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CT imaging for evaluation of calcium crystal deposition in the knee: initial experience from the Multicenter Osteoarthritis (MOST) study

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SUMMARY

Objective: Role of intra-articular calcium crystals in osteoarthritis (OA) is unclear. Imaging modalities used to date for its evaluation have limitations in their ability to fully characterize intra-articular crystal deposition. Since Computed Tomography (CT) imaging provides excellent visualization of bones and calcified tissue, in this pilot project we evaluated the utility of CT scan in describing intra-articular calcium crystal deposition in the knees.

Method: We included 12 subjects with and four subjects without radiographic chondrocalcinosis in the most recent visit from the Multicenter Osteoarthritis (MOST) study, which is a longitudinal cohort of community-dwelling older adults with or at risk for knee OA. All subjects underwent CT scans of bilateral knees. Each knee was divided into 25 subregions and each subregion was read for presence of calcium crystals by a musculoskeletal radiologist. To assess reliability, readings were repeated 4 weeks later.

Results: CT images permitted visualization of 25 subregions with calcification within and around the tibio-femoral and patello-femoral joints in all 24 knees with radiographic chondrocalcinosis. Intra-articular calcification was seen universally including meniscal cartilage (most common site involved in 21/24 knees), hyaline cartilage, cruciate ligaments, medial collateral ligament and joint capsule. Readings showed good agreement for specific tissues involved with calcium deposition (kappa: 0.70, 95% CI 0.62–0.80).

Conclusion: We found CT scan to be a useful and reliable tool for describing calcium crystal deposition in the knee and therefore potentially for studying role of calcium crystals in OA. We also confirmed that "chondrocalcinosis" is a misnomer because calcification is present ubiquitously.

Introduction

Despite knee osteoarthritis (OA) being the most common form of joint disease affecting older adults and a leading cause of lower-extremity disability globally[1,2], no effective disease-modifying pharmacologic therapies are available at this time. This reflects, in part, an incomplete understanding of the underlying pathogenesis of OA. A relatively understudied potential contributor to the disease pathogenesis is intra-articular calcium crystals, which often co-exists with knee OA although their exact role is unclear[3]. There are two main types of calcium crystals i.e., calcium pyrophosphate (CPP) and basic calcium apatite (BCP) crystals, which differ in chemical properties, appearance and presentation and potentially in their role in OA[4,5]. While one school of thought considers these crystals as "innocent bystanders" or the natural consequence of the joint damage[6], others posit that these crystals play an active role in cartilage destruction by induction of "oxidative stress" through release of inflammatory cytokines and matrix metalloproteases[7]. If calcium crystals do in fact contribute to cartilage degeneration in OA, then it would cast them as a novel target for the treatment and prevention of OA.

A major challenge in assessing the role of calcium crystals in OA to date has been the practical imaging modality that provides

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accurate visualization of intra-articular calcium crystals. Conventional radiography is the most commonly used imaging method for visualization of intra-articular calcium. However, its use is limited because of its poor sensitivity, limiting insights into burden and localization[8]. While ultrasonography has been found to be a sensitive tool in identifying cartilage calcification[9], its inability to visualize tissues deep to bone surfaces, and thus inability to visualize some cartilage and soft tissue surfaces (including the cruciate ligaments) is a limitation[10,11]. There are also questions about specificity of ultrasound for CPP crystals[8]. Traditional MRI pulse sequences are also limited in sensitivity and in their ability to distinctly identify calcified cartilage from other abnormalities, such as meniscal tears[12,13] which may be overcome by using ultrashort-echo-time MR sequence, as shown in a feasibility study[14]. To that end, computed tomography (CT) is of interest because it provides highly spatial, 3-dimensional information to identify presence of pathologic processes within scanned anatomical regions with excellent visualization of bones and calcified tissues, yet it has not been studied extensively for calcium crystal deposition.[15,16]

As the burden of OA is rising, the need for understanding the role of depositions of calcium crystals as part of a larger effort to understand underlying pathophysiology of OA is becoming crucial. We therefore undertook this pilot project to examine the utility of CT scans in describing intra-articular calcium crystal deposition, particularly in evaluating the precise tissues involved, among subjects with and without radiographic presence of calcium crystals (chondrocalcinosis).

Methods

Study sample

All participants in this study were recruited from the Multicenter Osteoarthritis (MOST) Study, a NIH-funded multicenter, longitudinal, observational study of 3026 individuals at baseline, who had or were at high risk for knee OA, recruited from two US centers, Iowa City Iowa and Birmingham, Alabama. Details of the study population have been published elsewhere[17]. All participants in the MOST Study had fixed-flexion bilateral knee x-rays at baseline and at each follow-up study visit (30-, 60- and 84-month visits).

We included 16 subjects from the Iowa study site who had X-rays obtained at the 84-month (most recent) follow-up visit (5/5/11–12/17/12), 12 subjects read by the MOST X-ray readers as having chondrocalcinosis in both knees and four with no evidence of chondrocalcinosis in either knee.

Because cartilage loss and consequent joint space narrowing can compromise assessment of intra-articular calcification, we preferentially selected subjects who did not have radiographic OA (Kellgren and Lawrence grade <2)[18] to ensure that the joint space was preserved to optimize visualization of calcium deposition of intra-articular tissues. In fact, in a recent study evaluating sensitivity and specificity of CT scans for diagnosing gout, all false positives had advanced OA[19]. In our study, out of 32 knees, six had definite radiographic OA (KL grade ≥ 2) and none had a KL grade of 4.

CT scanning

An advance to conventional CT, Dual Energy CT (DECT) was obtained given its availability at the research facility (Department of Radiology, University of Iowa, Iowa city, Iowa) and plans for a future study of comparison of intra-articular calcium crystal vs urate crystal deposition. All 16 participants underwent CT scanning using a Definition Flash scanner Siemens Healthcare of bilateral knees. For this study, we utilized only the images from one of the two X-ray guns in the DECT acquisition mode. The scan protocol from the X-ray gun selected used an effective mAs of 45, kV of 140, 0.8 pitch and a rotation speed of 0.285 s. The raw projection data were reconstructed using a slice thickness of 0.6 mm and a slice interval of 0.3 mm with a standard 512 × 512 imaging matirx. Reconstruction diameters (DFOV) were standardized to approximately 15 cm for each respective knee data set. The DFOV provided a in-plane resolution 0.3 mm (× plane) × 0.3 mm (y plane) which corresponded to an isotrophic voxel dimension of 0.3 mm × 0.3 mm × 0.3 mm when using a slice interval of 0.3 mm in the z-plane. A high spatial reconstruction kernel of B70 was used to increase the CNR of the anatomical structures. The radiation dose for knee joint for DECT is the same as single energy CT scans, which is 0.15 mSv for one knee[20], compared to 0.001–0.005 mSv for knee X-ray, but less than the average annual natural background radiation dose (2.4 mSv).[21]

A two-step scoring system was devised. First, each knee was divided into 25 subregions. Then, each subregion within a knee was read by a board certified musculoskeletal radiologist with 15 years of experience in semi-quantitative scoring of knee OA features (AG) for presence (yes/no) of calcium crystals separately. The location of the calcium deposition and the shape of the structure in which calcium was deposited made it possible to identify the tissue affected. Readings were repeated after 4 weeks for calculation of intra-rater reliability. We used the axial images but also the coronal and sagittal reformatted images when semi-quantitatively scoring the knees. We performed multiplanar reformats (MPR) in sagittal and coronal planes and smooth reconstruction kernels in order to reduce the image noise. We also created maximum-intensity projection (MIP) images.

Statistical analysis

The intra-rater reliability for presence (yes/no) of intra-articular calcium crystals overall and in specific subregions (hyaline cartilage and meniscal cartilage) between readings 1 and 2 was measured by calculating kappa statistics (95% confidence interval) using SAS 9.3 (SAS Inc., NC).

This study was approved by Institutional Review Board as well as the Radiation Safety committee at University of Iowa, Iowa city, Iowa where subjects were scanned.

Results

In comparison with the participants without radiographic chondrocalcinosis ($n = 4$), those with radiographic chondrocalcinosis ($n = 12$) in this study were older (mean age 72 vs 64 years) and had lower mean BMI (26 kg/m^2 vs 32 kg/m^2). Seven out of 12 subjects and three out of four subjects were women in the chondrocalcinosis and non-chondrocalcinosis, respectively. While female predominace has been noted in prior studies of chondrocalcinosis[22], in our study that is not the case likely due to small number of total participants. A history of knee injury was present among two subjects with radiographic chondrocalcinosis.

Intra-articular calcium crystals were detected on CT images of all 24 knees (12 subjects) with bilateral radiographic chondrocalcinosis and not detected in any of the eight knees (four subjects) without radiographic chondrocalcinosis. CT images provided excellent visualization of intra-articular tissue structures and calcium crystal deposition was noted not only in meniscal and hyaline cartilage but also in deeper structures including cruciate ligaments and joint capsules. In Fig. 1, 3-D CT images of knee joint with and without intra-articular calcium deposition is shown. Fig. 2 demonstrates calcium crystal deposition in femoral hyaline cartilage, meniscal cartilage and joint capsule in a subject with