OA progression in a prospective, longitudinal magnetic resonance imaging (MRI) study (5).

CPP crystals are known to induce inflammatory reactions and synovitis and can cause acute or chronic crystal-induced inflammatory arthritis (6). CPP crystals induce the production of proinflammatory and catabolic mediators including nitric oxide (NO), matrix metalloproteinase-13 (MMP-13) and prostaglandin E2 (PGE2) in human chondrocytes and synoviocytes *in vitro* (7). Injections of CPP crystals into meniscectomized rabbit knee results in worsening of OA (8). Additionally, BCP crystals induce interleukin-1β (IL-1β) secretion from macrophages through the NLRP3 inflammasome *in vitro* (9) and intra-articular injection of BCP crystals elicits synovial inflammation and cartilage degradation in mice (10). However, the significance of these crystals in human joints is not completely understood. Particularly, it is unknown whether calcium-containing crystals seen as chondrocalcinosis induce synovitis or contribute to pathogenesis of OA.

Synovial volume as measured in non-contrast enhanced MRI has been found to change as knee pain severity changes (11) and has been found to predict both cartilage loss (12) and the development of OA (13). This evidence suggests that it is a validated marker for the amount of synovitis in the knee.

In this study, we evaluated whether chondrocalcinosis was associated with knee pain or synovitis measured on non-contrast enhanced MRI by examining data from the Osteoarthritis Initiative (OAI).

Patients and Methods

Study design and subjects

OAI is an NIH-initiated multi-center, prospective, observational study of knee OA which establishes and maintains a database for OA that includes clinical evaluation data, radiological images, and a biospecimen repository from 4796 participants. We obtained data from the OAI public use data sets. The study rationale and general inclusion criteria for the OAI (e.g., men and women ages 45–79 with symptoms of and/or knee radiographic OA or risk factors for developing knee OA) have been described previously and are publicly available (http://oai.epi-ucsf.org/datarelease/). All subjects were examined between 2004 and 2010. For the purpose of this study, we included subjects who were 60 years and older and knees with Kellgren-Lawrence (KL) grade 0, 1, or 2 on baseline radiographs (14).

We examined the relationship between chondrocalcinosis at baseline and knee pain at baseline and at the 4 year follow-up. In OAI, the presence of knee pain was assessed by using three measures (knee pain more than half the days of a month in the past 12 months, any knee pain in the past 30 days, and knee pain more than half the days in the past 30 days). The severity of knee pain was assessed by visual analog scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) (15), and Intermittent and Constant Osteoarthritis Pain (ICOAP) scores (16). ICOAP is a questionnaire designed to assess intermittent and constant pain for the past week with the scores ranging from 0 to 100.

Next, we examined the relationship between chondrocalcinosis and synovitis on MRI by comparing knees with chondrocalcinosis at baseline and age, gender, and KL grade-matched knees with no chondrocalcinosis. We selected controls by randomly choosing subjects who met the criteria in the list. Subjects who did not have MRI at the 4 year time point were excluded from the MRI analyses.

Given that reading MRIs involves time and effort, we tried to select knees that would be most informative in addressing the questions of interest. All the knees with KL grade 1 or 2 that had chondrocalcinosis and met the inclusion criteria were read for synovitis on MRI. Among knees with KL grade 0, there were very few cases of chondrocalcinosis and the first 13 knees with chondrocalcinosis that were randomly selected were read for synovitis on MRI. If the subject had chondrocalcinosis and the same KL grade in bilateral knees, we read one knee (left knee) per person in large part because we have found much symmetry in MRI findings when knees appear identical on radiographs and it would not be efficient to read

both knees in this circumstance. If the subject had chondrocalcinosis and the knees differed in KL grade, we read both knees.

Knee radiography

Flexed, weight-bearing posteroanterior (PA) radiographs of knee were obtained for all subjects in OAI. Each knee was graded for OA on the KL scale and for the presence of chondrocalcinosis at baseline or during 48-month follow-up. Chondrocalcinosis was defined as being present if there was definite linear cartilage calcification on the PA view in a compartment-specific manner (5). Radiographs of knees with KL grade 2 were read for chondrocalcinosis by central readers at Boston University. Radiographs with KL grade 0 or 1 in bilateral knees were read for chondrocalcinosis at the Cooper Medical Center. There was 100% agreement between the readers in the diagnosis of chondrocalcinosis in a sample of 25 films (with and without chondrocalcinosis) shared between the readers at the two sites.

Knee MRI grading of synovitis

MRI of the knee was obtained with a 3 Tesla scanner from subjects in OAI (17). MRI scans were graded for synovitis by one experienced musculoskeletal radiologist, blinded to clinical data, using a validated method, MRI Osteoarthritis Knee Score (MOAKS) (18). MOAKS synovitis score includes Hoffa synovitis and effusion-synovitis scores. Hoffa synovitis consists of signal changes in the Hoffa fat pad representing chronic synovitis and scored from 0 to 3 (19). These hyperintense signal changes are found within the fat pad on T2-weighted or PD-weighted fat saturated images of the mid-slices of sagittal plane (11). Effusion-synovitis scores are based on the maximal distention (mm) of intra-articular hyperintensity on T2-weighted or PD-weighted images of axial planes and represent a composite of effusion and synovial hypertrophy (20). In this study, the intra-rater intraclass correlation coefficients were 0.804 for Hoffa synovitis and 0.852 for effusion-synovitis.

Statistical Analysis

We used logistic and linear regression to assess whether baseline chondrocalcinosis was associated with the presence of knee pain at baseline and at 4 years. Linear regression was performed to compare pain severity, WOMAC scores and ICOAP scores at baseline and at 4 years, and the change between knees with and without chondrocalcinosis at baseline. Age, gender, BMI, and KL grade were adjusted and the correlation between two knees in a subject was controlled using generalized estimating equations. For the matched control study of synovitis on MRI, analysis of variance for repeated measures on normalized ranks was used for pair-wise comparisons. Data was transformed to normalized ranks prior to analysis to account for non-normal data. Results were considered to be significant for two tailed comparison at $p < 0.05$.

Results

Comparison of knee pain in knees with and without chondrocalcinosis

We compared pain between knees with chondrocalcinosis (n=162) and knees with no chondrocalcinosis (n=2030) on baseline radiographs. Baseline characteristics are described in Table 1. Compared with knees that did not have chondrocalcinosis, those with

chondrocalcinosis had a significantly higher prevalence of frequent pain at baseline assessed by all three pain questions (knee pain more than half the days of a month in the past 12 months, any knee pain in the past 30 days, and knee pain more than half the days in the past 30 days) after adjustment for age, gender, BMI, and KL grade. At 4 years, only any knee pain in the past 30 days was more prevalent in the chondrocalcinosis group (Table 2).

The knees with chondrocalcinosis at baseline had more severe knee pain assessed by VAS in the past 30 days at baseline compared to the knees with no chondrocalcinosis. At baseline and at 4 years, WOMAC knee pain subscale scores were higher in the knees with chondrocalcinosis. There was no difference in change of VAS or WOMAC scores over 4 years in the two groups (table 3). In addition, ICOAP intermittent pain was significantly higher in knees with baseline chondrocalcinosis at 4 years. ICOAP constant knee pain was not different between the two groups at any time point (Table 4).

Comparison of synovitis on knee MRI

We assessed MRIs of 201 knees (102 chondrocalcinosis, 99 controls) at baseline and at 4 years. Baseline characteristics are described in Table 1.

There was no difference in Hoffa synovitis score and effusion-synovitis score at baseline and at 4 years between the chondrocalcinosis group and the control group (Table 5). We also compared subjects within each KL grade and found there was no association with synovitis.

We examined whether there were differences in synovitis scores between baseline and year 4 and found there were no differences (data not shown). There was a weak but statistically significant correlation between Hoffa synovitis and effusion synovitis ($r=0.23$, $p < 0.01$).

Discussion

In these analyses, we demonstrated that chondrocalcinosis in knee joints was modestly associated with increased knee pain and was not associated with synovitis on knee MRI. After the results were adjusted for possible confounders including age, gender, BMI and KL grade, knees with chondrocalcinosis had increased pain by several different measures, including VAS, WOMAC and ICOAP for various time periods. Although there was no single primary outcome, several validated measures were used to assess pain. Knee OA pain can fluctuate over time and we showed consistently increased pain in knees with chondrocalcinosis. Our findings were consistent with a previous report which showed chondrocalcinosis is independently associated with pain and disability in knee OA patients (21)

In view of the association of CPP and BCP crystals with inflammation, we hypothesized that the calcium-containing crystals in chondrocalcinosis contribute to pain by inducing synovitis. However, our results do not support this hypothesis. In a subset of 201 knees assessed in this study, we observed that knees with chondrocalcinosis did not have increased MOAKS synovitis scores on MRI compared to knees without chondrocalcinosis. These synovitis scores include Hoffa synovitis and effusion synovitis scores and there were no differences in either score between the two groups at year 0 and year 4.

Synovial volume on MRI correlates with pain severity in OA (11, 22). Yet, recent work has suggested that fluctuating inflammatory changes in synovium, such as those that may be induced by intermittent release of crystals in the joint space, are likely to be related to synovial perfusion and vascularity which may be better assessed with dynamic rather than static imaging of synovial volume done either with or without contrast (23). Further, while synovitis is likely to be an important cause of pain, certain molecular mediators of the pain signal such as C-C motif chemokine 2(CCL2) (24) or brain-derived neurotropic factor(BDNF) (25), may contribute to pain independently of synovitis.

It has been reported that chondrocalcinosis is not associated with increased histological synovitis or angiogenesis in synovium specimens obtained from patients undergoing total knee joint replacement for OA and our findings support these results (26). One possible explanation is that calcium-containing crystals identified as chondrocalcinosis on radiographs may represent crystals embedded within cartilage (27) and these crystals are normally protected from interacting with synovial macrophages (28). CPP crystal shedding may occur only under certain uncommon circumstances including a rapid decrease of serum calcium levels (29) and this intermittent release may trigger fluctuations of synovial perfusion which would not be detected by a measure of synovial volume (23).

Additionally, it has been observed that calcium-containing crystal formation is regulated by extracellular matrix changes (30). We speculate that calcium-containing crystal deposition is a marker of a knee osteoarthritis phenotype with degenerative changes in extracellular matrix and increased pain, rather than a contributor to synovitis. Histologic studies have shown that calcification of cartilage correlates with the expression of type X collagen, a marker of chondrocyte hypertrophy (31). Furthermore, type II collagen suppresses the ability of ATP to stimulate calcification, while a combination of type II and type I collagen increase the effect of ATP and beta-glycerophosphate on calcification *in vitro*. Proteoglycans suppress calcium-containing crystal formation when added to either type I or type II collagen (32).

We selected subjects who were 60 years and older, and knees with KL grade 0, 1, or 2. Patients rarely develop chondrocalcinosis at a younger age, and it was not efficient to examine those younger than 60 years. We excluded knees with KL grade 3 or 4 because cartilage and meniscus are often eroded in knees with advanced OA and, as a consequence, chondrocalcinosis which is present in these tissues may be no longer visible. Further, subjects with KL grade 3 or 4 have more background pain and synovitis from their OA and it might be difficult to tease out the impact of chondrocalcinosis in this population.

Our study has several limitations. We assessed synovitis on non-contrast enhanced MRIs in the OAI database which may not be as accurate for evaluating synovitis as contrast-enhanced MRI (33), but as noted above, images without contrast have been successful in demonstrating the relation of synovitis with pain fluctuation and with cartilage loss (11, 12, 13). The OAI is a large cohort of subjects in the community and it would have been difficult to justify obtaining contrast-enhanced MRI for this study due to safety concerns related to the use of contrast. Secondly, variability in pain and synovitis of knee OA in a given subject over time could have potentially affected our results. However, these analyses showed

consistent findings of pain and synovitis confirmed by using various measures at year 0 and at year 4.

In summary, knees with chondrocalcinosis had increased knee pain but did not have higher synovitis scores on MRI compared to knees without chondrocalcinosis. These results suggest that calcium-containing crystals seen as chondrocalcinosis in knee joints do not appear to induce synovitis under usual circumstances. The mechanisms by which chondrocalcinosis is associated with increased pain remain to be determined.

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Significance and innovation

- This study examined the association of chondrocalcinosis in knee joints with pain and synovitis using the Osteoarthritis Initiative (OAI) database.
- Chondrocalcinosis was significantly associated with knee pain assessed by various questionnaires including Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores and Intermittent and Constant Osteoarthritis Pain (ICOAP) intermittent pain scores.
- Chondrocalcinosis was not associated with either Hoffa synovitis or effusion-synovitis measured on non-contrast enhanced magnetic resonance imaging (MRI).

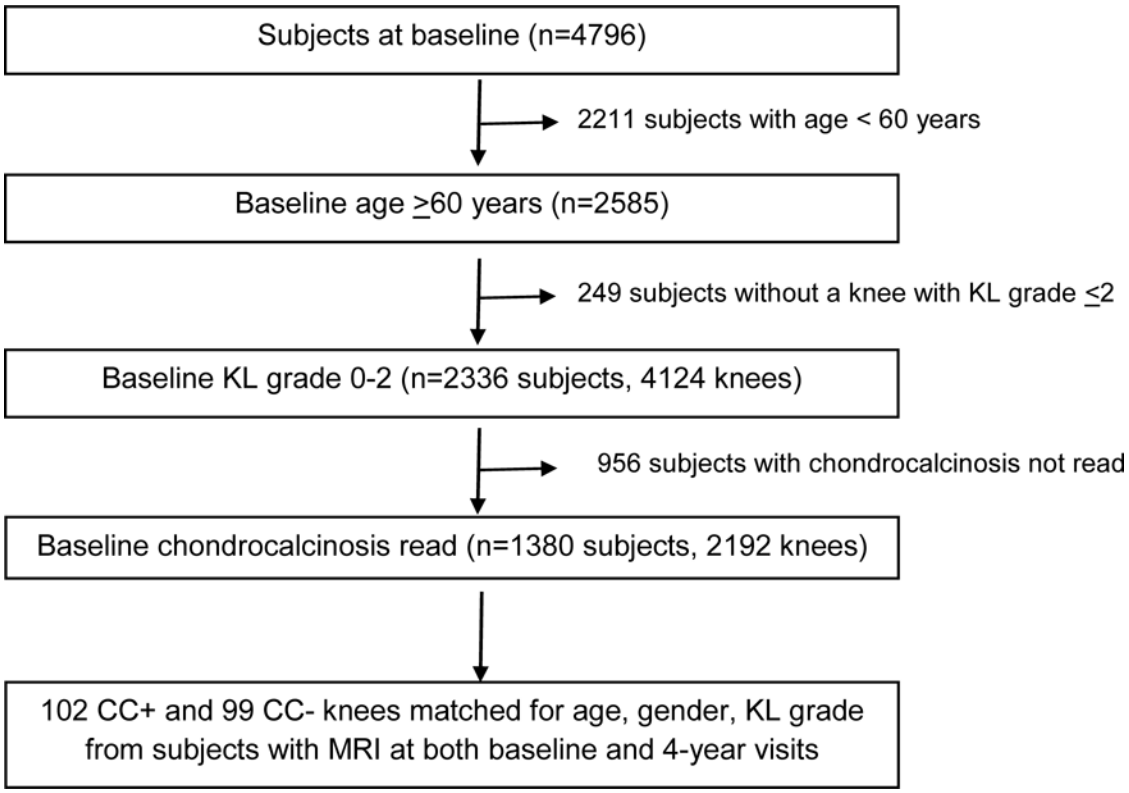

Figure 1.
Flowchart

Table 1

Baseline characteristics

Baseline characteristics		Subjects eligible at baseline (n=1380)		Subjects with MRI reading (n=201)	
		CC+	CC−	CC+	CC−
Subject level, n		114	1266	84	82
Age, mean (SD), year		70.1 (5.4)	68.3 (5.3)	68.8 (5.4)	69.0 (5.2)
BMI, mean (SD), kg/m^2		28.0 (3.9)	28.9 (4.5)		
Female, N(%)		65 (57.0)	803 (63.4)	47 (56.0)	46 (56.1)
Knee level, n		162	2030	102	99
KL grade, N(%)	0	26 (16.1)	379 (18.7)	13 (12.7)	12 (12.1)
	1	29 (17.9)	438 (21.6)	28 (27.5)	28 (28.3)
	2	107 (66.1)	1213 (59.8)	61 (59.8)	59 (59.6)

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Table 2

Baseline chondrocalcinosis and knee pain (yes vs no) at year 0 and year 4

		Crude model		Adjusted model*	
CC at baseline	**knee pain n(%)**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
knee pain more than half the days of a month, past 12 month					
at year 0					
CC− (n=2020)	584 (28.9)	1		1	
CC+ (n=161)	60 (37.3)	1.4 (1.0,2.0)	0.08	1.5 (1.0,2.1)	0.05
at year 4					
CC− (n=1894)	546 (28.8)	1		1	
CC+ (n=151)	48 (31.8)	1.2 (0.8,1.8)	0.29	1.3 (0.9,1.9)	0.21
any knee pain, past 30 days					
at year 0					
CC− (n=2027)	1156 (57.0)	1		1	
CC+ (n=162)	106 (65.4)	1.4 (1.0,2.0)	0.07	1.5 (1.0,2.1)	0.04
at year 4					
CC− (n=1895)	1069 (56.4)	1		1	
CC+ (n=151)	95 (62.9)	1.3 (0.9,1.9)	0.13	1.4 (1.0,2.1)	0.07
knee pain more than half the days, past 30 days					
at year 0					
CC− (n=2024)	534 (26.4)	1		1	
CC+ (n=162)	61 (37.7)	1.6 (1.1,2.3)	<0.01	1.7 (1.2,2.4)	<0.01
at year 4					
CC− (n=1889)	477 (25.3)	1		1	
CC+ (n=151)	45 (29.8)	1.3 (0.9,1.9)	0.19	1.3 (0.9,2.0)	0.15

*Adjusting for age, gender, BMI, and KL grade at baseline

Table 3

Baseline chondrocalcinosis and knee pain (continuous measurement) at year 0 and year 4, and change of knee pain

	Crude model		Adjusted model*	
CC at baseline	**mean (95% CI)**	**p-value**	**adjusted mean (95% CI)**	**p-value**
knee pain severity, past 30 days (0–10)				
at year 0				
CC− (n=2026)	2.3 (2.2,2.4)	0.04	2.0 (1.9,2.2)	0.02
CC+ (n=162)	2.8 (2.3,3.3)		2.6 (2.2,3.1)	
at year 4				
CC− (n=1895)	2.2 (2.1,2.4)	0.19	2.0 (1.8,2.1)	0.11
CC+ (n=151)	2.6 (2.1,3.1)		2.4 (1.9,2.9)	
change from year 0 to year 4				
CC− (n=1891)	0.0 (−0.2,0.1)	0.47	−0.1 (−0.2,0.1)	0.50
CC+ (n=151)	−0.3 (−0.8,0.3)		−0.3 (−0.9,0.3)	
WOMAC knee pain subscale (0–20)				
at year 0				
CC− (n=2030)	2.1 (1.9,2.2)	0.08	1.8 (1.7,1.9)	0.03
CC+ (n=162)	2.6 (2.0,3.1)		2.4 (1.9,2.9)	
at year 4				
CC− (n=1898)	1.8 (1.7,2.0)	0.01	1.6 (1.5,1.8)	<0.01
CC+ (n=151)	2.6 (2.0,3.2)		2.5 (1.9,3.1)	
change from year 0 to year 4				
CC− (n=1898)	−0.2 (−0.3,0.0)	0.63	−0.1 (−0.3,0.0)	0.68
CC+ (n=151)	0.0 (−0.7,0.6)		0.0 (−0.6,0.6)	

*Adjusting for age, gender, BMI, and KL grade at baseline

Table 4

Baseline chondrocalcinosis and intermittent, constant knee pain (continuous measurements) at year 4

	Crude model		Adjusted model*	
CC at baseline	**mean (95% CI)**	**p-value**	**adjusted mean (95% CI)**	**p-value**
ICOAP Knee Intermittent Pain Score at Year 4 (0–100)				
CC− (n=1760)	9.2 (8.3,10.0)	0.05	8.2 (7.4,9.1)	0.02
CC+ (n=138)	12.0 (9.2,14.9)		11.7 (8.7,14.6)	
ICOAP Knee Constant Pain Score at Year 4 (0–100)				
CC− (n=1760)	1.9 (1.4,2.4)	0.20	1.9 (1.4,2.4)	0.12
CC+ (n=138)	3.2 (1.2,5.2)		3.5 (1.4,5.5)	
ICOAP Knee Intermittent and Constant Pain Total Score at Year 4 (0–100)				
CC− (n=1759)	5.8 (5.3,6.4)	0.03	5.3 (4.8,5.9)	0.01
CC+ (n=138)	8.1 (6.1,10.1)		8.0 (6.0,10.1)	

*Adjusting for age, gender, BMI, and KL grade at baseline

Table 5

Baseline chondrocalcinosis and synovitis at year 0 and year 4

	Hoffa synovitis (0–3)		Effusion-synovitis (mm)	
CC at baseline	**mean (95% CI)**	**p-value**	**mean (95% CI)**	**p-value**
All KL grades				
at year 0				
CC− (n=99)	0.7 (0.6, 0.8)	0.30	3.4 (2.9, 3.9)	0.67
CC+ (n=102)	0.8 (0.7, 0.9)		3.7 (3.2, 4.3)	
at year 4				
CC− (n=99)	0.9 (0.8, 1.0)	0.37	3.7 (3.2, 4.2)	0.94
CC+ (n=102)	0.9 (0.8, 1.0)		3.6 (3.1, 4.1)	
KL grade 0				
at year 0				
CC− (n=12)	0.4 (0.1, 0.7)	0.22	3.1 (1.3, 4.8)	0.44
CC+ (n=13)	0.6 (0.2, 1.0)		2.9 (1.6, 4.2)	
at year 4				
CC− (n=12)	0.7 (0.3, 1.1)	0.49	2.5 (1.3, 3.5)	0.97
CC+ (n=13)	0.8 (0.4, 1.1)		3.0 (1.8, 4.3)	
KL grade 1				
at year 0				
CC− (n=28)	0.8 (0.5, 1.0)	0.63	3.1 (2.3, 3.9)	0.12
CC+ (n=28)	0.8 (0.6, 1.0)		3.5 (2.5, 4.4)	
at year 4				
CC− (n=28)	0.9 (0.6, 1.1)	0.31	3.5 (2.7, 4.4)	0.51
CC+ (n=28)	1.0 (0.8, 1.1)		3.3 (2.4, 4.2)	
KL grade 2				
at year 0				
CC− (n=59)	0.8 (0.6, 0.9)	0.84	3.6 (3.0, 4.3)	0.58
CC+ (n=61)	0.8 (0.6, 0.9)		4.1 (3.4, 4.7)	
at year 4				
CC− (n=59)	0.9 (0.7, 1.1)	0.99	4.0 (3.4, 4.6)	0.52
CC+ (n=61)	0.9 (0.8, 1.1)		3.9 (3.2, 4.5)	