Title

Prevalence of intra-articular mineralization on knee computed tomography: the multicenter osteoarthritis study.

Journal
Osteoarthritis and Cartilage, 31(8)

Authors
Jarraya, M
Guermazi, A
Liew, J
et al.

Publication Date
2023-08-01

DOI
10.1016/j.joca.2023.04.004

Peer reviewed

HHS Public Access

Author manuscript

Osteoarthritis Cartilage. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Osteoarthritis Cartilage. 2023 August ; 31(8): 1111–1120. doi:10.1016/j.joca.2023.04.004.

Prevalence of Intra-articular Mineralization on Knee Computed Tomography: The Multicenter Osteoarthritis Study

Mohamed Jarraya[1], **Ali Guermazi**[2], **Jean W. Liew**[5], **Irina Tolstykh**[3], **John A Lynch**[3], **Piran Aliabadi**[4], **David T Felson**[5], **Margaret Clancy**[5], **Michael Nevitt**[3], **Cora E. Lewis**[6], **James Torner**[7], **Tuhina Neogi**[5]

(1)Department of Radiology, Massachusetts General Hospital, Harvard Medical School Boston, MA

(2)Department of Radiology, VA Healthcare System, Boston University School of Medicine, Boston, MA

(3)Department of Epidemiology and Biostatistics, University of California San Francisco, CA

(4)Brigham and Women's Hospital, Harvard Medical School, Boston, MA

(5)Department of Medicine, Boston University School of Medicine, Boston University, Boston MA

(6)Department of Epidemiology, University of Alabama at Birmingham, AL

(7)Department of Epidemiology, College of Public Health, University of Iowa, IA

Abstract

Objective: The aim of this work was to report the prevalence of computed tomography (CT)-detected intra-articular mineralization.

Design: We included participants from the Multicenter Osteoarthritis (MOST) Study. At the 12th year visit of the MOST study, bilateral knee CTs were first obtained. All participants also had posteroanterior and lateral radiographs of bilateral knees and completed standard questionnaires. Knee radiographs were assessed for Kellgren & Lawrence grade (KLG) and radiographic evidence of intra-articular mineralization. CT images were scored using the Boston University Calcium Knee Score (BUCKS) for cartilage, menisci, ligaments, capsule, and vasculature. Prevalence of intra-articular mineralization was computed for the total sample, and stratified by age, sex, race,

---

Corresponding Author: Mohamed Jarraya, MD, Massachusetts General Hospital, Department of Radiology, 32 Fruit Street, YAW 6033, Boston, MA 02114, mjarraya@mgh.harvard.edu.

Author contributions:
All authors contributed to the concept and design of the study, the acquisition of data, and the analysis and interpretation of data. All authors contributed to the drafting of the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

Other contributions: None

Conflict of Interest: AG is shareholder of BICL, LLC, and a consultant to MerckSerono, Pfizer, AstraZeneca, Novartis, Regeneron, and TissueGene. TN: Novartis, Pfizer/Lilly, and Regeneron. Other authors have nothing to disclose.

BMI, presence of frequent knee pain, and KLG. We also determined distribution of mineralization in the cartilage and meniscus, and co-localization.

Results: 4140 bilateral knees from 2070 participants were included (56.7% female, mean age 61.1 years, mean BMI: 28.8 kg/m^2). On radiographs 240 knees (5.8%) had intraarticular mineralization, while CT-detected mineralization was present in 9.8% of knees. Prevalence of hyaline articular and meniscus mineralization increased with age and KL grade, and was similar by sex, BMI categories, and comparable in subjects with and without frequent knee pain. Mineralization tended to be ubiquitous in the joint, most commonly involving all three (medial/lateral tibiofemoral and patellofemoral) compartments (3.1%), while the patellofemoral compartment was the most involved compartment in isolation (1.4%).

Conclusions: CT of the knee provides greater visualization of intra-articular mineralization than radiographs and allows better localization of the crystal deposition within the joint. Further studies should focus on the co-localization of intra-articular crystal deposition and corresponding MRI-features of knee OA.

INTRODUCTION:

Intra-articular mineralization, often referred to as chondrocalcinosis, most commonly affects the knee joint. Its presence is associated with older age and knee osteoarthritis (OA) [1-4]. Chondrocalcinosis on radiographs, reflecting calcium crystal deposition, has been associated with OA disease severity [5,6], although studies of the relationship between chondrocalcinosis and radiographic or MRI-based OA progression have shown mixed results [7-10]. Based on the findings of some studies, intra-articular mineralization is hypothesized to be largely related to age and independent of OA [5,11]. Others have described mineralization as having an active pathogenic role in OA, a phenomenon that is referred to as “microcrystal-induced stress” [12], which appears to be supported by a large epidemiological study that demonstrated an association between intra-articular mineralization and pain, as well as physical disability[13]. Similarly, a recent study from the Osteoarthritis Initiative (OAI) found that chondrocalcinosis on baseline knee radiographs was significantly associated with change in magnetic resonance imaging (MRI)-detected structural damage over four years of follow-up [10]. In contrast, in a French cohort with symptomatic knee and hip OA, chondrocalcinosis on knee radiographs at baseline was not significantly associated with the risk of joint replacement, radiographic progression, or changes in worsening pain or function over five years [9].

Epidemiological study of intra-articular mineralization of the knee is challenging because its presence is often asymptomatic[14], and most studies have used radiographically-detected chondrocalcinosis, which lacks sensitivity due to its limited projectional nature [1-4]. Ultrasonography has much higher sensitivity for the detection of intra-articular mineralization [15], but is limited by its inability to visualize the inner margins of the articular cartilage and soft tissues deep to the osseous surfaces such as the cruciate ligaments [16], and is operator-dependent. Traditional MRI pulses are less sensitive than high resolution radiography for intra-articular mineralization [17].

Technological advances in computed tomography (CT), including thinner collimation and multidetector technology, have contributed to its increased sensitivity for the detection of soft tissue mineralization calcific deposits [18]. For example, a recent study from 2013 showed a prevalence of atlantoaxial chondrocalcinosis of 12.5% [19], which was two-times higher than a prior study from 1995 using earlier CT technology [20].

In our preliminary study, we demonstrated the feasibility of using CT to illustrate that intra-articular mineralization involves nearly all soft tissue components within the knee [21]. Patterns of intra-articular mineralization have not been systematically studied to date, including locations of tissue involvement and co-involvement in a large epidemiological study with the higher sensitivity CT modality. The aim of the current study was to understand the epidemiology and patterns of CT-detected intra-articular and vascular mineralization in a large cohort of older adults with or at risk of knee OA.

METHODS:

The Multicenter Osteoarthritis Study (MOST) Study is a NIH-funded cohort study of community-dwelling older adults with or at risk of knee OA[22]. The original cohort was recruited in 2003-05 and included adults aged 50-79 years with or at risk of knee OA. In addition to the original cohort, a new cohort was recruited in 2016-18 (coinciding with the 12th year visit of the original cohort, and the first year that knee CTs were obtained). The new cohort included adults aged 45-69 years, with minimal knee pain and Kellgren and Lawrence KL grade (KLG) ≤ 2 in both knees. During the study visit, participants from both cohorts underwent CT scans, and PA and lateral radiographs of bilateral knees, and filled out standard questionnaires.

CT Scanning Protocol

Examinations were performed at 2 sites using dual energy CT: The University of Alabama at Birmingham using a GE Discovery CT750HD scanner (80/140 kVp, 260mAs, 0.9mm pitch, 0.8s exposure, rotation speed 50ms), and the University of Iowa using a Siemens SOMATOM Force scanner (80/150 kVp, 250 mAs, 0.8mm pitch, tin filtration at 150kVp, rotation speed 15ms). For the purpose of this study, we only utilized the 80 kVp images from both sites. The use of the lower kilovoltage images (80 Kvp) for the detection of calcium crystals is explained by the high atomic number (Z) of calcium, therefore an associated k-edge that is more closely matched to the mean energy of the low kilovoltage photon source[23-25]. The raw projection data were reconstructed using a slice thickness of 0.6mm and a slice interval of 0.3mm with a standard 512 × 512 imaging matrix. Display field-of-view (DFOV) was standardized to approximately 14 cm for each respective knee data set, using the standard kernel (University of Alabama at Birmingham) and Qr40 kernel (University of Iowa). The DFOV provided an in-plane resolution of 0.3mm (x plane) × 0.3mm (y plane) which corresponded to an isotropic voxel dimension of 0.3mm × 0.3mm × 0.3mm when using a slice interval of 0.3mm in the z-plane. The CT acquisition covered the distal 20% of femur and proximal 20% of tibia.

Image Scoring

Participants obtained bilateral posterior-anterior knee radiographs which were assessed by a musculoskeletal radiologist with more than 30 years of experience (P.A.). Each knee radiograph was scored for the presence or absence of chondrocalcinosis. For CTs, we used the Boston University Calcium Score (BUCKS) scoring system to grade each knee for the presence and severity of intra-articular mineralization [24]. The presence of intra-articular mineralization was based on visual assessment of differential density of mineralization compared to the adjacent cartilage/soft tissue density. Specifically, we applied the Whole Organ Magnetic Resonance Imaging Score (WORMS) scoring system [25] to divide each knee into 14 cartilage subregions. Both medial and lateral menisci were each divided into 4 subregions (anterior horn, body, posterior horn, and posterior root), resulting in 8 meniscus scores. The anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), lateral collateral ligament (LCL), and joint capsule were scored.

Each hyaline cartilage subregion was graded for calcium-crystal deposition using BUCKS [26], yielding a 0-3 ordinal scale based on the extent of crystal mineralization (% of surface area as related to the size of each individual region): Grade 0 = none, grade 1 < 10% of region of cartilage surface area, grade 2 = 10-75% of region of cartilage surface area, and grade 3 >75% of region of cartilage surface area [27]. An identical scoring system was used for meniscus body, and anterior/posterior horns. The posterior meniscus root attachments, MCL and LCL, ACL and PCL, and joint capsule were each graded either 0 (absent) or 1 (present).

A single musculoskeletal radiologist with 8 years of experience in semi-quantitative scoring of knee OA features (M.J.) scored CT examinations of both knees of all participants using axial images, along with multiplanar reformats in the sagittal and coronal views. The location of calcium deposition and the shape of the structure in which calcium was deposited made it possible to identify the tissue affected. The presence of intra-articular mineralization in meniscus and cartilage was defined as present when the score was ≥ grade 1.

The intra-rater reliability of BUCKS scoring system was assessed in a sample of 31 subjects (61 knees) read 12 weeks after the initial reading. The details and rationale for the selection of this sample was previously reported[26]. Another board-certified musculoskeletal radiologist with 20 years of experience in semi-quantitative scoring of knee OA features (A.G.) independently read the scans for assessment of inter-rater reliability. All reliability measures demonstrated at minimum very good agreement according to the criteria developed by Landis and Koch[28]. Intra-rater reliability ranged from 0.93 to 1.0, while the inter-rater reliability ranged from 0.92 to 1.0, using weighted kappa for cartilage and meniscal mineralization and regular kappa for capsular and ligament mineralization, since the 0-1 scoring of capsular and ligament mineralization did not allow for weighting[26].

The study protocol was approved by the institutional review boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco, and Boston University Medical Center.

Pain Measure:

All participants completed standard questionnaires, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[29] and the Intermittent and Constant Osteoarthritis Pain (ICOAP)[30]." We defined frequent knee pain as a response of yes to the question, "During the past 30 days, have you had pain, aching, or stiffness in your knee on most days?" during the same study visit. We specified this definition of frequent knee pain as it allowed for the most consistency in terms of measurement.

Statistical Analysis

We calculated the prevalence of intra-articular mineralization from both the CT and radiographs for the whole sample, and by age, sex, race, BMI, KLG, and presence of frequent knee pain. The prevalence of CT-detected mineralization was calculated excluding ligaments and capsule, to fairly compare radiographs and CT for detection of intraarticular mineralization. We categorized age as 45-56, 57-64, and ≥65 years. We also evaluated the prevalence of mineralization at different locations within the joint, by number of subregions involved both for cartilage and meniscus, as well as co-localization of cartilage and meniscus mineralization. We additionally calculated the adjusted prevalence of intra-articular mineralization by race/ethnicity groups, using generalized estimating equation (GEE) models adjusted for age, sex, BMI and KLG.

RESULTS:

We included 4140 knees from 2170 participants (56.7% female, 82.9% white, mean age 61.1 (SD 9.6) years, mean BMI 28.8 (SD 5.2)) kg/m^2 with complete radiographic and CT scoring, and pain data. Figure 1 shows a flowchart of the participants' selection criteria. Participants characteristics are summarized in Table 1. Participants characteristics for the Original and New Cohorts are presented in supplementary table 1. More than half of the knees had a score of KLG0 (n=2318, 56%) in the tibiofemoral compartment, and 824 knees (19.9%) were KLG1. Approximately 24% of the knees had radiographic tibiofemoral OA; 712 (17.2%), 217 (5.2%) and 69 (1.7%) knees had KLG2, KLG3, and KLG4, respectively.

Prevalence of radiographic chondrocalcinosis at the knee-level was 5.8%, while intra-articular mineralization of cartilage or meniscus on CT was 9.8%; the prevalence at the person-level was 6.8% vs. 12.9%, respectively. If mineralization in the ligaments and capsule was considered, then the prevalence of intra-articular mineralization on CT rose to 10.2%. At the person-level, 121 participants (5.9%) had unilateral intra-articular mineralization, while 114 (7%) had bilateral knee involvement. The agreement between radiographic chondrocalcinosis and CT-detected intra-articular mineralization is shown in Table 2. Regardless of tissue or location, mineralization was detected numerically more frequently on CT than on radiograph (Table 2).

Using radiography, the prevalence of intra-articular mineralization was 2.5%, 7.9%, 10.3%, 16.1% and 11.6% from KLG0 to KLG4, respectively. The prevalence of any intra-articular mineralization on CT also increased with KLG (5.5% for KLG0 to 37.7% for KLG4 knees) and with age (3.4% in age group 45-56 years to 19.5% for age group 65+ years)

(Table 3). The increase of intra-articular mineralization with KLG and age was consistent for all joint tissues (cartilage, menisci, ligament, and capsule). The crude prevalence of CT-detected intra-articular mineralization among participants with frequent knee pain was 11% vs. 9.6% for those without frequent knee pain. The prevalence across different BMI groups was 9-10%. The prevalence of CT-detected mineralization was 10.8% among those who self-identified as white, vs. 7.1%, 7.3% and 2.4% among those who identified as African-American, Hispanic and other, respectively. Of note, the African-American group was substantially younger with few KLG3 and KLG4 knees as shown in the knee-level distribution of Table 2. When adjusted for age, BMI and KL grade, and accounting for correlations within individuals, the prevalence of intra-articular mineralization was 7.6% for White participants, 6.8% for African-American, 8.2% for Hispanic, and 2.6% for other (supplemental table 3 B).

The prevalence of meniscus mineralization was comparable to cartilage mineralization for the whole sample (8% vs. 7.1%), and across KLG. For instance, knees with KLG 0 (4.4% vs. 3.6%), KLG1 (9.5% vs. 7.9%), and KLG4 knees (16.5% vs. 14%) all showed similar differences.

Table 4 shows the distribution of intra-articular mineralization by number of cartilage and meniscus subregions involved. When intra-articular mineralization involved the hyaline cartilage, it was more likely to involve 1-3 (out of 14) subregions (3.6% of all knees), rather than 4-6 subregions (1.4%) or 7-14 subregions (2.1%). That is, of the 7.1% of knees with cartilage mineralization, just over half (50.7%) had only 1-3 subregions involved, suggesting a predilection for mineralization to be more localized. In contrast, in the 8% of knees with mineralization in the menisci, mineralization tended to be more widespread, with a higher prevalence of knees demonstrating mineralization in 4-8 meniscus locations (62.5% of knees with meniscus mineralization (5% of all knees)) than in 1-3 locations (37.5% of knees with meniscus mineralization (3% of all knees)).

Figure 2 shows the distribution of cartilage and meniscus mineralization by compartment and meniscus side. When cartilage mineralization was present, it most frequently affected all three compartments of the knee (medial and lateral tibiofemoral and patellofemoral) (3.1% of all knees (i.e., 43.7% of knees with cartilage mineralization)), whereas the PF compartment was the compartment most frequently involved in isolation (1.4% of all knees, or 19.7% of knees with mineralization). When meniscus mineralization was present, it most frequently involved both medial and lateral sides (5.7%, or 71.3% of knees with meniscus mineralization), versus 1.1 %–1.2% (13.8%–15% of knees with meniscus mineralization) for either side in isolation.

DISCUSSION:

In this study we investigated the prevalence of CT-detected intra-articular mineralization in adults with or at risk of knee OA. The prevalence of intra-articular mineralization of the knee was 5.8% using conventional radiographs, and 9.8% using CT. We also noted an increase in prevalence of intra-articular mineralization with age, as previously reported [31], and with increasing severity by KLG. We did not see differences in the prevalence of intra-articular mineralization by sex, BMI, or presence of frequent knee pain. Finally, mineralization, when present, tended to be present in all three compartments of the joint.

Studies to date have not been able to determine a definite pathogenic role for intra-articular mineralization in knee OA. Whether intra-articular mineralization represents a pathogenic process in the development and progression of OA, or is an “innocent bystander”, remains unclear. One step towards clarifying this question is identifying means by which intra-articular mineralization can be more accurately identified. To the best of our knowledge this is the first estimate of prevalence of intra-articular mineralization based on CT in a large epidemiological cohort. The prevalence of radiographically detected intra-articular mineralization was similar to other large epidemiological cohorts of similar age in the U.S. [4], U.K. [32] and Italy [2] which reported prevalence ranging from 7 to 9.8%. The prevalence of radiographically detected intra-articular mineralization was like other large epidemiological cohorts of similar age in the U.S. (mean age 73 years, 59% female), U.K. (mean age 64 years, 63% female) and Italy (mean age 78 years, 58% female), which reported prevalence ranging from 7 to 9.8%. These studies were mostly performed in the community setting regardless of pain status or history of OA[2,32]. However, radiographic knee OA was present in 27% of the UK cohort and 20% of the Italian cohort. In smaller clinical cohorts that were not community-based but also using conventional radiographs, the prevalence was reported to be as high as 26% [3,6], and reached 60% when relying on the synovial fluid analysis and 100% with digital-contact radiography in end-stage OA knees at the time of joint replacement[6]. Lastly, the reported prevalence in cadaveric studies ranges from 5.6 to 21% [33-35].

The higher prevalence of intra-articular mineralization on CT compared to radiographs is predictable due to the greater visualization by CT of soft tissue mineralization. It is also in line with prior studies showing higher prevalence of soft tissue mineralization than previously thought in the cervical spine [19] and the sternoclavicular joint [36] when using CT. In addition to the higher prevalence of intra-articular mineralization using CT compared to radiography, we noted that the difference in prevalence between these 2 modalities was highest for KLG4 knees. This may be explained by the challenge of detecting mineralization on radiographs when the cartilage loss is advanced. Our finding of increasing prevalence of intra-articular mineralization with KLG is also consistent with numerous epidemiological [2,4,32,37], clinical [3], and cadaveric studies [17,33,35]. For instance, a meta-analysis on the relationship between calcium pyrophosphate deposition disease (CPPD) and OA suggested that people with OA are three times more likely to have CPPD than people without OA [38]. Of note, there were few KLG4 knees included in this study, as many KLG4 knees were not eligible for CT examination at 144-month visit (participants with end stage OA at previous visit were not eligible for CT).

In our study, hyaline cartilage mineralization, when present, was most commonly present in all three compartments (medial and lateral TF, and PF). That is, of the 7.1% of knees with cartilage mineralization, ~43.6% of those knees had mineralization in all three compartments. In contrast, though, when mineralization was present in the cartilage, it tended to occur in just a few subregions (1-3 subregions) for about half of those knees. Interestingly, the PF compartment was the most frequently involved compartment in isolation. This finding is at odds with a prior study by Neame *et al.,* which included both PA and skyline radiographs, showing a markedly lower prevalence of radiographically-detected chondrocalcinosis in the PF joint (only 9 out of 119 cases of chondrocalcinosis were noted in the PF joint, and they all also had chondrocalcinosis in the TF joint) [32]. We hypothesize that the use of CT in our cohort accounts for the much higher proportion of PF chondrocalcinosis in our study, versus the use of skyline radiographs in the above-mentioned study[32].

Our study supports the utility of CT as a more performant modality than radiography. However, location-specific data may be more informative to understand local intra-articular effects. The identification of meniscus mineralization involvement using ultrasound has allowed for improved sensitivity beyond conventional radiography [39], but the biologic relevance of particular anatomic location of mineralization hasn't been fully elucidated in clinical and *in vitro* studies [40]. A novel finding emanating from our study owing to the greater visualization of all joint tissues with CT compared with radiography is that we noted the common tricompartmental but relatively limited subregional involvement of intra-articular hyaline articular cartilage mineralization as well as involvement of the menisci in multiple subregions, ligaments, and the joint capsule. Calcification of the joint capsule and ligaments in the knee has been even less well studied [41].

In terms of other characteristics of individuals with intra-articular mineralization, we found no difference in prevalence of intra-articular mineralization between men and women, in contrast to numerous prior reports showing higher prevalence among women [2,4,32,37]. However our findings appear in line with Mussachio, et al. who reported in a large cohort of 3,099 participants no sex difference in prevalence of intra-articular mineralization after adjusting for severity of radiographic OA [13]. We also found no differences in intra-articular mineralization with BMI. Mussachio, et al. also reported a significant association between intra-articular mineralization and knee pain and limited physical function after adjusting for radiographic severity. In our study, we found no crude association between intra-articular mineralization and presence of frequent knee pain. However, the possible contributing role of subclinical inflammatory episodes from crystal deposition on pain fluctuation in OA cannot be excluded from these data.

In the current study, we observed race/ethnicity crude differences in intra-articular mineralization; however, after adjustment for sex, age, BMI and KLG those differences were not significant or clinically meaningful, and largely reflected differences in the age and KLG distribution. We conclude that the prevalence of intra-articular mineralization was similar by ethnicity/race. Of note, the presence of intra-articular mineralization by race/ethnicity has not been well-studied to date, although a prior study reported lower prevalence of radiographically detected chondrocalcinosis on frontal radiographs of the hands and knees among Chinese participants from Beijing (1.8% in men and 2.7% in women), in comparison with white participants in the United States (6.2% in men, 7.7% in women) [37]. Additionally, a large longitudinal study on 5,018 participants in Korea reported a crude incidence of radiographically detected knee chondrocalcinosis of 3.19 per 1000 person-years[31]. The underlying etiology for these differences is not known.

We acknowledge the radiation exposure from CT as an important consideration, however the effective dose of a CT of the knees (0.15mSV) is very low and comparable to equivalent to 2 chest radiographs (0.08 mSv per radiograph)[42]. Depending on the site, scanner, and participant size, the CTDIvol ranged from approximately 5.7 to 10.8 mGy, while the DLP varied from 8.7 to 43.3 mGy-cm.

The strength of this study lies in its large sample size of a wide range of radiographic severity of OA, from none to end-stage disease. Our study has some limitations which must be acknowledged. First, since MOST is a large epidemiological cohort study, and thus the use of invasive diagnostic methods is not feasible, we were unable to use further confirmatory methods for the presence of intra-articular mineralization that could not be detected by CT, which requires a certain concentration or volume to be detectable. Another limitation of our study is the different age and KLG distribution of the different race groups, which therefore limits the power to draw any conclusions about influence of race in chondrocalcinosis. Also, the use of hydroxyapatite phantoms could have been useful for quantitative measurements of areas of intraarticular mineralization, however in our study the severity of intra-articular mineralization was based on its extent within the meniscal and cartilage subregions rather than its HU measurement. Finally, we were unable to elucidate the exact nature of crystal deposits by differentiating the various types of calcium crystals (calcium pyrophosphate vs. basic calcium phosphate). Of note, the detection of intra-articular monosodium urate (gout deposits) was outside the scope of this study, although technically possible considering the dual energy acquisition.

In summary, we report here the first study of the prevalence in a large cohort recruited from the population of intra-articular mineralization detected by CT and its association with age, gender, radiographic OA severity, and frequent knee pain. CT provides greater visualization of intra-articular mineralization than radiographs. These data will provide opportunity to evaluate the longitudinal relation of intra-articular mineralization to adjacent articular tissue pathology and overall OA progression, particularly in a location-specific and tissue-specific manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Funding Sources:

The MOST Study is supported by NIH grants from the National Institute on Aging to Drs. Lewis (U01-AG-18947), Torner (U01-AG-18832), Nevitt (U01-AG-19069), and Felson (U01-AG-18820). This study was also supported by K24 AR070892 (Neogi), and P30 AR072571 (Felson).

REFERENCES:

1. Bergström G, Bjelle A, Sundh V, Svanborg A. Joint disorders at ages 70, 75 and 79 years--a cross-sectional comparison. Br J Rheumatol. 1986;25(4):333–341. [PubMed: 2946352]

2. 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. 27(6):981–984. [PubMed: 20149316]
3. Sanmarti R, Pañella D, Brancós MA, Canela J, Collado A, Brugués J. Prevalence of articular chondrocalcinosis in elderly subjects in a rural area of Catalonia. Ann Rheum Dis. 1993;52(6):418–422. doi:10.1136/ARD.52.6.418 [PubMed: 8323393]
4. 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. [PubMed: 2810282]
5. Mitsuyama H, Healey RM, Terkeltaub RA, Coutts RD, Amiel D. Calcification of human articular knee cartilage is primarily an effect of aging rather than osteoarthritis. Osteoarthritis Cartilage. 2007;15(5):559–565. doi:10.1016/j.joca.2006.10.017 [PubMed: 17276093]
6. Fuerst M, Bertrand J, Lammers L, et al. Calcification of articular cartilage in human osteoarthritis. Arthritis Rheum. 2009;60(9):2694–2703. doi:10.1002/art.24774 [PubMed: 19714647]
7. 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. doi:10.1002/art.21903 [PubMed: 16729275]
8. Muehleman C, Li J, Aigner T, et al. Association between crystals and cartilage degeneration in the ankle. J Rheumatol. 2008;35(6): 1108–1117. [PubMed: 18412302]
9. Latourte A, Rat AC, Ngueyon 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. doi:10.1002/art.41186 [PubMed: 31804010]
10. 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. doi:10.1016/j.joca.2019.10.003 [PubMed: 31629813]
11. Pritzker KPH. Counterpoint: Hydroxyapatite Crystal Deposition Is Not Intimately Involved in the Pathogenesis and Progression of Human Osteoarthritis. Curr Rheumatol Rep. 2009;11:148–153. [PubMed: 19296888]
12. Ea HK, Lioté F. Advances in understanding calcium-containing crystal disease. Curr Opin Rheumatol. 2009;21(2):150–157. doi:10.1097/BOR.0b013e3283257ba9 [PubMed: 19339926]
13. 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. doi:10.1136/ard.2011.150508 [PubMed: 21821868]
14. Abhishek A, Doherty M. Epidemiology of Calcium Pyrophosphate Crystal Arthritis and Basic Calcium Phosphate Crystal Arthropathy. Rheum Dis Clin N Am. 2014;40(2):177–191. doi:10.1016/j.rdc.2014.01.002
15. Ellabban AS, Kamel SR, Omar HASA, El-Sherif AMH, Abdel-Magied RA. Ultrasonographic diagnosis of articular chondrocalcinosis. Rheumatol Int. 2012;32(12):3863–3868. doi:10.1007/s00296-011-2320-1 [PubMed: 22193232]
16. Sofka CM, Adler RS, Cordasco FA. Ultrasound diagnosis of chondrocalcinosis in the knee. Skeletal Radiol. 2002;31(1):43–45. doi:10.1007/s002560100434 [PubMed: 11807593]
17. Dirim B, Resnick D, Abreu M, Wangwinyuvirat M, Trudell DJ, Haghighi P. Relationship between the degeneration of the cruciate ligaments and calcium pyrophosphate dihydrate crystal deposition: anatomic, radiologic study with histologic correlation. Clin Imaging. 2013;37(2):342–347. doi:10.1016/j.clinimag.2012.03.002 [PubMed: 23465989]
18. Miksanek J, Rosenthal AK. Imaging of Calcium Pyrophosphate Deposition Disease. doi:10.1007/s11926-015-0496-1
19. Chang EY, Yen Lim W, Tanya Wolfson M, et al. Frequency of atlantoaxial calcium Pyrophosphate Dihydrate Deposition at cT 1. Radiology. 269. doi:10.1148/radiol.13130125
20. Zapletal J, Hekster RE, Straver JS, Wilmink JT, Hermans J. Association of transverse ligament calcification with anterior atlanto-odontoid osteoarthritis: CT findings. Neuroradiology. 1995;37(8):667–669. [PubMed: 8748903]

21. Misra D, Guermazi A, Sieren JP, et al. CT imaging for evaluation of calcium crystal deposition in the knee: initial experience from the Multicenter Osteoarthritis (MOST) study. Osteoarthritis Cartilage. 2015;23(2):244–248. doi:10.1016/j.joca.2014.10.009 [PubMed: 25451303]

22. Segal NA, Nevitt MC, Gross KD, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM R. 2013;5(8):647–654. doi:10.1016/j.pmrj.2013.04.014 [PubMed: 23953013]

23. Mallinson PI, Coupal TM, McLaughlin PD, Nicolaou S, Munk PL, Ouellette HA. Dual-Energy CT for the Musculoskeletal System. Radiology. 2016;281(3):690–707. doi:10.1148/radiol.2016151109 [PubMed: 27870622]

24. Guermazi A, Jarraya M, Lynch JA, et al. Reliability of a new scoring system for intraarticular mineralization of the knee: Boston University Calcium Knee Score (BUCKS). Osteoarthritis Cartilage. 2020;28(6):802–810. doi:10.1016/j.joca.2020.03.003 [PubMed: 32173626]

25. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004;12(3):177–190. doi:10.1016/j.joca.2003.11.003 [PubMed: 14972335]

26. Guermazi A, Jarraya M, Lynch JA, et al. Reliability of a new scoring system for intraarticular mineralization of the knee: Boston University Calcium Knee Score (BUCKS). Osteoarthritis Cartilage. 2020;28(6):802–810. doi:10.1016/j.joca.2020.03.003 [PubMed: 32173626]

27. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19(8):990–1002. doi:10.1016/j.joca.2011.05.004 [PubMed: 21645627]

28. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–174. [PubMed: 843571]

29. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988; 15(12): 1833–1840. [PubMed: 3068365]

30. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis Cartilage. 2008;16(4):409–414. doi:10.1016/j.joca.2007.12.015 [PubMed: 18381179]

31. Cho NH, Song Y, Lee S, Sung YK, Jun JB. Incidence of knee chondrocalcinosis and its risk factors in a community-based cohort. Int J Rheum Dis. 2018;21(7):1391–1397. doi:10.1111/1756-185X.13317 [PubMed: 29968327]

32. 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. doi:10.1136/ard.62.6.513 [PubMed: 12759286]

33. Mitrovic DR, Stankovic A, Iriarte-Borda O, et al. The prevalence of chondrocalcinosis in the human knee joint. An autopsy survey. J Rheumatol. 1988; 15(4):633–641. [PubMed: 3397973]

34. Ryu K, Iriuchishima T, Oshida M, et al. The prevalence of and factors related to calcium pyrophosphate dihydrate crystal deposition in the knee joint. Osteoarthritis Cartilage. 2014;22(7):975–979. doi:10.1016/j.joca.2014.04.022 [PubMed: 24814686]

35. Mccarty DJ, Hogan JM, Gatter RA, Grossman M. Studies on pathological calcifications in human cartilage. I. Prevalence and types of crystal deposits in the menisci of two hundred fifteen cadavera. J Bone Joint Surg Am. 1966;48(2):309–325. [PubMed: 5932916]

36. Shirazian H, Chang EY, Wolfson T, Gamst AC, Chung CB, Resnick DL. Prevalence of sternoclavicular joint calcium pyrophosphate dihydrate crystal deposition on computed tomography ☆ , ☆☆. Published online 2014. doi:10.1016/j.clinimag.2014.02.016

37. Zhang Y, Terkeltaub R, Nevitt M, et al. Lower prevalence of chondrocalcinosis in Chinese subjects in Beijing than in white subjects in the United States: The Beijing Osteoarthritis Study. Arthritis Rheum. 2006;54(11):3508–3512. doi:10.1002/art.22189 [PubMed: 17075853]

38. Richette P, Bardin T, Doherty M. An update on the epidemiology of calcium pyrophosphate dihydrate crystal deposition disease. Rheumatology. 2009;48(7):711–715. doi:10.1093/rheumatology/kep081 [PubMed: 19398486]

Author Manuscript

Author Manuscript

Author Manuscript

39. Filippou G, Adinolfi A, Cimmino MA, et al. Diagnostic accuracy of ultrasound, conventional radiography and synovial fluid analysis in the diagnosis of calcium pyrophosphate dihydrate crystal deposition disease. Clin Exp Rheumatol. 2016;34(2):254–260. [PubMed: 26886247]
40. Sun Y, Mauerhan DR, Honeycutt PR, et al. Calcium deposition in osteoarthritic meniscus and meniscal cell culture. Arthritis Res Ther. 2010;12(2):R56. doi:10.1186/ar2968 [PubMed: 20353559]
41. Abreu M, Johnson K, Chung CB, et al. Calcification in calcium pyrophosphate dihydrate (CPPD) crystalline deposits in the knee: anatomic, radiographic, MR imaging, and histologic study in cadavers. Skeletal Radiol. 2004;33(7):392–398. doi:10.1007/s00256-004-0767-9 [PubMed: 15138720]
42. Biswas D, Bible JE, Bohan M, Simpson AK, Whang PG, Grauer JN. Radiation Exposure from Musculoskeletal Computerized Tomographic Scans: J Bone Jt Surg-Am Vol. 2009;91(8):1882–1889. doi:10.2106/JBJS.H.01199

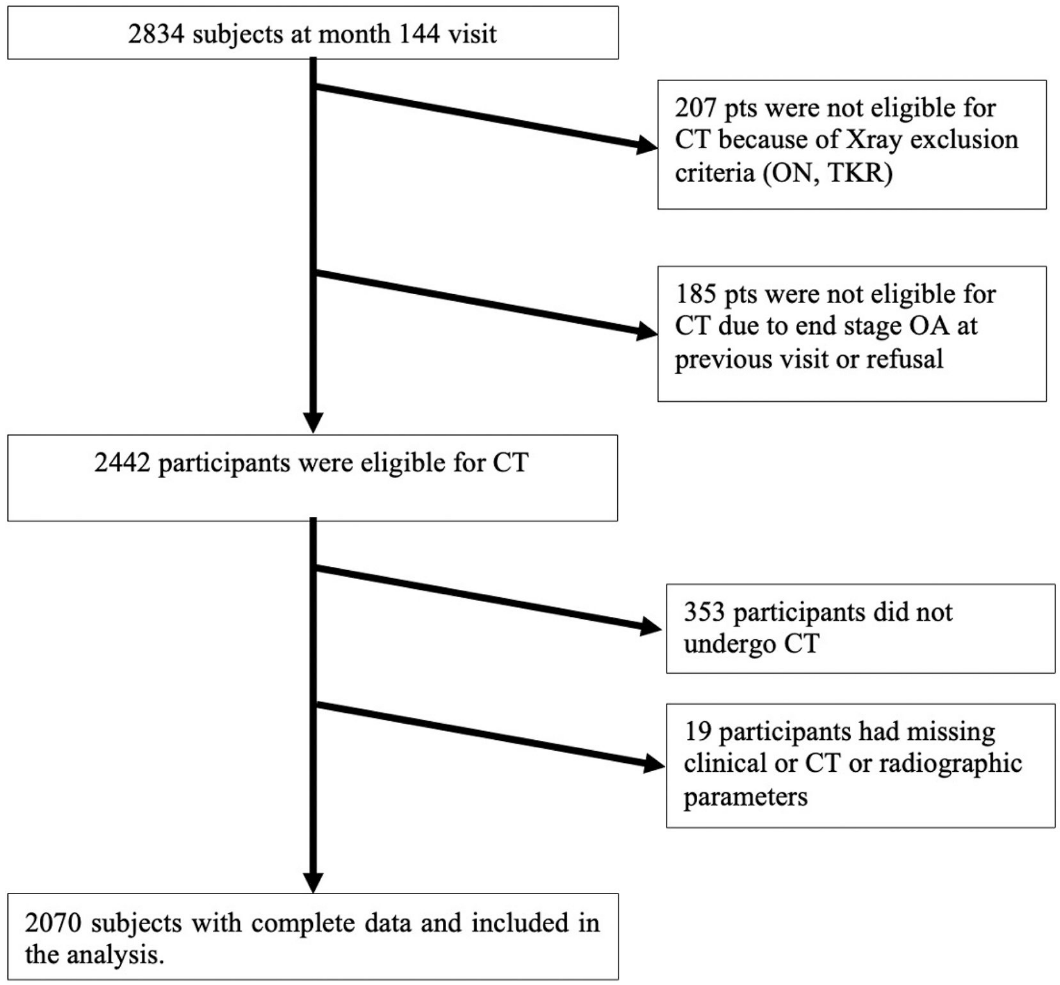

Figure 1:
Flowchart of the selection criteria for the study

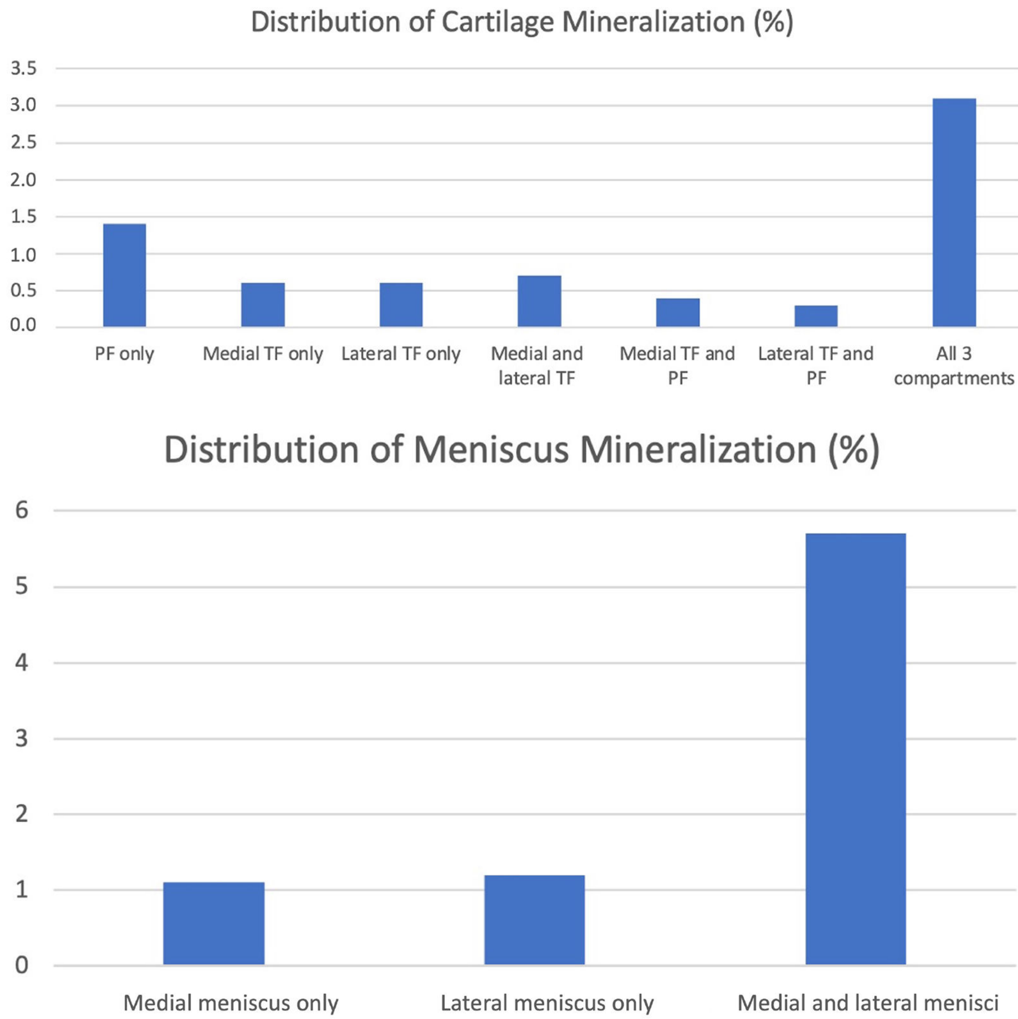

Figure 2:

Distribution of (a) cartilage and (b) meniscus mineralization. The Y axis represents proportion of knees with intra-articular mineralization in the whole sample

Figure 3.
(A-D): CT images of two participants with intra-articular mineralization from the two sites of the MOST study. **(A)** Coronal and **(B)** Sagittal 80 kVp CT reformats from the University of Alabama at Birmingham site using a GE Discovery CT750HD scanner (80/140 kVp, 260mAs,0.9mm pitch, 0.8s exposure, rotation speed 50ms, standard kernel), showing intra-articular mineralization of the medial and lateral menisci (solid arrows) and menisci posterior roots (arrowheads), as well as the posterior capsule (empty arrows). **(C)** Coronal and **(D)** Sagittal reformats from the University of Iowa site using a Siemens SOMATOM Force scanner (80/150 kVp, 250 mAs, 0.8mm pitch, tin filtration at 150kVp, rotation speed 15ms, Qr40 kernel) show intraarticular mineralization in similar distribution including the medial and lateral menisci (solid arrows) as well as the posterior capsule.

Table 1.

Sample characteristics at the person level (by race/ethnicity) and knee level.

Person level	**N=2070**	**By race / ethnicity**			
		White N=1621 (78.3%)	**AA N=352 (17.0%)**	**Hispanic N=55 (2.7%)**	**Other N=42 (2.0%)**
Mean Age (SD), years	61.1 (9.6)	61.9 (9.8)	58.4 (8.4)	56.9 (8.2)	58.9 (7.6)
Mean BMI (SD), kg/m^2	28.8 (5.2)	28.5 (5.1)	30.5 (5.3)	28.3 (5.4)	26.3 (5.4)
Female	1174 (56.7%)	895 (55.2%)	221 (62.8%)	34 (61.8%)	24 1(57.1%)
Knee level	N=4140	N=3242	N=704	N=110	N=84
Kellgren & Lawrence Grade					
0	56.0%	54.7%	60.2%	60.9%	64.3%
1	19.9%	20.2%	16.9%	26.4%	25.0%
2	17.2%	17.6%	17.1%	10.9%	9.5%
3	5.2%	5.7%	4.1%	0.9%	1.2%
4	1.7%	1.7%	1.7%	0.9%	0
Frequency knee pain					
Yes	24.2%	23.2%	30.7%	15.5%	19.0%

Table 2.

Agreement between radiographic chondrocalcinosis (for the whole knee) and CT-detected intra-articular mineralization detected in different locations.

Presence of CT-based intra-articular mineralization	N knees	Radiographic Chondrocalcinosis Absent (n=3900)	Radiographic Chondrocalcinosis Present (n=240)
Any cartilage/meniscus Present	406	204 (5.2%)	202 (84.2%)
Any cartilage/meniscus Absent	3734	3696 (94.8)	38 (15.8)
Any cartilage /meniscus /capsule /ligament	424	222 (5.7%)	202 (84.2%)
By location			
Any cartilage	294	117 (3%)	177 (73.8%)
Cartilage (medial compartment)	199	45 (1.2%)	154 (64.2%)
Cartilage (lateral compartment)	194	40 (1%)	154 (64.2%)
Cartilage (TF joint)	236	67 (1.7%)	169 (70.4%)
Cartilage (PF joint)	214	79 (2%)	135 (56.3%)
Any meniscus	331	132 (3.4%)	199 (82.9%)
Meniscus (medial compartment)	283	90 (2.3%)	193 (80.4%)
Meniscus (lateral compartment)	284	94 (2.4%)	190 (79.2%)
Any capsule	185	46 (1.2%)	139 (57.9%)
Any ligament	174	46 (1.2%)	128 (53.3%)

Table 3.

Prevalence (percentage) of intra-articular mineralization on CT by age, gender, pain status, and KL grade

	Total	Prevalence (%) of any intra-articular mineralization in the knee	Cartilage (overall)	TF Cartilage	PF Cartilage	Meniscus	Capsule	Ligaments
Total	4140	9.8	7.1	5.7	5.2	8	4.5	4.2
Men	1792	10.4	7.4	5.4	5.9	8	4.3	4.2
Women	2348	9.5	6.9	5.9	4.6	8	4.6	4.2
White	3242	10.8	7.9	6.6	5.7	9.0	5.2	4.9
African-American	704	7.1	4.4	2.4	3.1	3.8	1.4	1.4
Hispanic	110	7.3	3.6	3.6	3.6	7.3	4.5	3.6
Other	84	2.4	2.4	0	2.4	2.4	0	0
No frequent knee pain	3909	9.6	6.8	5.3	5.1	7.7	4.3	4
Frequent Knee Pain	1002	11	8.1	7	5.4	8.9	4.9	4.9
Age 45-56	1456	3.4	2.6	1.8	2.1	2.3	1	1
Age 57-64	1220	6.1	3.9	2.5	3.1	4.6	2.3	1.8
Age 65+	1464	19.5	14.2	12.3	10	16.5	9.7	9.4
KL 0	2318	5.5	3.6	2.6	2.8	4.4	1.8	1.7
KL 1	824	11.2	7.9	6.1	6.1	9.5	5	4.9
KL 2	712	15.6	12.6	10.7	8.3	11.9	8.4	7.4
KL 3	217	24.4	18.4	15.7	13.4	8.4	13.4	13.8
KL 4	69	37.7	23.2	23.2	17.4	36.2	20.3	15.9
BMI 20-25	1026	9.6	7.4	6.6	5	8.7	4.3	3.6
BMI 25-30	1574	10	7.2	5.9	5.4	8.2	5	4.4
BMI >30	1540	9.9	6.8	4.9	5.1	7.3	4.1	4.4

Table 4:

Patterns and distribution of cartilage and meniscus mineralization by number of subregions involved, both in the whole sample and among knees with mineralization

	Distribution of mineralization in the whole sample (%)	**Distribution of mineralization among involved knees (%)**
Cartilage		
None	92.9	Not applicable
1-3 subregions with mineralization	3.6	*50.7*
4-6 subregions with mineralization	1.4	*19.7*
7-14 subregions with mineralization	2.1	*29.6*
Meniscus		
None	92	Not applicable
1-3 subregions with mineralization	3	*37.5*
4-8 subregions with mineralization	5	*62.5*